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Flavor Aversion Learning Based on Running: A Review

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Wheel running establishes aversion in rats to a flavored solution consumed shortly before the running. Many studies have shown that this is a case of Pavlovian conditioning, in which the flavor and running respectively act as the conditioned stimulus (CS) and the unconditioned stimulus (US). The present article introduces some procedural variables of this running-based flavor aversion learning (FAL), including subjects, CS agents, US agents, and drive operations. This article also summarizes various behavioral features of Pavlovian conditioning demonstrated in running-based FAL, including the law of contiguity despite long-delay learning, extinction, spontaneous recovery, CS-preexposure effect, remote and proximal US-preexposure effects, degraded contingency effect, inhibitory learning by backward conditioning, stimulus overshadowing, associative blocking, and higher-order contextual control. Also reviewed are several hypotheses proposed for the underlying psychophysiological causes of running-based FAL (i.e., activation of mesolimbic dopamine system, gastrointestinal discomfort, motion sickness, energy expenditure, general stress, and anticipatory contrast). At the end of the article, we visit the question of most general interest about running-based FAL: why the pleasurable activity of voluntary running yields aversive learning in rats.

Keywords: conditioned taste aversion, rats, running, swimming

Wheel running seems pleasurable for many species of rodents, including laboratory rats and mice. They not only voluntarily run in activity wheels (see Novak et al., 2012; Richter et al., 2014; Sherwin, 1998, for reviews) but also emit operant behavior (e.g., bar pressing) in order to run in the wheels (e.g., Belke, 1997; Belke & Garland, 2007; Collier & Hirsh, 1971; Iversen, 1993; Kagan & Berkun, 1954). Access to a wheel also serves as a reward for maze performance (Livesey et al., 1972). Rats running in the wheels (or approaching the wheels) make 50-kHz ultrasonic chirps (Heyse et al., 2015), which is an expression of joyful emotions (Panksepp, 2007). Activity wheels are frequently introduced to rodent cages for environmental enrichment, and their salubrious effects are well documented (e.g., Brandão & Mayer, 2011; Goodrick, 1980; Maniam & Morris, 2010; Olson et al., 2006; Van Praag et al., 2000). These findings are consistent with the general view that wheel running is pleasurable and beneficial for rats and mice. However, it also works as an agent to establish conditioned flavor aversion.

In 1996, Bow Tong Lett and Virginia Grant discovered that rats gradually learn to avoid a flavored solution consumed before voluntary running in activity wheels, indicating an apparently aversive nature of wheel running (Lett & Grant, 1996). This somewhat counterintuitive finding has been successfully replicated not only in their laboratory (e.g., Lett et al., 1998, 2001; Sparkes et al., 2003) but also in other research labs (e.g., Heth et al., 2001; Nakajima et al., 2000). These studies differ in procedural details (e.g., rat strains, flavors, characteristics of running activity, and deprivation levels), indicating the robustness and generality of the phenomenon. Because a positive correlation of a target flavor and running is necessary for this learning phenomenon, we can regard it as Pavlovian conditioning with the target flavor as the conditioned stimulus (CS) and wheel running as the unconditioned stimulus (US). In other words, as in conventional flavor aversion learning (FAL) based on poisonous drugs such as lithium chloride (LiCl), running-based FAL has been discussed in the framework of Pavlovian conditioned flavor aversion.

Figure 1 gives an example of running-based FAL of mildly water-deprived rats in an unpublished study conducted in my laboratory. Daily training began with a 15-min access to either a strawberry- or a melon-flavored solution, which was prepared daily by mixing 24 g artificial fruit juice powder (Matsuyama Confectionery, Nagoya, Japan) and 1 L tap water. The sequence of the two solutions employed over 20 days of training was SMSMSMSMMSSMSMSMSMMS (S = strawberry, M = melon) for all 16 rats used as subjects in the study. The target solution (CS+) was strawberry-flavored and the nontarget solution (CS−) was melon-flavored for 8 rats, while the combinations were reversed for the remaining 8 rats. Immediately after drinking the target solution, the rats were confined to individual activity wheels, where they remained for 30 min of voluntary running. On the nontarget days,

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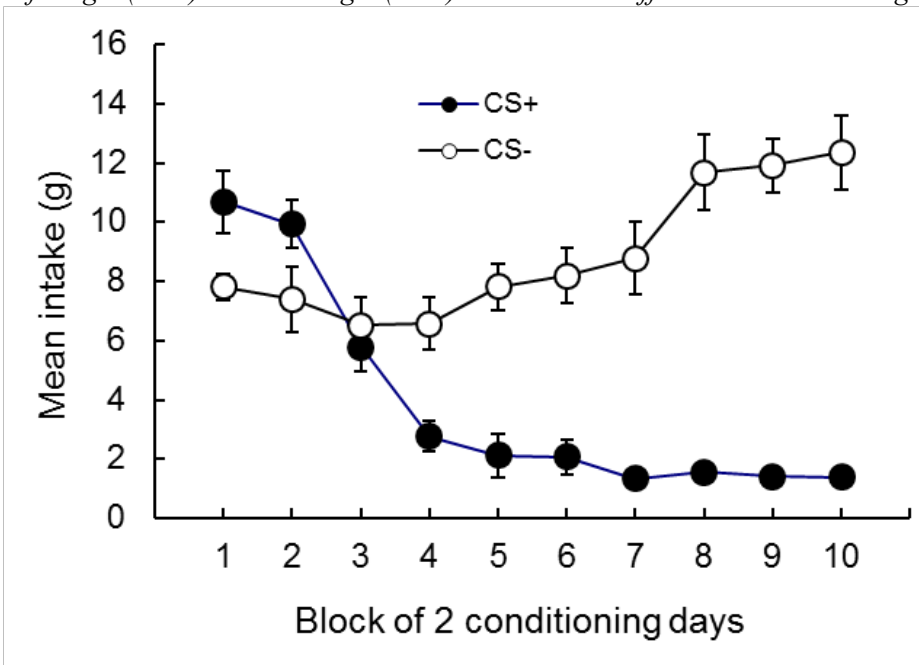
the rats were directly returned to the home cages after the drinking period. We see successful differential conditioning in Figure 1, implying that a positive taste–running correlation is necessary for establishing flavor aversion.

Figure 1

Mean Consumption of Target (CS+) and Nontarget (CS−) Solutions in Differential Conditioning of Rats (n = 16)



Note: The data were shown in 10 blocks of 2 training days, consisting of 1 day each for target and nontarget intakes. The bars indicate standard errors. Only the target intake was followed by wheel running. The rats were male Wistar and 12 weeks old when they entered the study. Tap water was available for 10 min in the home cages 3 hours before each daily session. Unpublished data.

Methodologies

As mentioned above, running-based FAL has been demonstrated in multiple laboratories with various procedures. Herein, I summarize some procedural variables used in these studies.

Subjects

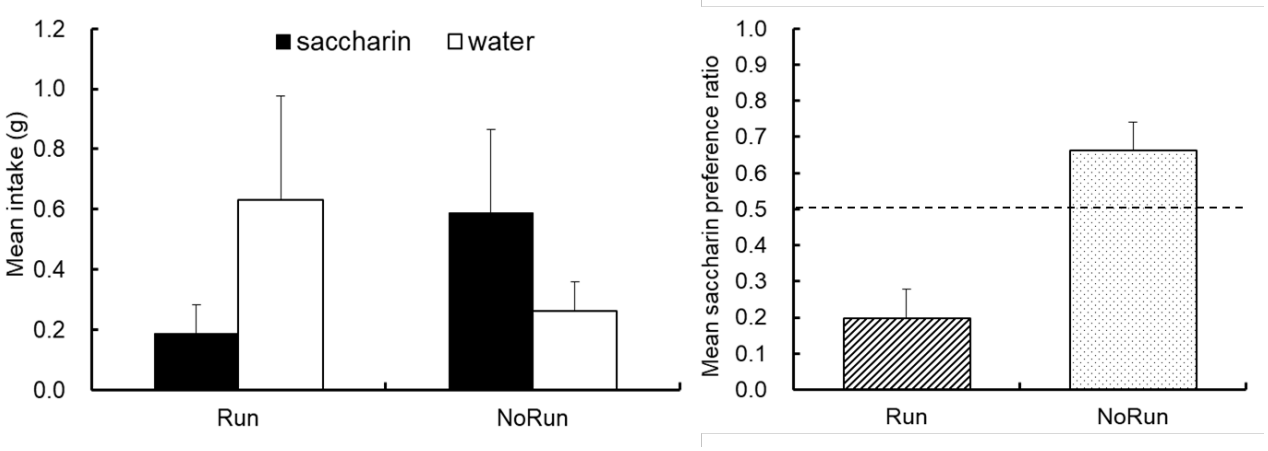
Running-based FAL has been demonstrated in many strains of rats. Sprague-Dawley rats were employed by Lett and Grant (1996; see also, e.g., Lett et al., 1998, 2001; Sparkes et al., 2003), while Wistar rats have been conventionally used in my laboratory (e.g., Hayashi et al., 2002; Nakajima et al., 2000). In another laboratory, the major subjects were JCR:LA-cp rats (e.g., Heth et al., 2001; Salvy, Heth, et al., 2004), a strain developed for the study of metabolic syndrome. Some studies have used two strains: Wistar and hooded Wistar rats (Baysari & Boakes, 2004), and Wistar and Lister rats (Dwyer et al., 2008). However, these studies did not investigate the strain differences. Notably, there are several reports on rats' strain differences in conventional, drug-based FAL (see Cunningham et al., 2009, for a review). Nakajima (2014b) compared the performances of Sprague-Dawley, Wistar, Long-Evans, Lewis, and Fischer rats using sweet (saccharin) and salty (NaCl+MSG) solutions as CSs. No reliable strain differences were obtained in terms of the strength of running-based flavor aversion despite wide variations in their body sizes and running activities.

Running-based FAL has also been demonstrated in humans (Havermans et al., 2009) with flavored syrup CSs and a treadmill-running US. A demonstration of running-based FAL in golden hamsters was reported in a conference article (Masaki, 2009), but attempts to reproduce the effect in my laboratory have been met with very limited success. Further exploration is needed to establish the standard procedures to obtain a reliable effect in hamsters.

After several failures to obtain a reliable effect in mice, we successfully demonstrated it (Nakajima & Oi, 2018): Water-deprived mice were given a 15-min access to 0.2% saccharin solution in the drinking chambers followed by a 30-min confinement in the wheels (Group Run, $n = 4$) or by a 30-min stay in the drinking chambers (Group No-Run, $n = 4$). After a 4-day training period, the saccharin solution and tap water were presented concurrently for 15 min to test the saccharin preference. Figure 2 summarizes the results of 2 test days. Saccharin avoidance in Group Run compared with Group No-Run is evident in the absolute intakes (the left panel) as well as in the saccharin preference ratio (the right panel), which was calculated by dividing the intake of saccharin solution by the combined intake of the saccharin solution and tap water. Group Run showed saccharin avoidance, while Group No-Run showed saccharin preference. Although this study did not control nonassociative factors, subsequent studies (Nakajima, 2019b, 2019c) controlled them and expanded the generality to solid CSs (cheese, chocolates, marshmallows, and raisins).

Figure 2

Choice Test Performance of Two Groups of Mice (each n = 4) after the Training Phase



Note. Left panel: Mean fluid consumptions. Right panel: Mean saccharin preference ratios. Half of the mice (Group Run) had been trained with saccharin-running trials, while the others (Group No-Run) had been directly returned to the home cages after the saccharin intake. The bars indicate standard errors. The mice were male ICR and 9 weeks old when they entered the study. Tap water was available for 15 min in the home cages after each training or test session. Adapted from Nakajima and Oi (2018).

CS Agents

The earliest studies on running-based FAL (Lett et al., 1998; Lett & Grant, 1996) employed complex flavor solutions as the target and control stimuli: a cocktail of sodium chloride (NaCl) and monosodium glutamate (MSG) and a cocktail of citric acid and saccharin. In later studies, however, much simpler flavored solutions, such as NaCl and saccharin solutions without added solutes were conventionally used (e.g., Hayashi et al., 2002; Nakajima et al., 2000). Some studies used solid CSs, such as flavored food pellets (Aoyama, 2007), dog biscuits (Sparkes et al., 2003), and cheese and raisins (Nakajima, 2019a).

It is notable that the word “flavor” includes not only gustatory sensation (i.e., taste) but also olfactory sensation (i.e., odor) and somatosensation (i.e., texture and temperature). As in poison-based FAL studies, a majority of research on running-based FAL does not explicitly distinguish these sensory components of the flavors, but we implicitly expect the primary cue to be gustatory in many cases especially when the target flavor provides little olfactory and somatosensory cues (e.g., saccharin solution at room temperature). Gustatory and olfactory cues were equally effective in the aforementioned human study (Havermans et al., 2009), but this issue has not been tested in rats.

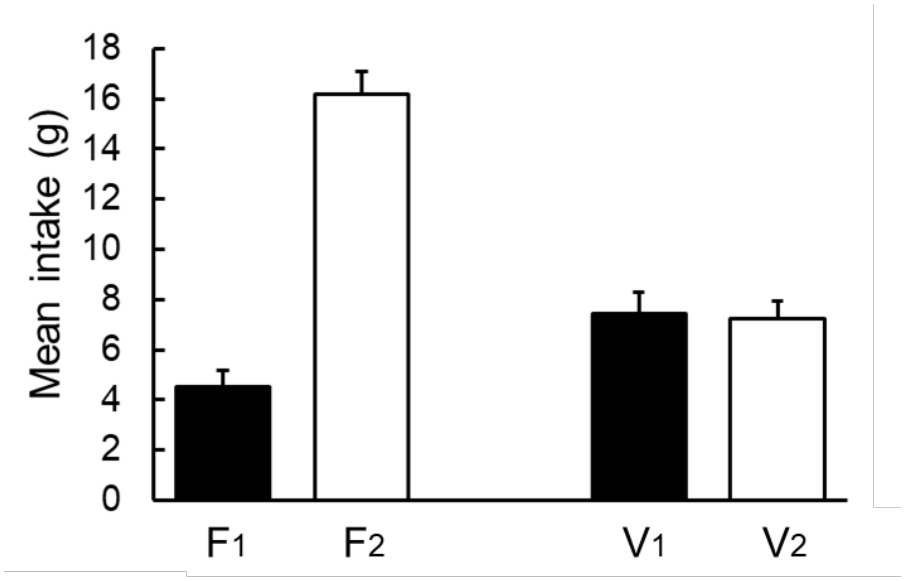
Voluntary wheel running establishes aversion not only to a paired flavor but also to a paired chamber, if rats are confined to the chamber immediately before the running (Masaki & Nakajima, 2008). In this study, the two adjacent chambers used were visually and textually unique: One had horizontally-striped walls and a stainless wire mesh floor, while the other had vertically-striped walls and a perforated aluminum floor. Differential conditioning was executed for 8 days with the physical identities of the target chamber (CS+) and the nontarget chamber (CS−) being

counterbalanced across subjects. In the post-training choice test, the rats avoided the target chamber and stayed in the nontarget chamber, implying that running established aversion to the visual and/or textual cues of the running-paired chamber.

Despite this finding, as in radiation- or drug-based aversion learning (Garcia et al., 1968; Miller & Domjan, 1981), flavor cues are more dominant than visual cues in running-based aversion learning. Figure 3 provides an example (Nakajima, 2008b). Water-deprived rats (n = 16) were given flavored solutions (F_1 and F_2: 0.2% saccharin and 0.3% NaCl, counterbalanced) in colored nozzles (V_1 and V_2: black and white, counterbalanced) for 12 days. Daily training began with a 15-min access to either an F_1V_1 or an F_2V_2 bottle (6 days each, intermixed). On the F_1V_1 days, the rats were allowed to run for 15 min immediately after drinking from the bottle. On the F_2V_2 days, the rats were directly returned to the home cages after the drinking period. This 12-day differential compound conditioning was followed by a 2-day element test, in which the rats chose between F_1 and F_2 (flavor-cue testing with neutral silver-colored nozzles) and between V_1 and V_2 (visual-cue testing with neutral tap water). As shown in Figure 3, the rats avoided F_1 compared to F_2, suggesting conditioned flavor aversion, while the consumption from the V_1 and V_2 bottles was equivalent, implying no conditioned color aversion.

Figure 3

Mean Fluid Consumption of Rats (n = 16) in the Element Test Executed after Differential Compound Conditioning



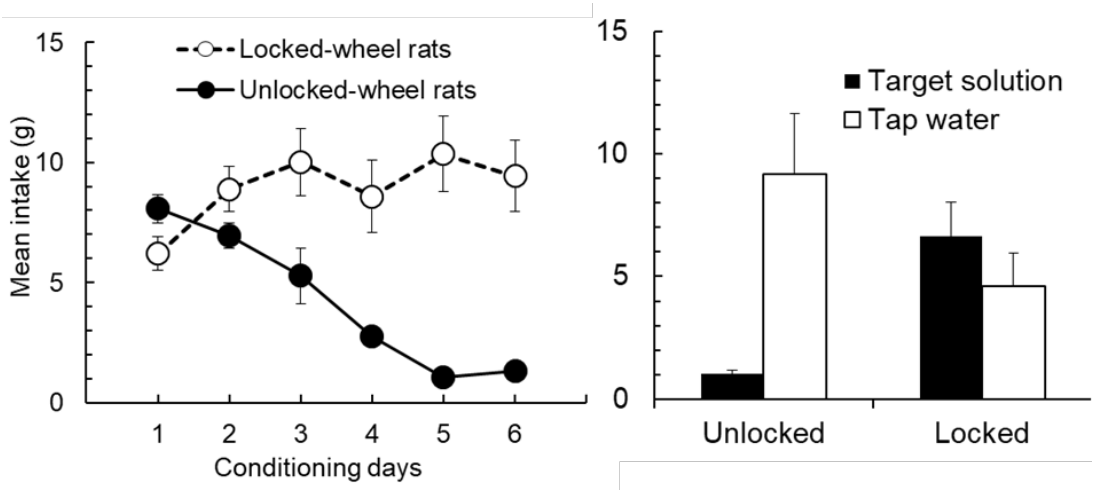
Note. The rats had been trained in 6 blocks of 2 training days, consisting of 1 day each for the F_1V_1 compound followed by running and the F_2V_2 compound followed by non-running. In the element test, the rats chose between F_1 and F_2 (flavor cue testing), and between V_1 and V_2 (visual cue testing). The bars indicate standard errors. The rats were male Wistar and 8 weeks old when they entered the study. Tap water was available for 15 min in the home cages after each training or test session. Adapted from Nakajima (2008b).

US Agents

Many studies on running-based FAL employed closed and freely moving activity wheels for creating flavor aversion in the rats. Confinement in the locked wheels had no effect (Hayashi et al., 2002; Heth et al., 2001). An example is depicted in Figure 4 (Nakajima, 2014a). Mildly-water-deprived rats (n = 7) were given a 15-min access to a melon-flavored solution. Immediately after the drinking period, 4 rats were confined to locked wheels for 30 min, while the remaining 3 rats were in unlocked wheels for the same period. Only the latter rats acquired aversion to the target flavor as illustrated in the conditioning performance and in the post-training choice test performance.

Figure 4

Mean Fluid Consumption of the Rats Confined to the Locked (n = 4) or Unlocked (n = 3) Wheels after Consumption of the Flavored Solution

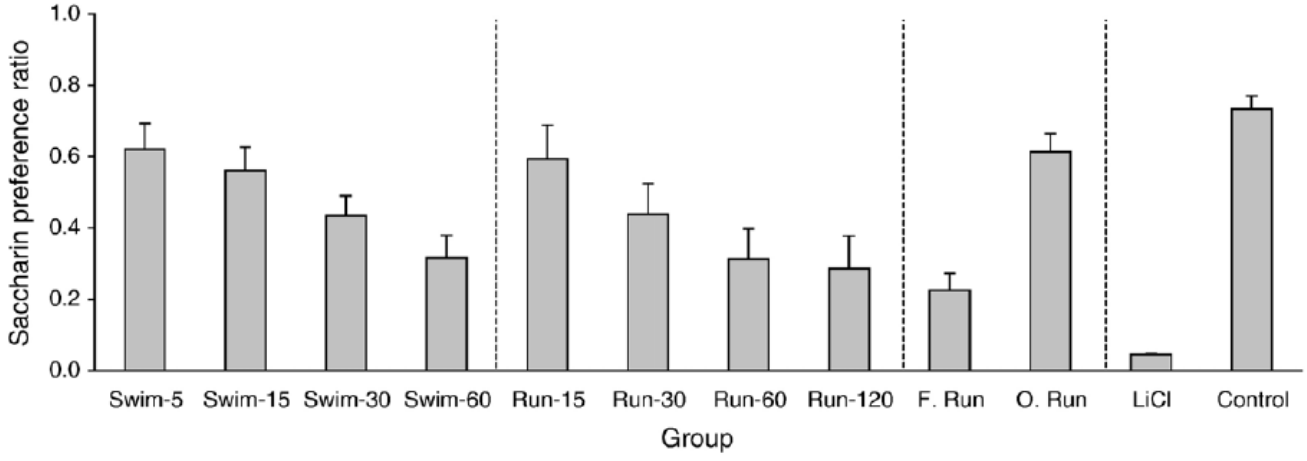


Note. Left panel: Performance of the two groups of rats in the conditioning phase. Right panel: Two-choice test data. The bars indicate standard errors. The rats were male Wistar and 9–10 weeks old when they entered the study. Tap water was available for 15 min in the home cages 3 hours before each training session. Adapted from Nakajima (2014a).

The degree of running-based flavor aversion is a positive function of the length of time (duration) that rats are confined to unlocked wheels. This claim comes from the results of Hayashi et al. (2002) who compared multi-trial FAL based on 5-, 15-, and 30-min running opportunities and of Masaki and Nakajima (2006) who assessed one-trial FAL based on 15-, 30-, 60-, and 120-min running opportunities (see the second section of Figure 5).

Figure 5

Mean Saccharin Preference Ratios of 12 Groups of Rats (Each n = 8) Calculated from the Choice Test after a Single Conditioning Trial



Note. Swim-5, Swim-15, Swim-30, and Swim-60 = forced swimming for 5, 15, 30, and 60 min, respectively. Run-15, Run-30, Run-60, and Run-120 = voluntary running for 15, 30, 60, and 120 min, respectively, in closed wheels. F. Run = forced running for 60 min, O. Run = voluntary running for 120 min in open wheels. LiCl = an injection of 0.15 M LiCl at 2% bodyweight. Control = directly retuning to the home cages. The bars indicate standard errors. The rats were male Wistar and 9–10 weeks old when they entered the study. Tap water was available for 60 min in the home cages 3 hr after the session. Adapted from Masaki and Nakajima (2006).

Flavor aversion can be established not only by voluntary running in an unlocked closed wheel, but also by forced running in a motor-driven closed wheel (Eccles et al., 2005; Forristall et al., 2007; Masaki & Nakajima, 2006). Although the comparison of Groups Run-60 and F. Run in Figure 5 gives an impression that forced running appears slightly more effective than voluntary running, the distance travelled by the forced running rats (Group F.Run) was twice as long as that by the voluntary running rats (Group Run-60) in this study. Forristall et al. (2007) reported that voluntary running produced greater flavor aversion than forced running when the distance travelled was matched between the groups.

Some studies have employed an open wheel with an adjacent cage (Wahmann wheel) to demonstrate running-based FAL in rats (e.g., Dobek et al., 2012; Salvy, Pierce, et al., 2004; Satvat & Eikelboom, 2006). Salvy, Heth, et al. (2004) failed to obtain a reliable difference in multitrial FAL between 20- and 60-min running opportunities in Wahmann wheels. Direct comparison between open and closed wheels (O. Run and Run-120 respectively in Figure 5) suggests the superiority of closed wheels. This is also the case in mice (Nakajima, 2019c).

Notably, there is a single report of FAL based on confinement in a flat circular alley for 30 min (Lett et al., 1999), implying that the curved surface structure of the activity wheel is not a necessary condition for establishing aversion. Future research needs to replicate this finding and clarify what kind of physical activities in the alley are critical to yield aversion to a paired flavor.

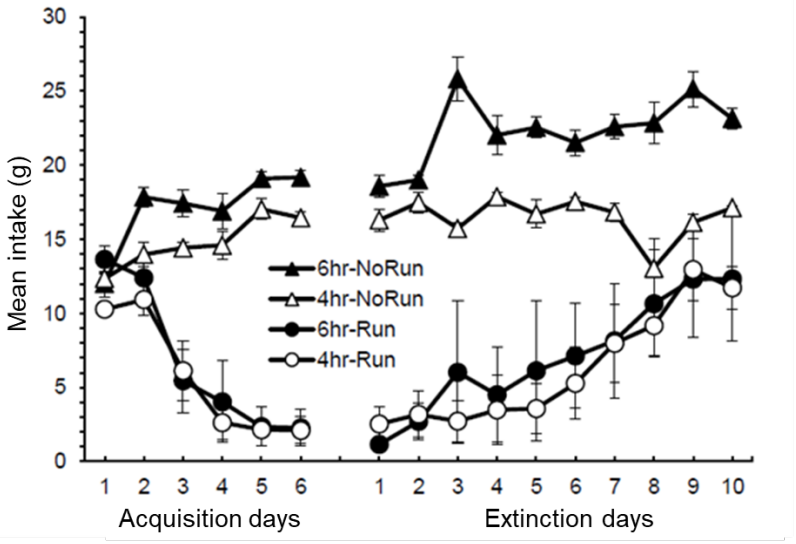
Swimming in a water pool also works as a US for FAL in rats. A series of studies conducted in my laboratory (Masaki & Nakajima, 2004a, 2004b, 2005, 2006, 2010; Nakajima, 2004, 2015b, 2018b; Nakajima & Masaki, 2004) have revealed several critical factors for this swimming-based FAL. First, water levels (i.e., the necessity of swimming) determine the degree of flavor aversion. Second, being wet is not effective in itself; a water shower yields no flavor aversion. Third, the degree of swimming-based flavor aversion is a positive function of the length of time (duration) that rats are confined to pools (see the first section of Figure 5). Fourth, 22°C water effectively establishes flavor aversion, while the aversion based on swimming in 30°C or 38°C water is weak and ambiguous. Fifth, swimming-based flavor aversion is establishable with a 30-min delay between CS and US. Finally, simultaneous conditioning procedures (swimming in flavored water) yield a very weak flavor aversion.

Drive Operations

Lett and Grant (1996) employed rats undergoing food and water deprivation, while Lett et al. (1998) used rats that were nondeprived. A majority of the later studies have employed water-deprived but not food-deprived rats as subjects in order for rats to drink a target solution. However, water deprivation prevents easy detection of FAL when deprivation-induced thirst overcomes conditioned aversion of a flavored solution. This is frequently the case in running-based FAL because the acquired aversion is conventionally weak. This difficulty is solved in two ways: (1) using mildly water-deprived rats as subjects in the studies (see, e.g., Figure 1 and the left panel of Figure 4), and (2) assessing FAL in post-training two choice testing (see, e.g., Figure 2 and the right panel of Figure 4). It is noteworthy that a brief access to tap water 4- or 6-hr before the daily sessions yields clear acquisition and extinction curves of running-based FAL (Figure 6).

Figure 6

Mean Fluid Consumption of 4 Groups of Rats (Each n = 4)



Note. All rats were given a 15-min access to an NaCl+MSG solution before confinement in activity wheels or plastic cases for 30 min. Rats were given access to tap water for 15 min in the home cages either 6 or 4 hr before the session. In the extinction phase, all rats were directly returned to the home cage after the NaCl+MSG solution intake. The bars indicate standard errors. The rats were male Long-Evans and 24 weeks old when they entered the study. Adapted from Nakajima and Hashimoto (2013).

Parallels with Other Pavlovian Conditioning Preparations Including Poison-based FAL

Although the running-based flavor aversion is weak in effect compared with poison-based flavor aversion, many behavioral features of Pavlovian conditioning have been demonstrated in this preparation as shown in Table 1 (see also Boakes & Nakajima, 2009, for an early review). All of the features shown in this table have been also demonstrated in poison-based FAL: law of contiguity despite long-delay learning (e.g., Garcia et al., 1966; Nachman, 1970), extinction and spontaneous recovery (e.g., Berman et al., 2003; Rosas & Bouton, 1996), CS-preexposure effect (e.g., Fenwick et al., 1975; Nagaishi & Nakajima, 2008), remote US-preexposure effect (see Riley & Simpson, 2000, for a review), proximal US-preexposure effect (see Best, 1982, for a review), degraded contingency effect (Monroe & Baker, 1979), inhibitory learning by backward conditioning (e.g., Green & Garcia, 1971; Hasegawa, 1981), stimulus overshadowing (e.g., Bond, 1983; Lindsey & Best, 1973), associative blocking (e.g., Gillan & Domjan, 1977; Revusky, 1977), and higher-order contextual control (e.g., Loy & López, 1999; Nakajima et al., 1995). Some of these have been reported in swimming-based FAL. For example, previous swimming experience strongly alleviates swimming-based flavor aversion (remote US pre-exposure effect; Masaki & Nakajima, 2004a, 2010).

Table 1

Features of Pavlovian Conditioning Demonstrated in Running-based Flavor Aversion Learning (FAL) in Rats

Features of Pavlovian conditioning	Running-based FAL studies
Conditioning is strong when the CS-US interval is short (law of contiguity)[a]	Hayashi et al., 2002
Conditioned responding disappears by presentation of the CS without the US (extinction) and reappearance of responding after a rest period (spontaneous recovery)	Nakajima, 2018c
Familiarization with a CS interferes with subsequent conditioning (CS-preexposure effect, latent inhibition)	Heth & Pierce, 2007; Satvat & Eikelboom, 2006; Sparkes et al., 2003

Features of Pavlovian conditioning	Running-based FAL studies
Familiarization with a US interferes with subsequent conditioning (remote US-preexposure effect)	Baysari & Boakes, 2004; Hughes & Boakes, 2008; Nakajima, 2015a; Nakajima et al., 2006; Salvy et al., 2002
Pretrial presentation of a US interferes with conditioning (proximal US-preexposure effect)	Nakajima, 2020a
Presentation of an extra US between the trials interferes with conditioning (degraded contingency effect)	Nakajima, 2008a
The US-then-CS trial sequence yields negative conditioned responding (inhibitory learning by backward conditioning)	Dobek et al., 2012; Hughes & Boakes, 2008; Salvy, Pierce, et al., 2004
An added cue interferes with conditioning to a target CS (stimulus overshadowing)	Nagaishi & Nakajima, 2010
A separately trained cue (CS_1) interferes with conditioned responding to CS_2, which is always presented with CS_1 in conditioning (associative blocking)	Pierce & Heth, 2010
Background cues modulate responding evoked by a target CS (higher-order contextual control)	Hashimoto & Nakajima, 2013

Note. [a] Long-delay conditioning is also available as in poison-based FAL.

Hypotheses

Several hypotheses have been proposed for the underlying psychophysiological process of running-based FAL. This section introduces them and discusses their validation and/or invalidation.

Activation of Mesolimbic Dopamine System

It is well documented that physical exercise influences the mesolimbic dopamine system in humans and animals (see Meeusen & Piacentini, 2001, for a review). Lett and Grant (1996) proposed, in their original report on running-based FAL, that running acts like rewarding drugs, such as amphetamine and morphine on the brain system. Because there is vast literature on FAL based on rewarding drugs (see Lin et al., 2014, 2017; Verendeev & Riley, 2012, for reviews), it is straightforward to conjecture that the same or at least a similar process operates in running-based FAL. Support for the mesolimbic dopamine hypothesis comes from conditioned place preference studies. Rats and mice learn to prefer the chamber paired with rewarding drugs (see Tzschentke, 1998, 2007, for reviews). The reports that rats come to prefer the place paired with wheel running (Belke & Wagner, 2005; Lett et al., 2000, 2001, 2002) appear to validate the mesolimbic dopamine hypothesis. However, all of these reports employ a trial sequence of running-then-chamber, which is a procedure of backward conditioning (i.e., US-CS pairing). In contrast, forward pairings (i.e., chamber-then-running) yield aversion to the paired chamber (Masaki & Nakajima, 2008). Backward pairings sometimes cause conditioning of a process which is opposite of the process primarily elicited by the US (Schull, 1979; Solomon, 1980; Wagner, 1981; Wagner & Larew, 1985). Acquisition of the opponent process by the backward conditioning procedure has been demonstrated in poison-based FAL in rats (i.e., conditioned taste preference rather than taste aversion), if the poison-then-flavor trial was repeated in training (e.g., Green & Garcia, 1971; Hasegawa, 1981). In running-based FAL, Dobek et al. (2012), Salvy, Pierce, et al. (2004), and Hughes and Boakes (2008) reported conditioned flavor preference when wheel running preceded target flavor intake (i.e., backward conditioning; see the seventh feature of Table 1). Notably, a study reports conditioned place preference in golden hamsters by a simultaneous conditioning procedure (Antoniadis et al., 2000). However, this is explicable in terms of the opponent process theory (Solomon, 1980), as these hamsters had a prior running experience in the home cages (E. A. Antoniadis, personal communication, August 8, 2007), which would have fostered a pleasant sensation of

relief from the aversive property of running. Hence, such a post-running pleasant state would condition preference for the running chamber (see Masaki & Nakajima, 2008, for a detailed account).

Another inconvenient fact for the mesolimbic dopamine hypothesis comes from microstructure analysis of fluid-licking behavior conducted by Dwyer et al. (2008). These researchers revealed that running-based flavor aversion differs from amphetamine-based flavor aversion in the palatability change of the target flavor, implying that these aversions do not share a common psychophysiological state (Dwyer et al., 2008). A more recent study, however, found similar palatability changes between running- and amphetamine-based flavor aversions (Lin et al., 2012).

Gastrointestinal Discomfort

In a personal communication to Lett et al. (1999), John Garcia ascribed the psychophysiological cause of FAL to gastrointestinal discomfort (e.g., nausea) induced by running. Unfortunately, we are unable to directly measure nausea in rats because they cannot vomit due to neuroanatomical reasons (Horn et al., 2013). Nevertheless, we have at least five positive pieces of evidence for this hypothesis. First, Eccles et al. (2005) reported that an anti-emetic drug (granisetron) injection prevented running-based FAL, implying that nausea plays a major role in establishing running-based FAL. Second, Nakajima et al. (2006) demonstrated that running-based FAL is alleviated not only by preexposure to running (remote US-preexposure effect; see the fourth section of Table 1) but also by prior injection of emetic LiCl (cross-US familiarization effect), suggesting that a common process (presumably nausea) is physiologically habituated by preexposure.

Third, Dwyer et al. (2008) found a reduction in taste palatability, reflected in the microstructure of fluid-licking behavior, for running-based FAL as well as for LiCl-based FAL, concluding that running- and LiCl-based flavor aversions are commonly caused by nausea. Fourth, negative orofacial and somatic reactions, such as gaping, chin rubbing, and paw treading (Grill & Norgren, 1978) are evoked by the flavor paired with running, at least when the running is accompanied with a rocking movement of the wheel (Grant et al., 2012). Because similar disgust reactions are evoked by the flavor paired with emetics such as LiCl but not the flavor paired with rewarding drugs (Parker, 2014), we straightforwardly deduce that running-based FAL and emetic-based FAL share the same psychophysiological state (i.e., nausea).

Finally, rats consume kaolin clay in the home cages after running in wheels (Nakajima, 2016a, 2018d, 2019a; Nakajima & Katayama, 2014) or swimming in water pools (Nakajima, 2016b, 2020b). Because kaolin clay intake is generated by a variety of nausea-inducing treatments, including the administration of irradiation (Yamamoto et al., 2002, 2011) and emetic drugs such as LiCl (e.g., Mitchell et al., 1976; Nakajima, 2018a; Watson & Leitner, 1988; Yamamoto et al., 2004), it has been regarded as indicative of nausea in rats (Andrews & Horn, 2006). Running- and swimming-generated kaolin consumptions, hence, indicate that these activities induce nausea in rats.

These findings, taken together, strongly suggest that the psychophysiological state responsible for running-based FAL is gastrointestinal discomfort. However, there is a negative piece of evidence against this hypothesis. The amount of gastrointestinal discomfort reported by human participants after treadmill running did not predict the size of acquired flavor aversion (Havermans et al., 2009).

Motion Sickness

The gastrointestinal discomfort hypothesis does not specify which characteristics of wheel running cause nausea in rats. Forristal et al. (2007), however, have argued that motion sickness induced by the collateral back-and-forth “rocking” movements of free wheels results in nausea in rats. We consider this conjecture here. It is well documented that motion sickness induced by rotation of a turn table works as an effective US agent for establishing FAL in rats (e.g., Braun & McIntosh, 1973; Green & Rachlin, 1973, 1976; Haroutunian & Riccio, 1975). Rotation-induced motion sickness also produces disgust reactions (Ossenkopp et al., 2003) and kaolin clay intake (e.g., McCaffrey, 1985; Mitchell, Krusemark, et al., 1977; Mitchell, Laycock, et al., 1977). Therefore, the motion sickness hypothesis seems to be a reasonable explanation for running-based FAL. Furthermore, Grant et al. (2012), who carefully manipulated the rocking movements of the wheels, demonstrated that reduction of rocking movements reduced the disgust reactions.

It is notable, however, that reduction of rocking movements had little effect on running-based FAL, suggesting that the major psychophysiological cause of running-based FAL is not gastrointestinal discomfort. As mentioned earlier, FAL has been reported with motorized wheels, which had no rocking movements (Eccles et al., 2005; Forristall et al., 2007; Masaki & Nakajima, 2006). According to Forristall et al. (2007), wheel running activates the mesolimbic dopamine system, which is the major factor of FAL, and rocking movements add another US agent (nausea) to augment the FAL. Contrary to this claim, running in a motorized wheel itself appears to induce nausea because it also generates kaolin clay consumption in rats (Nakajima, 2016a). Another shortcoming of the motion sickness hypothesis is that it cannot explain FAL based on running in a circular alley (Lett et al., 1999) or a treadmill (Havermans et al., 2009). Swimming-based FAL (e.g., Nakajima & Masaki, 2004) is also inexplicable according to the motion sickness hypothesis. Thus, another psychophysiological process is needed for these types of learning.

Energy Expenditure

In concluding our first article on running-based FAL in rats, we proposed another possibility as follows: "Rats learn to prefer flavors that are associated with caloric restoration (Fedorchak, 1997). Conceivably, they can also learn to avoid the tastes that are associated with energy expenditure, a result of wheel running" (Nakajima et al., 2000, pp. 40–41). If energy expenditure resulting from wheel running works as a US for FAL, other physical activities or motor exercises should also create flavor aversion in rats. Indeed, our initial research on swimming-based FAL (Nakajima & Masaki, 2004) was driven by this hypothesis. Successful demonstration of swimming-based FAL, thus, is a good piece of evidence for the energy- expenditure hypothesis. However, there are two rebuttals to this hypothesis. First, energy supply by glucose, which is expected to compensate energy expenditure, did not alleviate running-based FAL in rats (Nakajima, 2011). Second, conspecific fighting, which is another exhausting activity, failed to work as an effective US for establishing flavor aversion in rats (Nakajima et al., 2012).

General Stress

Mainly drawing on his cross-US familiarization studies of drugs and motion sickness (e.g., Braveman 1975), Braveman (1977) claimed that flavor aversions caused by a variety of USs have a common underlying process that he ascribed to certain stress-induced physiological changes such as the elevation of plasma corticosterone levels (e.g., Ader, 1976; Hennessy et al., 1976; Smotherman et al., 1976). Following this line of speculation, we proposed that the underlying psychophysical cause of running- and swimming-based flavor aversions is general stress (Nakajima et al., 2006). The aforementioned failure to demonstrate fighting-based FAL (Nakajima et al., 2012), however, makes this hypothesis improbable because conspecific fighting is highly stressful (see Blanchard et al., 2001; Caldwell, 2006; Martinez et al., 1998, for reviews).

Anticipatory Contrast

All of the aforementioned hypotheses are based on the aversive property of running. However, voluntary wheel running is a pleasurable activity for rats and mice, as discussed in detail in the next section. It is noteworthy that Grigson (1997, 2008) has interpreted FAL based on rewarding drugs in the theoretical framework of anticipatory contrast developed by Flaherty (1982, 1996), namely, anticipation of the availability of a highly preferred drug lowers the hedonic valence of a target solution. For example, saccharin–morphine pairings lead to a reduction in rats' saccharin intake, which is accompanied by a conditioned blunting of the accumbens' dopamine response (i.e., pleasurable neural reaction) to the saccharin cue (Grigson & Hajnal, 2007). The same process might be at work for running-based FAL: Rats gradually become reluctant to consume a target solution because they favorably anticipate wheel running. This possibility, recently proposed by Nakajima (2019b), should be evaluated in future research.

Why Rats Voluntarily Run in Activity Wheels to Acquire a Flavor Aversion

As noted in the introduction of this article, wheel running is pleasurable and beneficial for rats and mice. However, it is a physical stressor: It activates both the sympathetic nervous system, resulting in epinephrine production, and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in glucocorticoid production and HPA axis feedback (Mul, 2018). Wheel running also induces gastrointestinal discomfort, as mentioned earlier. Thus, these negative effects may serve as a US for FAL in rats and mice.

The hedonically bivalent nature of wheel running might be related to the biphasic nature of running: The onset of running is pleasurable, but the aversive property of running gradually overtakes its pleasant nature. In short, running has a delightful start with a distressful ending. More than half a century ago, Hundt and Premack (1963) argued that all self-initiated behaviors, including wheel activity, are self-terminated, and the "on–off systems" of these behaviors are capable of generating both positive and negative reinforcement. In the framework of this argument, the US agent of running-based FAL should be the secondary, aversive property of wheel running.

Running and Swimming

Running- and swimming-based flavor aversions have been addressed in the same framework, because these are both physical activities (Boakes & Nakajima, 2009). However, rats do not voluntarily swim in water pools, and, thus, the forced procedure is employed in swimming-based FAL studies. Forced swimming evokes many stress-related physiological, endocrine, and immune changes including elevation of plasma corticosterone and alterations in monoamine levels in a variety of brain regions (e.g., Abel, 1993, 1994; Connor et al., 1997). There seems to be no pleasurable period of activity in the case of swimming. In other words, swimming is hedonically monophasic and not biphasic, as wheel running is.

Prior swimming does not hinder subsequent running-based FAL in rats (Nakajima, 2015a). This failure to demonstrate cross-familiarization from swimming to running provides another piece of evidence that these activities cause FAL via different psychophysiological processes. Lack of cross-familiarization from LiCl to swimming (Nakajima, in press, Experiments 1A and 1B), despite cross-familiarization from LiCl to running (Nakajima et al., 2006), also implies the disparity in the psychophysiological states induced by swimming and running, only the latter of which has similarities with LiCl. The claim that swimming and LiCl induce qualitatively different psychophysiological states is also supported by the finding that sucrose aversion is stronger than saccharin aversion with the swimming US, while the opposite is the case when the US is LiCl (Nakajima, in press, Experiment 2). This CS–US suitability implies selective associations or sensitization (Bevins, 1992; Domjan, 1982), suggesting that the psychophysiological states induced by swimming and LiCl are qualitatively different.

On the other hand, the similarity of running- and LiCl-based aversions shown in the cross-familiarization test suggests that the underlying processes of these aversions share a common physiological process as already noted in the section on gastrointestinal discomfort in the "Hypotheses" section of this article.

Closing Remarks

Running-based FAL has attracted attention of researchers mainly because of its hedonically bivalent nature; rats and mice voluntarily run to acquire a flavor aversion. Although its underlying psychophysiological processes have not yet been well clarified, accumulating pieces of evidence will in time make it possible. To my best knowledge, there have been no neurobiological investigations in this field of research. Future research on the neurobiological basis of running-based FAL will help in understanding the nature of this learning. Other topics to be explored are the age and sex of the animals, not only because the amount and pattern of wheel running largely depends on these variables (e.g., Eikelboom & Mills, 1988; Jakubczak, 1973; Mondon et al., 1985; Tokuyama et al., 1982), but also because these variables affect conventional, drug-based FAL (e.g., Chambers et al., 1981; Hurwitz et al., 2013; Misanin et al., 1988, 2002; Randall-Thompson & Riley, 2003).

The running-based FAL paradigm provides a convenient tool for studying aversive conditioning with minimal discomfort in laboratory rats (Nakajima, 2019a). Although aversive conditioning research has greatly contributed to our understanding of behavioral and neural mechanisms of learning and memory (Archer & Nilsson, 1989), recent concerns for laboratory animal welfare (Bayne & Turner, 2014) lead us to seek and use more humane experimental techniques than the conventional ones. In this sense, running-based FAL is a good experimental paradigm. One might argue that wheel running shares many features with pathological behavior, such as stereotypy and addiction (Richter et al., 2014; Sherwin, 1998), and that long-term exposure to wheels may cause activity anorexia under some conditions (Epling & Pierce, 1996). However, because the period of wheel confinement is brief in most studies of running-based FAL, any health problem arising from wheel running is minimal.

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