Abstract

Developing social strategies to share the limited resources equally and maximize the long-term benefits of conflict resolution is critical for appropriate social interactions. During social interactions, making social decisions depend not only on the external environment but also on internal factors such as hunger, thirst, or fatigue. In particular, the hunger state, which is related to food as a physical need, plays a dominant role in social decision-making. However, the consequences of food deprivation on social decision-making are not well understood. We have previously shown that mice in rule-observance behavior are capable of resolving conflict during social decision-making by observing the well-established social strategy based on reward zone allocation. Here, we develop a rule-observance behavior paradigm, in which the hunger state is achieved by applying food restrictions on mice prior to social behavior. We found that the hunger state in mice deteriorated the established social strategy by decreasing the reaction time, implying an increase in impulsivity. In contrast, the hunger state did not affect the reward zone allocation, indicating no effect on spatial memory. This decrease in reaction time led to a significant increase in the percentage of wrong social decisions (violation) and a significant decrease in the amount of reward (payoff equity). Our study proposes that the hunger state exerts a detrimental effect on appropriate social decision-making by decreasing reaction time, increasing violation, and decreasing payoff equity in rule-observance behavior.

Introduction

Food, territory, and well-matched mate are pivotal resources for humans and animals. Securing stable resources is crucial for survival and the stability of society. However, in reality, it is not easy to be achieved. Aggression and social conflict, on the other hand, are risky and costly (Animal Conflict, 1987; Guo, 2020). Physical conflict might cause injuries and disabilities on the body level. In addition, it causes stress and depression on the psychological level. Moreover, the mutual violation is time and resource-consuming. Therefore, developing social strategies to resolve conflicts and share the resources equally and wisely is critical to animal survival. Human and non-human animals are qualified to establish a social strategy to share resources and solve a conflict. These strategies do not depend only on external factors such as environment or availability of resources, but also on internal states such as hunger, fatigue, and thirst. There have been studies on the role of internal states in modifying the behavior of mice in many cognitive tasks. For instance, it has been shown that food availability affects the representation and valuation of choices during decision-making (Rangel et al., 2008). In addition, it has been reported that fatigue affects the performance of
mice during learning tasks (MIZUNOYA et al., 2004). Moreover, mounting lines of evidence point out that physiological needs such as water and food shape valuation, and motivation and guide decision-making to restore homeostasis (Betley et al., 2015; Eiselt et al., 2021). Food as a physiological need with physical shape has an influential role in decision-making (Choe et al., 2017; Betley et al., 2015). Despite these numerous studies, however, the influence of the hunger state on social decision-making and social interactions is not well-understood.

The hunger state is known to exert a negative effect on the decision-making and motivational states (Burnett et al., 2016). Delay discounting is the preference of the agent for an immediate reward even smaller one than a large, long-term reward (Steward, 2017). In humans, it has been shown that the hunger state increases the impact of delayed discounting on food and non-food rewards like money or music (Skrynka & Vincent, 2019). A Hunger state has a detrimental effect on the valuation of economic decision-making (Betley et al., 2015). In addition, there is a correlation between food deprivation and impulsivity response during decision-making in rodents (Viana et al., 2010). An increase in impulsivity leads to a negative effect on social cooperation (Stephens et al., 2006). Hungry impulsive mice are not capable of performing the right choice (G.Edman, 1983). It remains unclear how negative impulsivity affects the reward gained and social strategies during social decision-making.

To address these issues, we developed a modified form of the previously established rule-observance behavioral paradigm (Choe et al., 2017). With keeping the wireless-brain stimulation (WBS) as a rewarding system, we expanded the social conflict resolution test to test the effect of the hunger state on social conflict during rule-observance behavior. We tested the effect of the hunger state on mutual observance and mutual violation pairs. By calculating the observance percentage and violation percentage in each pair in normal and hunger states. We could monitor the influence of the hunger state on the behavior of mice during rule-observance behavior. Since social rule in rule-observance behavior is achieved by reward zone allocation, we tested the reward zone allocation in both normal and hunger state. Moreover, we checked the effect of the hunger state on reaction time response compared to the normal state. These spatial and temporal investigations were performed to understand the way through which the internal state (hunger) affects the behavior of mice during rule-observance behavior.

Results

Classical operant conditioning using Wireless Brain Stimulation (WBS)

The classical operant associative conditioning in rodent behavior is based on forming the association between animal behavior and reward (positive reinforcement) or punishment (negative reinforcement) with specific cues based on the animal behavioral response (“A Genetically Defined Compartmentalized Striatal Direct Pathway for Negative Reinforcement”, 2020; Yoo et al., 2016). In order to test the hunger state on the rule-observance behavior in mice, we first trained a mouse to perform the correct tasks by associating the cue (Blue LED light) with the correct reward zone. We used WBS as a reward and loud noise as punishment (Choe et al., 2017). The experiment timeline is shown in Fig. 1A for surgery, classical conditioning, social conflict resolution, and food restriction. We performed surgery on 22 mice to implant the bipolar electrode. Then, we found that 10 out of 22 mice (45%) passed the learning threshold (see Materials and Methods for detail). We found that the conditioning performance of mice started at 0.5 successful trials and steadily increased throughout the conditioning days to reach the threshold value of 0.75 (Fig. 1C). We next examined the required time to finish the 20 trials on conditioning days. During the initial days, it was required to take the entire duration (40 minutes) to finish the conditioning (Fig. 1D). In the progress of conditioning, the time...
decreased until reached less than a quarter of the time (10 minutes) to finish the sessions (Fig. 1D). These results imply the well-conditioned mice required a short amount of time to finish the conditioning sessions (Fig. 1C, D). From the total of 4651 conditioning trials, the mice showed 63% successful trials and 37% failed trials. (Fig. 1E). Taken together, mice showed efficient learning during operant conditioning in the rule-observance (RO) behavior.

**Fig. 1**

![Diagram of conditioning process]

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**Caption-1**
A) The diagram shows the chamber design (start zone and two reward zones and conditioning protocol (Trial start, successful trial, and failed trial). B) The increase of successful trial ratios through the 20 sessions of conditioning. C) Showing the decrease of conditioning time while the increase trained mice performance. d) Pie chart shows the ratio between successful trials 63% (n=2926) and failed trials 37% (n=1725).

The effect of hunger on the behavior of mice during rule-observance behavior

Next, we performed a social conflict resolution test. After 20 days of conditioning, we paired two well-trained mice from 10 conditioning mice to form 5 pairs and started a social conflict resolution test (Fig. 2A). We distinguished the two mice during social conflict resolution by red or green light bulb attached to the headset(Fig. 2A). In each trial, only one of two reward zones was assigned for reward based on a light cue(blue LED light), the conflict was initiated between two mice to take the reward or disturb the reword of another mouse. If one mouse takes the reward and another mouse stays in the start zone or away from the reward zone, it will be an observance trial. If the mouse disturbs the reward of another mouse the reward session was terminated and called a violation trial (Fig. 2A). As an example, we provided one day of Pair 4 in the normal state to show the types of trials (observance and violation), the type of reward from zones (left or right), and the calculation of the observance and violation percentage(Fig. 2B). In this example, there were a total of 40 trials in one day, of which 25 trials were observance trials and the remaining 15 violation trials (Fig. 2B). Based on these data, we calculated the percentage of observance of each mouse in the social conflict test pair with the observance percentage of 65% for mouse left and 60% for mouse right, and with the violation percentage of 35% for mouse left and 40% for mouse right (Fig. 2C). To present the observance and violation performance of the pair, we calculated the percentages of observance and violation in the last three days (18th, 19th, and 20th days) of each mouse, we plotted the average observance and violation percentages of the mouse Left on the x-axis and the average observance and violation percentages of the mouse right on the y-axis (Fig. 2C,D). Based on these data, mice could resolve the conflict and could set up a social rule and observe it.

Next, we tested the effect of the hunger state on rule observance behavior. After 20 days of food restriction with the pair test, there was a shift in the observance and violation behavior of both mice in the pair (Fig. 2D). The was an increase in violation level, on the other hand, there was a decrease in observance level(Fig. 2E). We could analyze the behavior of all pairs in normal and hunger states like this example. After finishing the social conflict resolution test, we had 5 pairs, 4 pairs of mutual rule-observance pairs (observance vs. observance), and one pair of mutual rule-violation (violation vs. violation) which showed in black dots in the upper right and lower left squares respectively (Fig. 2F). Consequently, we measure the observance percentage in the same 5 pairs in the hunger state. We found that two pairs become mutual violations, 2 pairs of violation-observance, and one pair of mutual observance(Fig. 2G). Despite these results, the data uncovers that most pairs even mutual violation, showed a decrease in observance percentage (Fig. 2H). In addition to that, we calculated the violation percentage in normal and hunger states. We found that, low violation percentage in the normal state and an increase in violation in the hunger state (Fig. 2I, J, K). That implies the hunger state could disturb the established rule observance behavior.

To sum up, we calculated the change in observance percentage in each quarter in normal and hunger states which represent 5 days of each quarter. The observance percentage increased during the normal state but strikingly dropped during the food restriction state (Fig. 2L). For differentiation between the acute and chronic effects on rule observance behavior, Our results showed a significant drop in observance percentage from the first day and the level continued to be low during the 20 days of the pair test during the hunger state (Fig. 2L). That indicates that both acute and chronic manipulation of the internal state affects social decision-making. There was a significant difference in observance percentage between the normals state and food restriction state (* P-value 0.0168 paired t-test) (Fig. 2M-left side) and there is a significant difference
between the normal state and food restriction state in the amount of reward and payoff equity (*P-value 0.0258 paired t-test) (Fig. 2M). The percentage of observance trails dropped from 71% in the normal state to 64% in the food restriction state (Fig. 2N). Finally, the hunger state had a bad effect on the well-established social rule and the acquired reward and payoff equity.

Fig. 2

A) The social conflict resolution (pair test) diagram in observance trial and violation trial. At the bottom,
are the photos of two distinct headsets (head and green). B) One-day example demonstrates the observation and violation trials and reward zone (left and right). This one-day pair example is observance (60% & 65%) percentage and violence with (40% and 35%) percentage. C) The pair with observance (60.9 & 66.3) and violation (39.1% & 33.7&) in normal state. D) The same repair in hunger state where an increase in violations (55% & 54%) and a decrease in observance (45% and 46%). E) State transition between normal and hunger state where an increase in violation and decrease in observance. F) Rule-observance percentage in a normal state for 5 pairs. G) Observance percentage for the 5 pairs in the food restriction state. H) The state transition of observance percentage between the normal state and food restriction state. I, J) Rule-violation percentage in a normal state for 5 pairs in normal and hunger state. K) The state transition of violation percentage between normal and food restriction state. L) The quarter figure shows the average observance percentage of mice for 5 days in both normal and hunger state. M) The significant difference in observance percentage between normal and food restriction states. Statistically, analysis was performed using a two-tailed pair test t-test of observance; 0.0168 *p < 0.05. and the right side is payoff equity or the amount of reward between normal and food restriction state. two-tailed paired t-test of the amount of reward: 0.0258 *p - p-value summary <0.05). N) Ratio of observance and violation in social conflict resolution test in normal state and hunger state.

The temporal and spatial effect on the behavior of mice during RO behavior in a food restriction state.

Choe et al. showed that, the mechanism through which the mice could resolve the conflict due to the limited resources by splitting the two reward zones by reward zone allocation strategy. Here, we investigated if the mice perform the same strategy (reward zone allocation) and we found that the mice could develop the reward zone allocation in a normal state in most of the mice (Fig. 3A, normal state). At the beginning of the pair test, the degree of occupation rate was low, while the development of the behavior could reach almost maximum occupation rate in the specified reward zone for both zones left and zone right (Fig. 3C, D). To test, if the mice forgot or disturb the strategy for rule-observance behavior during a food restriction state. We tested the reward zone allocation in hunger mice. We found the mice kept consistently with the already allocated reward zone (Fig. 3A, Food state). There was no significant difference between normal and food restriction states in reward zone allocation (Fig. 3B). For further investigation about the underlying pathway for shifting the observance behavior in mice during food restriction states. We calculated the reaction time in both states (normal and food-restriction states). After analysis of the reaction time in pair test trials, there was a significant difference in reaction time between the normal group and the food restriction group (Fig. 3F). The food restriction group showed a faster reaction time response than the normal group (Non-parametric: Mann-Whitney test ****, P < 0.0001). Taken together, these data showed the temporal variation not spatial variation in the behavior of mice between normal and hunger states.
Caption-3

A) Reward zone allocation in zone left and right in normal and food restriction state. B) Zone allocation diagram shows no significance in normal and food restriction states. C) Diagram shows the calculation of reaction time. D) Reaction time in normal and hunger state. (Mann-Whitney test: ****P value < 0.0001).
Discussion

Our study demonstrates for the first time that the scarcity of resources can disrupt the social contract between animals. We found that the internal state significantly reduced the well-established social agreement between mice. We used a previously established rule-observance behavior test (Choe et al., 2017) as a social decision-making behavioral paradigm to study the effect of the internal state (hunger state). The advantages of this behavioral paradigm are that we can study decision making, multi-agent reinforcement learning, social behavior, game theory, and control theory from mice. The social interactions consist of spatial and temporal components (Carstensen et al., 1999; Hoppler et al., 2022). As previously demonstrated, the spatial conflict resolution by reward zone allocation strategy leads to each mouse gaining most of its reward from one of two reward zones (left or right) without the disturbance of the other mouse (Choe et al., 2017). In this study, we found the internal state affects rule observance behavior without changing reward zone allocation, indicating no change in spatial memory. In contrast, we found temporal parameter (reaction time) in rule-observance was decreased by the hunger state (Fig. 3F). This could be due to the fact that the mice collect much less information through sensory cues and make a hasty decision (Heitz & Schall, 2012). Taken together, a hunger state affects the behavior of mice during the rule observance behavior by decreasing the reaction time.

The hunger state induces changes in neurotransmitters and neuromodulators that affect aggression

It has been well established that hunger and fasting increase the level of aggression in animal species (Fokidis et al., 2013; Janson CH, 2006). Hunger is regarded as a catalyst for aggression (Rohles & Wilson, 1974). The hunger state provokes a release of the hunger hormone, ghrelin, from the stomach, which passes the blood-brain barrier. Therefore, although we did not directly measure, it is possible that an elevated level of ghrelin could be present in the brain and affect the behavior during our rule observance behavior. It has also been reported that an increase of ghrelin hormones by central infusion is sufficient to increase inter-male aggression in mice (Vestlund et al., 2019), suggesting that hunger-induced ghrelin could have an important role in hunger-induced aggression. Indeed, this raises an interesting possibility that the ghrelin-induced aggression during our rule observance behavior could provide mechanistic insight. Future investigation is needed to test this exciting possibility.

In addition to hunger-related hormones like ghrelin, many neurohormones are affected by the hunger state. For instance, Serotonin is also affected by food restriction. It has been previously demonstrated that the hypothalamic and cortical serotonin is significantly decreased by food restriction (Haidar & Haleem, 2000; Haleem & Haidar, 1996; van & Miczek, 2000). In addition, the decrease in central serotonin level has been shown to be correlated with the increase in the level of aggression (Coccaro, 1989). Furthermore, suppression of serotonergic neuronal firing increases the level of aggression in mice (Audero et al., 2013). In contrast, a decrease in serotonin levels by depleting its precursor tryptophan has been shown to increase aggression due to the inability of the prefrontal cortex to control emotional response to anger (Passamonti et al., 2012). It is possible that the level of serotonin might have been decreased during our rule observance behavior and subsequently increased aggression and caused a disruption of proper decision making by reducing the reaction time. Future work is needed to determine the level of serotonin during the rule observance behavior.

Interestingly, we did not observe any physical aggression between mice during the sessions of rule observance behavior. This discrepancy could be due to our use of WBS as a rewarding system, but not physical rewards like food or sugar pellets. It is possible that the absence of physical rewards might have prevented the induction of physical aggression. Aggression can manifest in many different forms other than in forms of physical aggression. In our rule observance behavior, aggression was manifested in the form of
violating well-established rules or disturbing other mouse’s rewards. Such silent aggressive behavior can be considered “passive aggression,” which is a type of concealed aggression. Our study describes for the first time a behavioral paradigm that can assess a novel form of passive aggression in mice.

The controversy over the role of the hunger state in social decision-making

There has been a controversy over whether the hunger state affects decision-making and social interaction or not. On one hand, it has been claimed that the hunger state decreases social interactions with a male or female intruder (Burnett et al., 2019; Burnett et al., 2016). On the other hand, it has been reported that hunger does not impede prosociality during social decision-making (“Acute hunger does not always undermine prosociality - Nature Communications”, 2019). Moreover, the hunger state has been shown to have no effect on economic behavior (Elbæk et al., 2022). To make the matter more complex, it has been also reported that the effect of the hunger state on social behavior depends on the type of hunger: acute or chronic hunger (“Acute hunger does not always undermine prosociality - Nature Communications”, 2019). Our study is consistent with those reporting the hunger state affects decision-making and social interaction. Our results clearly demonstrate that the hunger state has a detrimental effect on social decision-making (Fig.2m). Moreover, our results clearly demonstrate that both acute and hunger states affect decision-making and social interaction (Fig.2l). Taken together, our study provides the compelling lines of evidence to strengthen the idea that the hunger state affects social interaction and decision-making.

Limitations of our study

In our behavioral model, we used a lightweight, well-established headset with WBS to stimulate the medial forebrain bundle after IR signal transmission of the headset in freely behaving mice. Our system shows an advantage over head-fixed mice or wired-connected mice, which suffer from limited movement. In addition, it allowed social interaction without confounding factors of physical fight or injury such as in the case of providing food rewards (Choe et al., 2017). Contrary to these advantages, one of the limitations of our system is that we are limited to only two mice for the rule observance behavior. This limitation was due to the technical issue of mouse detection by the software, which was designed for only two mice. It will be of great interest to investigate the social conflict and rule-observance behavior with more than two mice in the future.

In conclusion, we have demonstrated for the first time that the internal state as a hunger state has a detrimental effect on social decision-making in rule observance behavior. Much of the research done in the past has been focused on the effect of external stimuli and sensory input on social decision-making (Waskom & Kiani, 2018; Luczak et al., 2013). Little has been known about the effect of the internal state on social decision-making and animal behavior. We have demonstrated that the hunger state can disturb the social contract by making a fast and hasty social decision. The novel concepts and tools that have developed in this study should prove useful in delineating the detailed molecular and cellular and circuit mechanisms of social decision-making in the future.

Materials and Methods

Animal and surgery

All mice used during this study are male B6SPR/6J. Before stereotaxic surgery, mice kept in cages contained five mice in a 12:12 light/dark cycle with food and water accessible ad libitum. All animal studies
and experimental procedures were approved by the Animal Care and Use Committee of the Institute for Basic Science, Daejeon, Korea.

At week 8, a stereotaxic bipolar electrode (MS303T/2-B/SPC, Plastics One, Roanoke, Virginia) implantation surgery was performed in the right medial forebrain bundle. (-1.2; +1.2; -5.0 in millimeters from the bregma). The mice were anesthetized by ketamine (120 mg/kg) injected intraperitoneally. After that, the mouse was fixed in a Kopf stereotaxic set. The skull was exposed and adjusted where bregma and lambda were on the same horizontal line. The drill was used for making holes in the mouse skull for fixation screws and bipolar electrodes which were inserted vertically. Finally, the bipolar electrode was fixed using acrylic resin dental cement. After the electrode implantation, each pair of mice was housed together in one cage- during the conditioning and social conflict test- separated by a transparent partition. The location of the electrode was confirmed after sacrifice. After bipolar implementation, the mice were left for one week for recovery before conditioning.

Rewarding system

During rule-observance behavior, we used Wireless Brain stimulation as a rewarding system as used previously (Choe et al., 2017). The WBS headset was small (1.5 x 1.5 cm) and lightweight (1.2 g), and generated an electrical current when it sensed an infrared signal from the external controller. The WBS headset was connected to a bipolar electrode that was implanted into a part of the reward circuitry in the brain, the medial forebrain bundle (reward circuit). When the mouse enters the rewarding (payoff) zone the automatic IR signal is emitted from the transmitter above the reward zone to stimulate the headset receiver to produce an electrical current to stimulate the reward circuit.

Rule-Observance behavior

Conditioning

The conditioning and social conflict resolution chamber is a two-armed maze. It consists of a start zone, two rewards (payoff) zones where the mice receive WBS when entering these zones, two blue LED lights near to reward zones, speakers, and a camera for mice detection. This hardware is connected to custom-made software to detect the mice automatically based on the color of the bulb in the headset (red or green). The two arms of reward zones are separated by other parts of the chamber by transparent partitions.

In the conditioning phase, the training is done by only one mouse and the trial starts by entering the mouse into the start zone one of two blue lights (right or left blue light - cue) turns on indicating the right choice of reward zones (left or right reward zone). If the mouse entered the correct reward zone the positive reinforcement reward was delivered to the mouse by 5s of WBS IR reward signal and regarded as a successful trial. Otherwise, the punishment of negative reinforcement was delivered as loud noise through the speaker and regarded as a failed trial. After the mouse received the reward or the punishment the trial was terminated automatically and the system returned to its normal state.

The conditioning phase lasts for 20 days. Each day consists of 20 trials or 40 minutes each finished first. The mice were considered conditioned if they performed 100% of trials in the last three days (60 trials) and the number of successful trials during that period was more than 45 trials (binomial test: 20 trials - the probability of trial = 0.5 - P < 0.001).
Social conflict resolution test

In the social conflict resolution state, the behavior of the pair test was done by combining two well-conditioned mice from the conditioning phase. The social conflict resolution test consists of 40 trials or 20 minutes (which finished first). The pair test lasts for 20 days. The trails are initiated when both mice enter the start zone and one of the two blue LED lights turns on. The type of trials (observance or violation) is decided based on two scenarios. First, if only one mouse goes to receive the reward in front of the correct arm without the disturbance from the other mouse, we regard this trial as an observance trial. On the other hand, if the other mouse disturbs the 5s rewarding period the rewarding signal is terminated automatically and is regarded as (a violence trial). No negative reinforcement loud noise in pair test. This procedure is done automatically depending on the different headsets’ colors (red and green) with an automatic object detection system and camera. Based on the behavior of mice we could calculate the degree of rule observance by:

\[
\text{Degree of Rule Observance (MouseL)} = \frac{\text{No. of successful trials by MouseR}}{\text{Total trial number for the right cue}}
\]

and

\[
\text{Degree of Rule Observance (MouseR)} = \frac{\text{No. of successful trials by MouseL}}{\text{Total trial number for the left cue}}
\]

Food restriction protocol:

After social conflict resolution tests and before food restriction, we aimed to reach 80% of the mice’s initial body weight. To achieve this goal, restricting the food provided to mice by 30% of their daily needs is done during food restriction social behavior. The food provided after the test is to be consumed the day before the behavior test. That allowed the mice to be hungry during social tests. The mice’s body weight was monitored every day after the behavior test (Table--). The mice have free access to water. Moreover, In our research, we defined the reaction time that is the time from the initiation of the trial (two mice enter the start zone and the blue light turns on) to the entering the reward zone (IR signal turns on).

Statistical analysis

The significance level is represented as asterisks (*) p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001; n.s., not significant). Outliers were excluded by Grubb’s test or ROUT method. GraphPad Prism 9.3.1 for Windows (GraphPad Software, USA) was used for these analyses and to create the plots.

Acknowledgment

We thank the staff of the animal facility team at the Institute of Basic Science (IBS) due to the continuous and generous supply and care of mice throughout our experiment.

Supplementary materials

Conditioning (training) data
### Table 1: The conditioning (training) data for the 10 mice during the 20 days of conditioning

Mice body weight during Food restriction

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Note: The table above represents the conditioning (training) data for the 10 mice during the 20 days of conditioning. Mice body weight during Food restriction is shown in the table.
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Table 2: The body weight of mice during social conflict resolution test during food restriction state
Figure 2: The Supplementary Fig.1: The paired t-test analysis for observance percentage and payoff equity (amount of reward) between the normal state and food restriction state. a) Here, we show the paired t-test in observance percentage between the normal state and food restriction state. b) Paired t-test in the normal and food restriction state in the amount of reward acquired.

References


Hunger or thirst state uncertainty is resolved by outcome evaluation in medial prefrontal cortex to guide decision-making. (2021). Nature Neuroscience, 24(7), 907–912. https://doi.org/10.1038/s41593-021-00850-4


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