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# Social learning about rewards – how information from others helps to adapt to changing environment

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# 1a. Streszczenie

Dla wielu gatunków zwierząt bycie częścią struktury społecznej jest kluczem do przetrwania i reprodukcji. Funkcjonowanie w obrębie grupy pozwala na wydajniejsze korzystanie z zasobów środowiska naturalnego i szybsze reagowanie na potencjalne zagrożenia. Relacje pomiędzy osobnikami tworzącymi grupę wykształcają się w wyniku szeregu zachowań społecznych, takich jak ustalanie hierarchii czy nawiązywanie więzi. Uczenie społeczne, czyli zdolność do pozyskiwania informacji na podstawie zachowania innych osobników, jest jednym z najistotniejszych elementów społecznego repertuaru behawioralnego ssaków.

W niniejszej rozprawie opisano opracowanie protokołów eksperymentalnych do oceny uczenia społecznego w grupach myszy testowanych w warunkach zbliżonych do naturalnych. W tym celu wykorzystano system Eco-HAB, odzwierciedlający najważniejsze cechy naturalnego środowiska myszy. System ten pozwala na w pełni zautomatyzowaną ocenę zachowań społecznych. Opracowane protokoły posłużyły następnie do badania, w jaki sposób informacja o położeniu nagród w środowisku rozprzestrzenia się pomiędzy osobnikami stada i jak relacje społeczne w grupie, w tym sieć społeczna, wpływają na reakcję na informację o obecności nagrody w środowisku. Odkryto, że myszy posiadają zdolność efektywnego uczenia się o nagrodach znalezionych w środowisku przez inne znane osobniki na podstawie pozostawionych przez nie śladów zapachowych, bez konieczności bezpośredniego kontaktu z członkami stada. Ponadto, odkryto, że efektywność społecznego uczenia się jest zależna od pozycji w hierarchii społecznej. Mianowicie, osobniki stanowiące centra sieci społecznych, wykazują najbardziej intensywną reakcję na bodźce społeczne związane z nagrodą. Co więcej, opracowano także pionierski sposób badania powyższych parametrów w nowym, zasiedlonym wcześniej jedynie przez myszy “zwiadowców”, habitacie (międzyśrodowiskowy transfer informacji społecznej).

Stworzenie wyżej opisanych protokołów eksperymentalnych pozwoliło następnie na przeprowadzenie badań nad neuronalnymi mechanizmami społecznego uczenia się. Ponadto, w niniejszej rozprawie opisano badania nad znaczeniem plastyczności neuronalnej w części grzbietowej kory przedczołowej dla zdolności społecznego uczenia się od członków stada. W tym celu zastosowano specjalnie zaprojektowane nanocząsteczki zawierające TIMP1 (ang. Tissue Inhibitor of Metalloproteinases 1) - inhibitor kluczowego dla procesu plastyczności synaptycznej enzymu MMP9 (ang. Matrix Metallopeptidase 9). Enzym MMP9

w mózgu jest zaangażowany w tworzenie połączeń nerwowych poprzez regulację dojrzewania struktur zwanych kolcami dendrytycznymi. Ponadto liczne badania pokazują, że na poziomie behawioralnym manipulacja aktywnością enzymu MMP9 wpływa na proces uczenia się i utrwalania informacji. Wykorzystane w badaniach nanocząsteczki po wstrzyknięciu do mózgu są w stanie stopniowo uwalniać swoją zawartość, co umożliwiło długotrwałą manipulację plastycznością neuronalną, a co za tym idzie obserwację efektów behawioralnych na przestrzeni wielu dni.

W toku badań wykazano, że zdolność myszy do wzajemnego przekazywania informacji i uczenia się położenia potencjalnej nagrody na podstawie pozostawionych śladów zapachowych zależna jest od niezaburzonej aktywności enzymu MMP9 w części grzbietowej kory przedczołowej. Odkryto, że obniżenie poziomu aktywności enzymu MMP9 za pomocą jego inhibitora TIMP1 obniża motywację do poszukiwania nagrody w odpowiedzi na społecznie przekazywaną informację o niej. Co więcej, wykazano, że opisana manipulacja plastycznością neuronalną zaburza zdolność zwierząt do międzyśrodowiskowego transferu informacji społecznej. Skutkuje ona także znaczącą przebudową sieci społecznych, a co za tym idzie interakcji społecznych wewnątrz grupy.

Opracowane w niniejszej pracy wyniki badań stanowią istotny wkład w rozwój wiedzy na temat społecznego uczenia się oraz leżących u jego podłoża mechanizmów neuronalnych. Ponadto opracowanie nowych protokołów eksperymentalnych oraz metod pomiarowych przyczyniło się do rozwinięcia wszechstronności narzędzia, jakim jest opracowany w Instytucie Nenckiego PAN system Eco-HAB.

# 1b. Abstract

For many animal species, being part of a social structure is key to survival and reproduction. Functioning within a group allows for more efficient use of environmental resources and faster response to potential threats. Relationships between individuals that make up a group develop through a series of social behaviors, such as establishing hierarchies and forming bonds. Social learning, or the ability to gain information from the behavior of other individuals, is one of the most essential elements of the social behavioral repertoire of mammals.

The presented dissertation describes the development of experimental protocols for evaluating social learning in groups of mice tested under semi-natural conditions. For this purpose, the Eco-HAB system was used. The Eco-HAB reflects the most important features of the mice's natural environment, while allowing fully automated evaluation of social behavior. The developed protocols were then used to study how information about the location of rewards in the environment spreads among individuals in the group, and how social relationships in the group, including the social network, affects responses to social information about food. It was discovered that mice have the ability to effectively learn about rewards found in the environment by other familiar individuals based on the scent traces the conspecifics leave behind, without the need for direct contact with group members. In addition, it was discovered that the effectiveness of social learning depends on the social hierarchy and structure of the social network. Namely, individuals that are the centers of the network, show the most intense response to social stimuli associated with reward. What is more, a pioneering way to study the above-described parameters in a new habitat (inter-environmental transfer of social information) previously populated only by "scout" mice was also developed.

The creation of the aforementioned experimental protocols made it possible to conduct research on the neural mechanisms of social learning. The second part of this dissertation describes studies on the importance of neuronal plasticity in the prelimbic part of the prefrontal cortex for the ability to learn socially from group members. For this purpose, specially designed nanoparticles containing TIMP1 (Tissue Inhibitor of Metalloproteinases 1), an inhibitor of the enzyme MMP9 (Matrix Metallopeptidase 9) which is key for synaptic plasticity, were used. MMP9 in the brain is involved in the formation of neural connections by regulating the maturation of dendritic spines. In addition, numerous studies show that,

at the behavioral level, manipulation of MMP9 activity affects learning and memory consolidation. The nanoparticles used in this study, when injected into the brain, gradually release their contents, which made it possible to manipulate neuronal plasticity over a long period of time, and thus observe behavioral effects over many days.

Over the course of the study, it was shown that the ability of mice to transmit information and learn the location of a potential reward based on the odor traces left in the environment depends on the undisturbed activity of MMP9 protein in the prelimbic part of the prefrontal cortex. It was discovered that reducing the level of MMP9 protein activity with its inhibitor TIMP1 decreases reward-seeking motivation in response to socially transmitted reward information. Moreover, the described manipulation of neuronal plasticity has been shown to interfere with the animals' ability to use social information in novel environments. It also resulted in significant remodeling of the social networks and, consequently, the in-group social interactions.

The findings of the presented study are a significant contribution to the development of knowledge about social learning and the underlying neuronal mechanisms. In particular, the development of new experimental protocols contributes to the versatility of the Eco-HAB, the automated system for tracking social behavior developed at the Nencki Institute.

# 2. List of abbreviations

ADAM - a disintegrin and metalloproteinase

ADHD - attention deficit hyperactivity disorder

AI - artificial intelligence

BSA - bovine serum albumin

CTRL - control

IL – infralimbic part of the prefrontal cortex

LTP – long term potentiation

MMP - matrix metalloproteinases

mPFC – medial part of the prefrontal cortex

NCAM - neural cell adhesion molecule

NP – nanoparticles

PFC – prefrontal cortex

PL – prelimbic part of the prefrontal cortex

PLGA - poly(DL-lactide-co-glycolide

REW – reward

RFID - radio frequency identification

TIMP - tissue inhibitors of metalloproteinases

US – unconditioned stimulus

vmPFC - ventromedial part of prefrontal cortex

# 3. Introduction

## 3.1 Importance of sociability for evolutionary fitness

Empathy is most commonly defined as the ability to understand and share emotional states of another individual (Hall and Schwartz, 2019). It has been extensively studied in animals (Pérez-Manrique and Gomila, 2022; Sivaselvachandran et al., 2018; Young et al., 2018). One of the most influential models of empathy is a Russian doll model proposed by Preston and De Waal (Preston and Waal, 2002). The model assumes three dimensions of empathetic responses. The most basic, and at the same time core reaction related to empathy, is emotional contagion, the ability to share others' emotional states and imitate their behavior (Dugatkin and Driscoll, 2021). In fact, the ability to mimic responses of another individual is crucially important for social learning (Anderson and Kinnally, 2021; Keysers, 2022). Moreover, mimicry is a foundation for more complex reactions and responses. The next level of complexity is the empathic concern (or affective empathy), defined as the ability to understand others' emotions (Zahn-Waxler and Radke-Yarrow, 1990). The last and most advanced aspect in this empathy model is the ability to take perspective of another individual and thus understand what their emotional state is. In other words, the representation of emotions can be evoked by the perception of the others' emotional state, which gives an individual insight and leads to understanding what it might be like to experience what they feel (de Waal and Preston, 2017).

Empathy is one of the key mechanisms enabling animals to obtain information about changes in their environment based on the social contacts. Being able to avoid the potential dangers and use the opportunities offered by the environment is critical for survival (Alberts, 2019). Information encoded in behavior of another individual can be useful for understanding readiness for reproduction and social status of other animals (Hafez and Hafez, 2000). In addition to providing information about social interaction partner, reading emotional states of others can also provide information about the threats or rewards without the need for first-hand experience, which allows reducing risk and energy expenditure related to direct exploration (Danchin et al., 2004; Puścian et al., 2022a). Thus, living in social groups not only reduces the probability of being a victim of a predatory attack but also herd usually defends their members if they are in danger (Foster and Treherne, 1981) and helps to learn about the resources in the environment. Many-eyes hypothesis points out that one benefits from being

a part of a group by optimization of the proportion of time spent on looking for potential predators or other dangers, to the time spent on foraging (Olsson et al., 2015). Furthermore, in line with the Emergence theory, organization of individuals into groups creates new opportunities impossible to access by the individuals who live alone, such as better adaptation to ecological niches or more efficient management of environmental resources (Cazzolla Gatti et al., 2018).

## 3.2 Increasing complexity of social behavior – from single-cell organisms to mammals

Examples of social behavior can be widely observed across the whole Animalia kingdom. Interestingly, a rich palette of social behavior, including actions as advanced as cooperation in foraging, aggregation, and communicating, is also found in recent studies on microorganisms. Bacteria are able to aggregate and cooperate to build complex structures called biofilms (O'Toole et al., 2000); microbes from different areas of the biofilm show different specializations and related gene expression (Costerton, 1995). Such structures provide better-stabilized environments, help in nutrient accumulation and provide protection from antibiotics, toxins or physical damage (Decho, 1994). Myxobacteria are another example of microorganisms that exhibit social aspects of behavior. In response to starvation or inconvenient environmental conditions they communicate chemically and send signals to initiate aggregation into novel structure. This reorganization increases feeding efficiency thanks to improved enzyme aggregation and nutrient distribution (Muñoz-Dorado and Arias, 1995). Additionally, self-organization into the groups decreases the risk related to the hostile environment and increases the reliability of moving to safe areas (Ozkan-Aydin and Goldman, 2021).

The member of Annelida phylum, California blackworm, organizes with conspecifics into the blob-shaped structure to survive in cold areas that would be very hard or even impossible to inhabit by the individual worms (Ozkan-Aydin et al., 2021). Importantly, individual worms were faster in reaching the borders of the cold foraging destination in the experimental apparatus but most of them failed and did not get there at all.

Further, social behavior is well-documented in insects (Brian, 2012; Wheeler, 2016), especially when it comes to its role in kin selection and mutualism (Lin and Michener, 1972). Most studies in the area are based on ants, bees and termites (Leonhardt et al., 2016). Ants

are known for the division of labor, observed even in very small groups (Ravary et al., 2007). Specialization in performed tasks improves the nest homeostasis and increases evolutionary fitness, these positive effects scale up with increasing group size and seem to be crucial especially in the early stage of the nest development (Ulrich et al., 2018).

Even animals who belong to solitary species may benefit from social contact. Drosophila melanogaster is a great example of a solitary insect that profits from cooperation with conspecifics. It was shown that flies find favorable feeding areas quicker when they forage collectively, rather than on their own (Lihoreau et al., 2018). Moreover, reaction to aversive stimuli is also faster when flies are in a group which may have serious implications for the ability to avoid dangers (Wasserman and Frye, 2015).

Even more clearly, social behavior plays beneficial role in more evolutionary advanced animals. Fish use chemical signaling to organize themselves into the groups called shoals. They synchronize their individual behavior which makes shoals very organized and effective in avoiding predators (Miller and Gerlai, 2012). Minnows spread the information about danger (e.g. the predator) via chemical signaling which affects behavior of the whole group and increases its chance for survival (Magurran and Higham, 1988). Organization into the shoal does not only help to avoid dangers but also leads to the more effective finding of food and foraging, equally important from the evolutionary perspective (Pitcher et al., 1982).

Reptiles are not common models to study social behavior, since they are considered non-social animals, displaying little to no parental care and poor communication (Bull et al., 2017). In contrast to that opinion, observations and experiments showed that reptiles display clear evidence for social behavior. Turtle embryos detect vibrations of the siblings as a social information for earlier hatching upon dangerous environmental conditions (i.e., flood), which increases their chance to survive (Doody et al., 2013). Moreover, lizards from the Egernia genus form large groups and perform behaviors such as kin recognition, parental care, and cooperation against predators or for building long-term social relationships (Doody et al., 2013).

Contrary to studies in reptiles, studying social behavior in birds has a long and well-documented tradition (Collias, 1952; Schjelderup-Ebbe, 1935). Studies show that birds use social behavior to communicate (Todt and Naguib, 2000), defend territories (Brown, 1969), attract each other (Butcher and Rohwer, 1989), and even form basic culture (Aplin, 2019). Benefits from cooperation and group living are especially clear in migratory birds such as swans or pelicans (Badzinski, 2005; Brereton et al., 2021). Long-distance flights require complex logistics and cost a lot of energy. Thanks to communication skills birds are able

to save energy by flying in a “V” formation (Weimerskirch et al., 2001). Moreover, birds usually form characteristic flock-like group structures. Flocking behavior reduces the time of reaction to potential dangers and is a great anti-predator ability (Goldman, 1980). Markedly, for some birds interactions with conspecifics are considered to be rewarding, while social isolation has negative physiological and behavioral effects (Riters et al., 2019).

Mammals are a class of animals considered highly suitable for experimentation on social behavior and social learning. They have been documented to possess a wide range of social abilities, most remarkably, they are able to create groups and societies with complex networks of relationships. Moreover, their brains have specialized neuronal networks that support development of social behavior (Clutton-Brock, 2009; Isler and Van Schaik, 2009; Ricklefs, 2010; Silk, 2007). Further, mammals are known to express parental care; for the purpose of reproduction even solitary mammals show sociability, usually prolonged to a period of parental care and oftentimes even exceeding that period (Clutton-Brock, 2016). Notably, it was shown that social impact of the group increases survival and health conditions of the offspring (Silk, 2007).

## 3.3 Laboratory rodents as a suitable model of mammalian sociability

Rodents, due to their common use in laboratory experiments, are one of the most examined animals in the context of social behavior. They are able to show a wide range of social behaviors, including play, territorial behavior, social dominance, sexual behaviors and parental care (Provenzano et al., 2017; Puścian et al., 2022a; Wirth et al., 2021). The simplest approach for modeling social behavior in rodents under laboratory conditions is the observation of the dyadic social interactions or interactions with so called “social objects” (Brodkin, 2007; Kas et al., 2014). However, current discussion in the field points to the fact, that a simple interaction between two animals may not be enough to observe full complexity of social behavior (Hofmann et al., 2014; Kondrakiewicz et al., 2019a; Peters et al., 2015; Puścian et al., 2022a; Puścian and Knapska, 2022). Thus, novel approaches to studying social behavior in rodents, especially in mice focus on social groups (da Costa Araújo and Malafaia, 2021; Jedrzejewska-Szmek et al., 2019; Kurvers et al., 2014; Peleh et al., 2019; Puścian et al., 2016; Puścian and Knapska, 2022; Winiarski et al., 2022, 2021). Both wild and laboratory mice in semi-natural environments form complex social structures with dominance hierarchies, individual social strategies, and territorial behavior (Gray et al., 2002; Mackintosh, 1970; Mondragón et al., 1987).

Notably, social dominance is a well-studied aspect of social behavior that can be observed in all mammals (Kumaran et al., 2012; Noonan et al., 2014). In mice dominance can be tested in a number of ways. The most common ones are tests of direct physical aggressive encounters (e.g., resident-intruder test) and competition for resources (e.g., warm spot test, Zhou et al., 2018). The latter is often considered the most ecologically-valid approach that at the same time can be effectively applied under laboratory conditions (Fulenwider et al., 2022; Márquez et al., 2013).

One of the main characteristics of mammalian social behavior is parental care for the offspring. Mice dams protect and feed newborns (Orso et al., 2019). Furthermore, disturbances in maternal behavior and social isolation at the early stage of life can cause social deficits and depression-like behaviors in mice (Lavenda-Grosberg et al., 2022; Panksepp et al., 1991).. Socially isolated rats have altered number of dopamine and serotonin receptors in the prefrontal cortex and show abnormal behavioral responses to novelty (Lapiz et al., 2003). Deficits of social interactions are also related to social stress. Specifically, reduction of social contact in rats leads to adrenal gland hypertrophy, depressive-like behaviors, and affects the expression of neural cell adhesion molecule (NCAM) protein expressed during neuronal differentiation in development (Djordjevic et al., 2012). Interestingly, quality of paternal care may also affect the proper development of offspring. Experiments on degus showed that absence of paternal care leads to imbalance in excitatory-inhibitory synapses equilibrium in the cingulate cortex (Ovtscharoff et al., 2006).

Further, mice are able to share emotional state of another conspecific and some researchers argue they are able to display altruism (Mogil, 2019; Shin, 2022). For example, exposure to a stressed conspecific triggers stress response in the non-treated observers (Meyza et al., 2015; Meyza and Knapska, 2018). On the other hand, the presence of a cage mate reduces the effects of fear conditioning, which is called “social buffering” (Kiyokawa and Hennessy, 2018). That ability to share emotional state is the base for more complex empathy-related behaviors. Rats have been shown to cooperate and adjust the helping strategy depending on the actual needs (Schweinfurth and Taborsky, 2018). Furthermore, rodents are also able to share positive emotions (Olszyński et al., 2020). Interestingly, it was shown that appetitive emotional state can suppress the aversive emotional state in the laboratory rats (Silkstone and Brudzynski, 2019).

Researchers argue that well-developed repertoire of sociability and its similarities to human behavior make laboratory mice a suitable model for psychiatric disorders (Zhang et al., 2022) and empathy (Park et al., 2022). Additionally, the variety of available transgenic

strains and experimental approaches (see the following chapters) allowing to effectively address questions regarding human disorders of social behavior (Netser et al., 2020; Sgritta et al., 2019) put laboratory mice in the center of the presented research. Moreover, many tools and protocols based on genetic manipulation were developed and successfully used in laboratory mice in social tasks (Kondrakiewicz et al., 2019b, 2019a; Winiarski et al., 2022). Finally, mice can be effectively used for modeling complex group behavior such as formation of social networks (Puścian and Knapska, 2022, Winiarski et al. in prep.). In the presented work we show mice of C57BL/6j strain, which is commonly used to create transgenic models (Kondrakiewicz et al., 2019a; Puścian et al., 2016; Winiarski et al., 2022).

## 3.4 Channels of social information

Social information can be encoded in many different ways and be received via many sensual modalities (Bonnie and Earley, 2007; Isler and Van Schaik, 2009; Moles et al., 2007; Zerda et al., 2020). Animals from Amphibia class use their vocal apparatus, chemical attractants and skin color to communicate. Hyla faber, also known as Blacksmith tree frog, manifests different types of vocalization to communicate distress, territory marking, and sexual attraction during mating (Martins and Haddad, 1988). It is noteworthy, that amphibians communicate being poisonous to the potential predators, by a characteristic dappled skin color, which is an example of between species social communication (Nilsson Sköld et al., 2013).

Social deterrent signals are observed also in mammals, for example when dogs are in stressful situations or enraged they raise their hackles, wrinkled nose and show teeth to look more dangerous (Blackshaw, 1991). Visual information is also crucial for the manifestation and recognition of the signals related to sexual behavior and domination. For example, penis and scrotum of vervet monkeys turn red and blue to contrast with the white fur to signal sexual maturity (Snyder-Mackler et al., 2020). Moreover, studies in humans showed that visual signals are critical for sexual attraction and stimulate reward system in the brain (Ponseti et al., 2006).

It is noteworthy, that sexual information is also transferred via other modalities, for example, deer use characteristic vocal signals during the rut (Mysterud, 2011). Vocalization is also oftentimes used to demonstrate dominance. African lions use roaring to express their status and to scare away potential rivals (Gray et al., 2017). Birds are well known for their singing which is a notable example of vocally-convoyed social information about territory

borders and sexual attractants (Mirin and Klinck, 2021). Vocalizations are also used by animals to inform each other about potential predators or dangerous situations. Meerkats developed different alarm calls communicating different threats (Hollén and Radford, 2009). Also, individual emotional state can be communicated via vocalization (Netser et al., 2022). Laboratory rats emit ultrasonic vocalizations of different frequencies when subjected to appetitive and aversive situations (Branchi et al., 2001; Silkstone and Brudzynski, 2019; Willadsen et al., 2014; Wöhr et al., 2011).

Observation of animals in their natural/quasi natural environment and under the laboratory conditions showed that the olfactory system plays a key role in receiving and processing socially driven information. Ants code their caste affiliation in a specific social odor (d'Ettorre et al., 2017). Fish use olfactory information for social recognition and attraction (Ward et al., 2020). Also, birds widely use olfactory cues to communicate with the conspecifics (Maraci et al., 2018). Olfactory social information can be transferred via cues left in the environment or via direct interaction with another animal (Debiec and Olsson, 2017; Sullivan et al., 2015). In rodents, social identity is encoded in urine or in skin and scent glands secretions (Sanchez-Andrade and Kendrick, 2009; Stopka et al., 2007).

In mice, which were employed in the herein presented experiments, the dominant sense used for social communication is olfaction. Mice show marked interest in olfactory social stimuli when tested under laboratory conditions and discriminate between familiar and unfamiliar ones (Crawley, 2004; Puścian et al., 2014). Interestingly, both laboratory and field experiments show that to absorb social information mice engage all senses, however, olfactory processing is the most important (Dulac and Wagner, 2006; Lin et al., 2005; Puścian et al., 2016). Social odors are used to communicate, mark territory, position oneself in social hierarchy, and as attractant during mating season (Stockley et al., 2013). When meeting novel conspecifics, mice intensely sniff their head and anogenital area (Shemesh et al., 2013). Notably, the time of sniffing of novel subjects is much longer than that of the familiar ones (Mesa-Gresa et al., 2013). Further, disturbance of the olfactory system impairs social recognition (Tobin et al., 2010). Rodent pups highly prefer odor of their mother (Wilson and Sullivan, 1994), however, this effect is observed also with surrogate mothers, which suggests that pups learn to associate social odor with another conspecific highly important for their survival (McLean and Harley, 2004).

Olfactory information is also important in mouse group communication and is oftentimes used to mediate social relationships (Matsuo et al., 2015). Also, information about the health state of an individual is encoded in olfactory cues. For example, mouse females

prefer parasite free males in mating season and make their decision based on olfactory examination of males' urine (Kavaliers et al., 2004). Moreover, social scents of a sick mouse can lead to the avoidance of some parts of the territory by other groupmates (Renault et al., 2008). Based on all the aforementioned studies, in the our work we used social scents as the source of pertinent information about the changing environment.

## 3.6 The key role of social learning in adaptation

In the previous chapters I described benefits from living in social groups, and discussed some examples of social behavior and communication across the phylogenetic tree. However, in the context of the presented work I will further focus on a specific subset of social behavior - social learning - and its critical role in adaptation. Contact with conspecifics plays a key role in adaptation to changing environments, helps with information finding and increases chances for survival and reproduction (Keller, 2009; Rodriguez Parkitna and Engblom, 2012).

The most widely accepted definition of social learning is the ability to receive and assimilate socially-conveyed information, encoded in either behavior of another individual or the cues it left in the environment (Reed et al., 2010). Both those indicators may contain important information about dangers, rewards and shifting environmental conditions (Duboscq et al., 2016). Social information can be used to avoid, or if impossible, to appropriately prepare for danger (McLachlan, 2019).

The most robust types of social cues that inform about the potential danger are fresh carcasses or wounded individuals (Dall et al., 2005). Interestingly, the behavioral response to the threat communicated via social channels developed very early in the evolutionary tree. For instance, wounded cnidarians produce an alarming hormone - other polyps exposed to that hormone take a defensive and safer stance (Howe, 1976). Similarly, damselflies reduce their activity when they detect injured conspecifics (Wisenden et al., 1997). Also bumble bees avoid spots for foraging with signs of freshly killed conspecifics (Abbott, 2006). Zebrafish produce and secrete alarm substances where they find freshly dead conspecific (Lima and Dill, 1990; Verheggen et al., 2010). In the laboratory experiments, guppies learn from harmed demonstrators where they need to hide to avoid an electric shock (Brown and Laland, 2003). Finally, data shows that collective monitoring and reaction to the behavior of nearest conspecifics increases the efficiency of avoiding predators (Pays et al., 2013).

## 3.7 Social learning about threats

Alarm cues from dead or wounded animals are a very robust type of information. However, many species are able to detect weaker social signals of disturbances (Bairos-Novak et al., 2017; Ferrari et al., 2010; Jordão and Volpato, 2000). The most common substance produced in response to danger is urine (Kiesecker et al., 1999). Observation of wood frogs shows that urine secretion level can be controlled and adjusted depending on the intensity of danger (Bairos-Novak et al., 2017). Production of such signals may be a more precise, and at the same time contextual alternative, to sharing social information via direct alarm signals. Still, production of danger or disturbance signals costs energy. Nevertheless, the ability of an animal to share and learn these signals can increase its chances for survival in the group (Hamilton, 1964).

The ability to exhibit emotional states and to share emotions of others are crucial factors in social learning (Krakenberg et al., 2020). Many social animals are able to adapt their behavior according to the recognized emotional state of other conspecifics (Andraka et al., 2021; Ferretti and Papaleo, 2019; Knapska et al., 2006a; Meyza et al., 2015). Interestingly, the effect of the socially evoked emotions can be observed a relatively long time after the emotional event has ended. Rats, for example, show anxiety-like behaviors even days after traumatic encounters with a predator (Adamec and Shallow, 1993). Animals are also able to evaluate the intensity of the other conspecific's manifested emotions. Andraka and colleagues (Andraka et al., 2021) showed that depending on the stress level of the demonstrator (animal subjected to the aversive experience), observer (animal obtaining socially conveyed information about what has happened to their conspecific) increases their exploration or freezes, depending on the intensity of the threat (remote vs. imminent) to which the demonstrator was subjected. Also interaction with a fearful conspecific improves subsequent learning of fear and avoidance in rats and mice (Knapska et al., 2010; Nowak et al., 2013). Moreover, animals are able to associate gained social information with environmental context, which is the key mechanism in social learning. For instance, mice can be conditioned to be afraid of the context by the observation of a shocked conspecific (Jeon and Shin, 2011). Similar observations were made not only in mammals, zebrafish are also able to associate neutral odor with a potential danger when odor was previously demonstrated together with a frightened conspecific (Oliveira et al., 2014). Ability to socially learn about dangerous factors found in many species from different branches of the phylogenetic tree strongly supports the notion that it may be useful for surviving and thriving of individuals.

## 3.8 Social learning about rewards

Information about the availability of rewards in the environment, such as areas plentiful with food or safe shelters, is as crucial for survival as is being aware of the potential threats, however, mechanisms of reward learning are much less understood than those of aversive learning, which was one of the main research these processes in the presented dissertation. Knowledge about the sources of safe food or water is critical especially in novel, unknown habitats. Thus, recognizing conspecifics' emotions evoked by food finding or consumption, as well as their subsequent health status is a useful skill (Galef and Giraldeau, 2001). Data shows that social behavior and social recognition are involved in passing information about the food location and safety (Choleris et al., 2009). Mice who had contact with other mice who had previously eaten cumin-flavored pellets prefer consumption of such food type, without changing their total consumption levels (Loureiro et al., 2019). Socially-navigated food seeking can be observed very early in the development; pup rats use olfactory social cues left by their mother to find nourishment (Galef and Heiber, 1976).

Social learning about rewards is widely documented in many species other than rodents. Observations of bumblebees show that they use social information to find the best place for foraging (Worden and Papaj, 2005). Consumption of a given food type by a conspecific increases preference to that food in social wasps (D'adamo and Lozada, 2003). Also, a lot of data on social learning about rewards comes from observations of birds. European shags learn where the best place for hunting is by using social cues left by the birds who successfully caught their prey (Evans et al., 2019). Ravens also use social information to find better places to forage. They are also able to assess the "value" of other birds as social sources of information based on their success in food finding (Bugnyar and Kotrschal, 2002).

Another important set of experiments describing appetitive social learning was conducted in primates. Studies in macaques showed that the perceived value of the received reward is dependent on social context (Azzi et al., 2012). Similar results were described in Capuchin monkeys; observation of another monkey eating enhances the motivation to gain the food and the competitive behavior between conspecifics (de Waal, 2012). In monkeys food rewards are a very effective learning factor. Furthermore, in well-trained monkeys it is common that subjects exhibit expectation for reward and display stress reaction when reward does not occur when expected. Further, it was shown that if the subjective value of a reward is lesser than the value of a reward given to another present subject, animals display frustration and refuse to continue training (de Waal and Suchak, 2010). Some argue,

that motivation and willingness to pursue rewards is the main reason for developing cooperative learning and other complex social interactions (Hall and Brosnan, 2017).

## 3.9 Relationship between the animals as a factor influencing social learning

One of the most important aspects of social learning is choosing a suitable source of information (Puścian et al., 2022a). For that purpose, animals oftentimes rely on kinship and familiarity with the individual who is the source of information as a good proxy for its relevance (Cruz et al., 2020; Kurvers et al., 2014). Notably, data suggest that position in social hierarchy is also a key factor for both, obtaining and transmitting social information (Hobson, 2020). Experiments in mice show that subordination induced by repeated physical defeat impairs cognitive and learning abilities (Colas-Zelin et al., 2012). Moreover, socially defeated rats display long-term memory impairments (Von Frijtag et al., 2002). On the other hand, subordinate deer-mice who obtain social information about defensive responses show better acquisition and retention of learned responses (Kavaliers et al., 2005). Fear-conditioned subordinate rats, show stronger fear responses when they previously interacted with fear-conditioned dominants (Jones and Monfils, 2016). Further, subordinate mice learn to avoid social cues left in the environment by the dominants (Bourne et al., 2013).

Notably, social hierarchy was shown to be a significant factor in tasks requiring focusing attention on the behavior of other individuals. Specifically, experiments in macaques demonstrate that the subordinate individuals are more likely to follow the gaze of another monkey than the dominant ones (Shepherd and Freiwald, 2018). Similar observations were made in humans (Jones et al., 2010). High social status is associated with longer and stronger attention being focused on the dominant's face (Foulsham et al., 2010). Furthermore, people remember faces of dominants more vividly than those of subordinates, which may suggest that high social status is considered an indication of noteworthy information being possessed by the individual (Dalmaso et al., 2014; Gachomba et al., 2022).

## 3.10 Social learning from animals of different species

Usually the experiments and observations of social learning are conducted in the same-species subjects. However, there exists evidence that social information can be shared between animals of different species. Notably, animals differ in how they perceive the environment

and in methods they use to gather information (Goodale et al., 2010; Raine, 2008). Thus, social information from animals of other species may contain aspects that cannot be detected by the means of first-hand experience or even observed in conspecifics (Chittka and Leadbeater, 2005).

Animals living in close relations with humans (i.e., pets or farm animals) are great examples. Horses who observe human handlers opening the feeder are better in learning that ability, than subjects from the control groups (Schuetz et al., 2017). Dogs are very efficient in recognizing human emotions by observing human face and behavior (Karl et al., 2020). Moreover, they are able to use that information to make decisions (King and Cowlishaw, 2007). Also, information gathered from the animals of a different species who share similar habitat or prefer the same food can be very valuable (Romero-González et al., 2020). As an example, hyenas learn to observe characteristic behavior of vultures (circling) indicating the spot of a dead or wounded prey (Avarguès-Weber et al., 2013). Social olfactory cues can also be used to encode information about the territory (Mitchell et al., 2018). Predators commonly use their olfactory system to collect information about the potential prey. It is noteworthy that observations of wild foxes show that they use olfactory information not only from the conspecifics but also from other species of predators (Jones et al., 2016).

## 3.11 Experimental approaches used to study social learning

In behavioral neuroscience, behavioral testing techniques can be divided into two broad groups: classic (traditional) assays, which use single or paired subjects in experimental environment specially designed for a realization of a given task, and ethologically-relevant assays, in which subjects are tested in ecologically-valid experimental environments, oftentimes in rich social context (Kondrakiewicz et al., 2019a). Importantly, both approaches have pros and cons that should be considered in experimental planning.

Classic behavioral techniques are widely and successfully used in many, even most recent, publications (Beery and Shambaugh, 2021). This type of behavioral experiments due to its long history of use have many well-established testing protocols (Crawley, 1999). Furthermore, most of them can be conducted at a low cost and within short timeframe (Antunes and Biala, 2012). Another advantage is the relative ease of combining classic behavioral experiments with several neuronal manipulation techniques, such as optogenetic stimulation (Bi et al., 2015) and chemogenetic manipulation (Smith et al., 2016). Experimental apparatus and design usually are quite universal and thus can be used in different animal models (Liu

et al., 2016). What is important, classic behavioral tests oftentimes focus on specific and simple behavioral tasks usually isolated from a wider context, which may be considered an advantage or a disadvantage, depending on the experimental questions (Berkowitz, 1982; Genzel, 2021; Harda et al., 2022). Although relatively easy-looking, classic approaches usually require input of experienced behavioral specialists to design and conduct experiments in accordance with the state-of-the-art standards. Also, poor cross-laboratory standardization of protocols usually causes problems with replicability of the results (Puścian et al., 2016).

## 3.12 Classic assays of social learning

The origins of modern studies on social learning can be found in the series of observation experiments conducted by Bandura and colleges (Bandura, 1961). Their results demonstrate that learning is not only based on directly experiencing reinforcements and punishments but can also happen via observation of rewarding or punishing experiences of others (Hollis and Guillette, 2015).

A majority of the classical behavioral techniques used to study social learning under laboratory conditions use an approach in which pairs (or triplets) of animal subjects are assigned roles of an observer and a demonstrator. A notable example is the social fear conditioning experiment, where mice or rats are paired and placed on the two sides of the cage divided by a separator. The demonstrator is treated with unconditioned aversive stimulus (US, usually a footshock), while the observer is a witness to the situation. Such experiments have a lot of variants and modifications but the general idea is usually to observe the process of social transmission of fear (Jones and Monfils, 2018; Kim et al., 2019). Freezing and other fear-related behavioral responses in the observer animals indicate that transfer of information about the threat took place (Atsak et al., 2012). It was also shown that the observer mice learn fear by the observation of a shocked mouse, without the need for direct electrical shock (Jeon et al., 2010). It is noteworthy, that first-hand participation in conditioning is not necessary to develop conditioned fear response. Thus, mice and rats can be aversively conditioned by proxy, by interacting with an already conditioned subject (Jones et al., 2018; Noworyta-Sokolowska et al., 2019), which is a key example of social learning.

Except for aversive social learning, laboratory rodents are also well known for their ability to use socially-shared appetitive information. The most common classic tests employed to study appetitive social learning is the social transmission of food preference. Designed by Galef (Galef, 1977), the protocol also uses the demonstrator-observer pairs of subjects,

but in this case the demonstrator eats food containing specific novel odor (i.e., pine) just before the experimental session. In the next step, the demonstrator and the observer have an interaction, during which social information is being transferred via olfactory cues. When observers are then given a choice between two flavored food sources they most often chose that of the flavors consumed by the demonstrator (Galef, 2012). Social transmission of information is also used in the experiments based on competition for the reward. In a warm spot test, a group of subjects, usually mice, are placed on a cold-floor open area where one small subarea is warmed, which in a given situation is highly rewarding and the tested animals are motivated to occupy that spot (Zhou et al., 2018). Food rewards are also used in competition experiments, frequently in the food deprived subjects (Merlot et al., 2004). Other types of reward include sucrose (Millard and Gentsch, 2006) or cues from a conspecific of a different sex (Wang et al., 2011). Reward competition tests are very interesting tools for exploring reward processing, however, their results may be confounded by an important social factor – dominance status (Zhou et al., 2018).

The most popular classic test used to study social hierarchy is the tube test (Fan et al., 2019), a very simple and powerful task in which mice are tested in pairs. The test can be applied to larger groups of animals. Then all animals are tested with all possible pair combinations, usually in the round robin system. Individuals are placed at the two opposite entrances to a simple tube, sometimes U-shaped. A mouse or rat who pushes out its opponent is considered the winner (Fan et al., 2019). It was shown that results from the tube tests correlate with results from previously described reward competition experiments and other widely used protocols, such as territory urine marking or barbering (Costa et al., 2021; Wang et al., 2011). However, some discoveries contradict that notion (Drickamer, 2001). Nevertheless, much evidence suggests that social structure is a complex phenomenon and the tube test is too simple to study its sophisticated mechanisms. For example, it was shown that social hierarchy is dynamically updated and highly dependent on the previous experience (Zhou et al., 2017). In that context the tube test may be considered a hierarchy-forming tool rather than its test. Furthermore, observation of mice behavior under natural conditions shows that most commonly they avoid direct confrontation, which is exactly opposite to the tube test situation (Łopucki, 2007), thus undermining its ethological validity.

## 3.13 Ethologically-relevant assays of social learning

Novel ecologically validated behavioral tests enabling studies of social learning were designed to alleviate the main problems of classic behavioral assays. Most importantly, such experiments are based on natural abilities and preferences of the tested animals. For example, even if it is possible to train mice to learn based on visual cues, still training based on olfaction is more natural and effective (Puścian et al., 2020). Over the last two decades scientists designed a number of assays that fit the requirements of ecological standards in social learning experiments. It is noteworthy, that social behavior can be tested in the ecologically relevant environments also in non-mammalian species, such as zebrafishes. However, most of the research in that area focuses on laboratory rodents.

IntelliCage system is a commercially available assay for testing behavior in group-housed mice (Endo et al., 2011; Kiryk et al., 2020). The system comprises of a large home cage which is also an experimental environment. The core element of the IntelliCage are the corners serving as electronically controlled conditioning units. Corners have presence sensors and RFID antennas to record presence and behavior of individually tagged mice. Furthermore, each corner enables controlled access to two bottles (Endo et al., 2011). It was shown that IntelliCage experiments can be used for experiments on social learning about threats and rewards (Ismail et al., 2017; Smutek et al., 2014). Further, there are also several non-commercial approaches that can be considered ecologically-valid methods for assessment of social learning. For example, rodent behavior can be tracked based on video recordings combined with RFID data in specially prepared home cage (de Chaumont et al., 2019; Ebbesen and Froemke, 2020; Krynitsky et al., 2020; Peleh et al., 2019). Notably, recent boom in the development of custom-made software supported by the artificial intelligence (AI) facilitates the analysis of group and individual behavior of mice in social interaction tasks. Interesting novel approach to study natural behavior and social abilities in mice is conducting automated behavioral experiments in the controlled natural habitats (Akam et al., 2021; Bedford et al., 2021).

In the Eco-HAB system used in the herein presented studies, groups of mice are placed in a burrow-like environment, which is in line with their natural tendency to avoid open spaces and prefer secluded areas (Ennaceur et al., 2006). Furthermore, experiments are conducted 24/7 thus testing may take place in the dark phase of the day-night cycle, which is also natural time for mice to explore and be active (Andrzejewski et al., 2011). Another important aspect is the process of habituation. In the classic behavioral tests habituation is problematic due to its poor standardization and impact of experimenters (Bohlen et al., 2014; Lewejohann et al., 2006). It was shown that the effects of improper or too weak habituation especially affect

anxious strains of laboratory animals (Puścian et al., 2016). Proper ecological approach to the process of habituation focuses on reducing to a minimum the time of contact with experimenters and letting subjects to freely explore the habitat before the behavioral tests. A good indicator of the habituation level is the characteristic decrease of habitat exploration (Kondrakiewicz et al., 2019a). Based on the observation of mouse behavior in the Eco-HAB 24-48 h is enough time for the animals to get familiar with the environment as this is when activity measured by the system reaches the plateau (Puścian et al., 2016). Widely discussed general problem of the classic testing is the relatively short time of the test usually reduced to minutes or hours of observation (Crawley, 2003). Usually the main reason for that is that the tested behavior is video recorded; such files need a lot of memory to be stored. Furthermore, extracting data from video is time consuming, even with novel AI based approaches (Gerós et al., 2020; Holly et al., 2016). The radio frequency identification (RFID)-based automated assays such as Eco-HAB seem to be a noteworthy alternative. Data collected this way is much easier to process and store (Howerton et al., 2012). However, it is important that data collected by RFID system is much simpler than that which can be extracted from the video recording, and provide only the information about the position of the animal within the system. Some systems combine RFID positioning with video recording, for example by reducing the video recordings only to special situations detected by the RFID system (Peleh et al., 2019). It is also worth mentioning that automated systems for longitudinal observation provide the possibility to test subjects expressing fully voluntary behavior and individual preferences (Matzel et al., 2003). In the studies on social behavior and social learning in particular, individual preferences seem especially pertinent to consider. Social relations and hierarchy are based on the unique reactions of the individuals forming the group. The advanced high-level analysis of mice group behavior show that they are able to create human-like social networks (Lopes and König, 2020; Misiołek et al., 2022; Raulo et al., 2021; Winiarski et al., 2022). Additionally, such social networks can be studied with a use of the RFID technology in natural environment (Bedford et al., 2021).

## 3.14 Prefrontal cortex and the role of its neuronal circuits in social learning

Receiving social information engages all senses and requires constant updates and interpretation (Stowers and Kuo, 2015). Information of diverse modalities and types is processed by the specialized brain circuits. Several brain structures hosting the circuits

processing social information have been identified. They include the amygdala, which is engaged in processing emotions perceived socially, as well as in social learning (Andraka et al., 2021; Jeon et al., 2010; Knapska et al., 2006a). Expression of empathic behavior is correlated with activation of the insular cortex (Gogolla, 2017). Socially-driven motivation is modulated by the ventral tegmental area (Bellone and Lüscher, 2006; Froemke and Young, 2021; Mameli et al., 2011). Some elements of social memory are stored and processed in specific regions of the hippocampus (Okuyama et al., 2016).

Nevertheless, the prefrontal cortex (PFC) seems to be a region where information of social provenience is compiled and further processed (Kennedy and Adolphs, 2012; Márquez et al., 2013). The PFC is a complex structure, however, in the context of social learning some of its characteristics are more crucial than others. Specifically, its anatomical division into the medial prefrontal cortex (mPFC) containing prelimbic (PL) and infralimbic (IL) parts - structural and functional homologs of the anterior cingulate and ventromedial prefrontal regions in primates plays a key role (Carlén, 2017).

The critical role of the mPFC in processing information during social fear learning is well-documented (Olsson and Phelps, 2007). The mPFC is also engaged in social recognition tasks (Tan et al., 2019). Brain imaging in human studies also shows activation of the PFC areas during social tasks, such as social interaction or retrieving social memories (Amido and Firth, 2016). In the cases of head damage and resulting injuries of the PFC regions reported in humans, patients oftentimes report changes in their social behavior. Lesions of the ventromedial PFC (vmPFC) cause difficulties in expressing and understanding emotions (Mah et al., 2016). Moreover, injuries of the PFC negatively affect recognition of social dominance and social judgements (Pellis et al., 2006). In empathy-related tasks patients with focal damage to the vmPFC are more avaricious and less empathic than subjects from the control group (Beadle et al., 2018). Further, they also show impairments in recognition of emotions as based on observing faces (Vandekerckhove et al., 2014).

Studies in other animals support these notions. Macaques who had the PFC lesions have significant difficulties in interacting and assimilating back into their social group (Myers et al., 1973). The same type of the brain damage causes impairments in social interactions and play in laboratory mice (Schneider and Koch, 2005). Social isolation and poor social environment at the early stages of the development are also associated with social impairments and structural changes in the PFC. Mice that have very limited contact with conspecifics display defective maturation of oligodendrocytes and impaired myelination in neuronal outputs from the PFC

(Makinodan et al., 2012). Proper socialization in the juvenile period is also crucial for maturation of the PFC's parvalbumin interneurons (Bicks et al., 2020).

Recent studies making use of the novel neuronal imaging techniques, performed mostly in rodents, provide plenty of results explaining the role of the PFC in processing of social information and social learning. Lee and colleagues showed that neuronal activity in the mPFC is highly correlated with distance to another conspecific (Lee et al., 2016). Kumar et al. (Kumar et al., 2014) reported that in chronic social defeat stress experiments firing rate in the PFC neurons is significantly decreased, which additionally correlates with stress level. Furthermore, studies in freely moving mice showed that neurons in the PFC react differently to social and non-social olfactory stimuli (Levy et al., 2019).

The PFC is known for the dynamic processes of neuronal plasticity. For example, although gender recognition is associated with the PFC, hypothalamus and medial amygdala, the refinement of the neuronal connectivity and activity in the PFC is observed much faster than in those other brain areas (Yizhar and Levy, 2021). Those findings support the role of the PFC as a structure highly adaptable to novel information from changing environments (Murray et al., 2015; Passecker et al., 2019). One of the general roles of the PFC in processing social information is the integration of the already possessed knowledge with the novel information about self and others (Denny et al., 2012). This concept can be very useful in the interpretation of the emotional processing on behavioral and neuronal levels. Studies in primates show that activity of neurons in the dorsal anterior cingulate cortex predict decisions of other conspecifics during cooperation tasks (Haroush and Williams, 2015). Scheggia with colleagues showed that social preference for an emotionally-aroused individual disappears when a somatostatin but not parvalbumin-expressing interneurons in the PFC are silenced (Scheggia et al., 2020). Moreover, the observations of the synchronization of neuronal activity in the PFC of two interacting mice, suggest that PFC is a structure highly engaged in empathy-like behavior and social learning (Kingsbury et al., 2019). Interestingly, two neuronal populations are engaged in that synchronization, the first is the population mainly associated with partner's behavior, while the second mostly reflects self-behavior. Moreover, dominants seem to have more influence on the synchronization process. This finding could be crucial to furthering the understanding of the mechanisms of social dominance, especially in the face of evidence from different species showing the crucial role of the neuronal activity in the PFC in regulation of hierarchy (Wang et al., 2011).

The PFC is a structure that is also highly involved in processing information about rewards and a key player in neuronal encoding of appetitive learning. Connectomics studies

show that subjective value of the reward and reward-motivated decision making are represented in the PFC and connected structures (Cieślak et al., 2018; Levy and Glimcher, 2012; Murray and Rudebeck, 2018). Experiments in primates illustrated how neurons in the PFC encode relative value of the reward in barter-like protocols (Padoa-Schioppa and Assad, 2006). Neuronal activity in the PFC dynamically changes in response to different reward value (Padoa-Schioppa, 2009). Furthermore, human studies with atomoxetine, a drug commonly used in the attention deficit hyperactivity disorder (ADHD) treatment, show it modulates neuronal activity in the PFC during reward presence and affects reward value (Suzuki et al., 2019).

Activity in the orbitofrontal cortex, which is the important functional and anatomical part of the PFC, is also associated with prediction of future events and expectations (Roesch and Olson, 2004). However, in gambling-like behavioral experiments, where rats were subjected to changing tasks to obtain the reward, neurons in the PFC were activated when the reward was received but not when it was expected (Zeeb et al., 2015). Most research on reward processing are based on material rewards (e.g., attractive food, Márquez et al., 2015; Tobler et al., 2008). However, social interactions are also considered a rewarding factor (Noritake et al., 2018). Damage in the PFC may result in social anhedonia (Barrash et al., 2000). Human studies showed that the vmPFC is activated in response to the individual's attractiveness (Dang et al., 2019). The rewarding aspects of cooperative behaviors are also processed by the PFC (Luo and Maunsell, 2018). In rodents, the role of the PFC in social reward was demonstrated in social motivation tests (Avale et al., 2011). Increase of excitatory/inhibitory balance in the medial PFC results in decreased motivation to social contact (Yizhar et al., 2011). Electrophysiological experiments performed in freely moving rats show that neurons in the PFC encode the value of competing for a reward (Hillman and Bilkey, 2012). Manipulations and disruption in that region affect both motivation to social contact and reward-based decision making (Rushworth et al., 2007). Those findings strongly suggest that the PFC plays a key role in socially-driven appetitive learning and evaluating reward value from social cues (Olsson et al., 2020).

## 3.15 Tissue inhibitors of matrix metalloproteinases

Tissue inhibitors of metalloproteinases (TIMP) are a family of endogenous proteins that affect the synaptic plasticity by inhibiting the enzymatic activity of matrix metalloproteinases (MMPs) (Dziembowska and Wlodarczyk, 2012). MMPs are the enzymes mainly reported

to remodel the extracellular matrix and regulate homeostasis between cells in the tissues (Wlodarczyk et al., 2011). In the brain MMPs' participate in axonal growth and dendritic maturation (Gonthier et al., 2009). Expression of MMP's genes is not constant and is promoted by various stimuli such as neuronal activation or presence of growth factors (Wright and Harding, 2010). Experiments in mice showed that abnormal activity of MMP9, a member of the MMMs family, is related to immaturity of synaptic connections and behavioral phenotype characteristic for Autism Spectrum Disorder (Puścian and Knapska, 2022).

Tissue inhibitor of metalloproteinases 1 (TIMP1) is widely used in laboratory practice as a regulator of MMPs activity (Vafadari et al., 2016). However, it is a multifunctional protein engaged also in carcinogenesis (Lugowska et al., 2015), angiogenesis (Ikenaka et al., 2003) and osteogenesis (Breckon et al., 1995). Nevertheless, TIMP1 role in the brain is associated with neuronal development and maturation of synaptic connectivity (Ould-yahoui et al., 2009), reported, i.a., in the hippocampus and cerebellum (Rivera et al., 1997; Vaillant et al., 1999). A large body of studies investigated TIMPs' role in neuronal plasticity after brain seizures or a stroke (Hansson et al., 2011; Pu et al., 2022). TIMP1 expression is rapidly increased in the brains of rats exposed to kainate excitotoxic seizures (Rivera et al., 1997). Similar findings were observed in the studies on brain recovery after different types of ischemia (Rivera et al., 2002; Wang et al., 1998) or infection (Khuth et al., 2001).

One of the most critical targets of TIMP1 is matrix metalloproteinase 9 (MMP9), the enzyme crucial for dendritic spines maturation (Michaluk et al., 2011; Puścian et al., 2022b). Herein, TIMP1 is used to inhibit the activity of MMP9, and thus disrupt the processes of MMP9-relared neuronal plasticity. Notably, under physiological conditions TIMP1 was reported to play a role in synaptic plasticity induced by stimuli inducing long term potentiation (LTP, Gorkiewicz et al., 2015), a process crucial for forming long term memory on the cellular level.

# 4 Research goals

- Develop novel experimental protocols for testing appetitive social learning under semi-naturalistic conditions of the Eco-HAB system
- Examine how social learning about potential rewards affects the behavior of group-housed mice
- Test the role of environment familiarity/novelty in appetitive social learning
- Investigate how disruption of synaptic plasticity in the MMP9-dependent neuronal circuits in the prelimbic cortex affects social learning about rewards

# 5 Materials and Methods

## 5.1 Subjects

In the presented studies C57BL/6j mice (Figure 1), the most common and well-described strain of laboratory mice are used as experimental subjects. All the subjects were male and 2 to 3-months-old at the beginning of the experimental procedures. Animals were treated according to the ethical standards of the European Union (directive no.2010/63/UE) and respective Polish regulations. All the experiments were pre-approved by the Local Ethics Committee no. 1. In Warsaw, Poland. Mice were bred in the Animal House of Nencki Institute of Experimental Biology, Polish Academy of Sciences or Mossakowski Medical Research Centre, Polish Academy of Sciences. The animals were transferred to the experimental room at least two weeks before the start of the procedures, to habituate them to the room conditions: humidity, temperature, personnel, scents and the 2h/12h light-dark cycle, shifted by 5 hours in comparison to the one implemented in the mouse colony. During the pre-experimental period mice were housed in groups of 12-15 animals. The cage (56 cm x 34 cm x 20cm) assured access to water and food *ad libitum*, monitored daily and refilled once per week during cage cleaning. Cage environment was enriched with paper tubes, shelters and nesting materials. Before each experiment, subjects were monitored for potential excluding factors such as tooth overgrowth, poor physical condition, etc.

Figure 1. C57BL/6j mouse, source: https://animalab.pl/mysz-c57bl-6j-jax

## 5.2 RFID tagging

At least one week before the experiment mice were electronically tagged with glass-coated RFID (radio frequency-based identification) microchips (also called transponders, 9.5 mm - length and 2.2 mm - diameter, RFIP Ltd) (Figure 2). During the subsequent Eco-HAB experiments individual RFID codes were read by the antennas every time the animals passed

through its corridors, and thus data about animals' behavior in the system was collected. Before implantation the RFID microchips were sterilized in 70% ethanol, dried on a paper towel, loaded into the syringes. Next they were subcutaneously injected into the subjects anesthetized with isoflurane (Baxter). After the injection subjects were monitored for breathing and other basic life functions and placed back in the home cage when fully awake. On the next day the presence and the correct position of the microchips under animals' skin was additionally verified. Right before the experiment transponders' numbers were checked with the use of the Eco-HAB tag reader and a list of animals (tags) tested in a given experiment was created. In a very rare case of the transponder loss or malfunction animals were reinjected with the new one in accordance with the previously described procedure. After perfusion (see subsequent section of Materials and Methods) microchips were recovered, cleaned in ethanol for sterilization purposes and stored for further reuse.

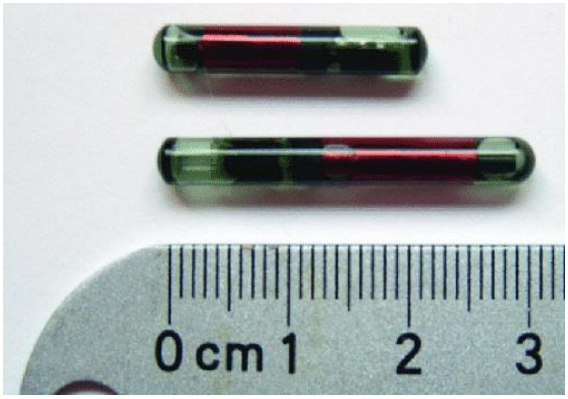


Figure 2. A glass coated RFID-transponder, source: https://www.researchgate.net/figure/23mm-and-32mm-Passive-Integrated-Transponder-PIT-Tags_fig6_235052120

## 5.3 Poly(DL-lactide-co-glycolide) nanoparticles containing TIMP metallopeptidase inhibitor 1 (TIMP1) or Bovine serum albumin (BSA)

To manipulate neuronal plasticity in the prelimbic cortex (PL) of the tested animals we used **TIMP metallopeptidase inhibitor 1 (**TIMP1), delivered in poly(DL-lactide-co-glycolide, PLGA) nanoparticles (NPs). TIMP1 protein used in the experiments was kindly provided by the laboratory of prof. Leszek Kaczmarek. Specifically, the protein was extracted from the human kidney 293 T-cell line expressing TIMP1 with histag, purified on Talon affinity chromatography and dialyzed at 4°C against phosphate-buffered saline, pH 7.5; then the protein was characterized by Western blot, reverse zymography, and gelatinase assay. In the control

condition with bovine serum albumin, (BSA, Sigma-Aldrich). Loading the NPs with TIMP1- or BSA was performed in accordance with the protocol published by Chaturvedi et al. (2014). Namely, NPs were prepared in the process of multiple emulsifications and evaporations (MW 45.000–75.000, copolymer ratio: 50:50, Sigma-Aldrich). 100 mg PLGA was dissolved in 5 ml dichloromethane and 4ml of dimethyl tartaric acid (Signa-Aldrich). In the next step, 1 mg of TIMP1 or BSA was dissolved in 500 µl of MiliQ water. The protein solution was mixed with dichloromethane containing PLGA, sonicated and emulsified in 1% polyvinyl alcohol (on average MW 30.000–70.000, Sigma-Aldrich). Additionally, Fluorescein isothiocyanate (FITC) was added to enable localization of the site of NP's delivery in the brain. Subsequently, the solution was stirred at room temperature overnight to evaporate dichloromethane. Next, the NPs were centrifuged at 10.000 x g, washed three times with MiliQ, dissolved in phosphate-buffered saline (PBS), and stored in a 15ml falcon at 4°C ready for use.

## 5.4 Stereotaxic surgeries

Before the start of surgical procedures all tools were sterilized in 70% ethanol. Mice were transferred to the surgical facility in small, clean cages and placed in the ventilated rack in the preparatory room to minimize the time between leaving the home cage and placement in the initial anesthesia box.

Mice were anesthetized with isoflurane (Baxter, inhalation started in a small container at 5% and was reduced to 2-1,5% of isoflurane, during surgery, delivered via mask) and then placed in a stereotaxic apparatus (Kopf Instruments) on a heating pad (37.8°C). Additionally, the mice were subcutaneously injected with the analgesic (Butamidor, Richter, 1:20 in saline, 2.5 ml/kg) and reflexes were checked to ensure the absence of pain. To protect animals' eyes from drying we used a moisturizing gel (Carbonerum, Vidisic). Ear bar tips, which were placed directly in the ear canal were dipped in vaseline before use. Next, animals; head was shaved using a depilatory cream for sensitive skin (Veet) and qtips. The skin was then rinsed with saline and cut to expose the skull. The small craniotomies over the injection sites were made with a use of the surgical drill and Nanofil 35G needles were used to bilaterally inject NPs into the PL (coordinates: AP +1.8 mm, LM +/- 0.92 mm, DV -1.67 mm, at 20° angle). The delivery was controlled by the Micro Syringe Pump (World Precision Instruments, 500 nl of total volume, 100 nl/min). To let the NPs diffuse in the tissue the needle was left in the brain for an additional 5 min after the injection. Afterwards, the incision was sutured (Dafilon, C0935204) and lubricated with the analgesic lignocainum hydrochloricum (10 mg, Polfa).

Moreover, the mice received subcutaneous injections of the anti-inflammatory drug (Tolfedine, Vetoquinol, 4 mg/kg) and of the wide-spectrum antibiotic (Baytril 2.5%, Bayer, 1:3 in saline, 5 ml/kg). Then animals were placed in the cages previously warmed on a heating pad and singly-housed for the next 5 days to allow for full recovery. During the recovery the health status of mice was monitored by the experimenters.

## 5.5 Perfusions and subsequent verification of TIMP1/BSA injection sites

After the end of the behavioral testing, mice injected with the NPs releasing TIMP1 or BSA were anesthetized with intraperitoneal injection of sodium pentobarbital (100 mg/kg, dissolved in PBS) and transcardially perfused with 80 ml of ice-cold PBS followed by 60 ml of 4% paraformaldehyde (PFA) in PBS (4°C). The brains were isolated and placed overnight in 4% PFA in PBS (4°C). After 24h, the brains were moved to 30% sucrose solution in PBS for 2-3 days (4°C) for cryoprotection. Next, the brains were cut on a cryostat into 50 μm-thick coronal slices. The slices containing the brain region of interest (PL) were then washed in PBS, placed on the microscope glass slides and fluorescence of the FITC encapsulated in NPs was imaged under the Nikon Eclipse Ni fluorescence microscope.

## 5.6 Eco-HAB system

### 5.6.1 Apparatus and its workings

Eco-HAB (Figure 3 and 4) is a fully automated, open source system for testing social behavior in group-housed mice living under semi-naturalistic conditions (Puścian et al., 2016). The system comprises 4 polycarbonate compartments (30cm x 30cm x 18cm) connected with tube-shaped corridors (inner diameter 36mm, outer diameter 40mm), and covered with stainless steel grid lids. All housing elements can be autoclaved and disinfected with 70% alcohol. In 2 out of 4 compartments mice have access to food and water (*ad libitum*); the other 2 compartments have a separated space allowing for the presentation of olfactory stimuli (in a corner, behind a perforated partition) or placement of additional drinking bottles. Access to all the compartments, olfactory stimuli and additional bottles is unrestricted and voluntary. To record movement of animals within the Eco-HAB system the corridors are equipped with circular RFID antennas registering transponders' numbers. The data from

the antennas are collected by a dedicated electronic system, which then sends them to the computer. Results are then further analyzed with a use of the pyEcoHAB python library (https://github.com/Neuroinflab/pyEcoHAB).

Experiments were conducted in a three-level designer rack with 3 autonomous, individually lit Eco-HAB systems placed one above the other. The designer rack was built from the materials providing acoustic isolation from external sounds. Each level had a separate ventilation system. Such architecture provided proper airflow in each Eco-HAB system without any mixing of the air, potentially carrying scents. Additionally, Eco-HAB electronic master units were connected to the computers outside the rack, thus reducing contact between the experimenter and the animal subjects to a minimum.

Figure 3. Eco-HAB system inside, soundproof designer rack floor. Each level contains autonomous, individually-lit and -ventilated Eco-HAB, enabling simultaneous, high-throughput experimentation.

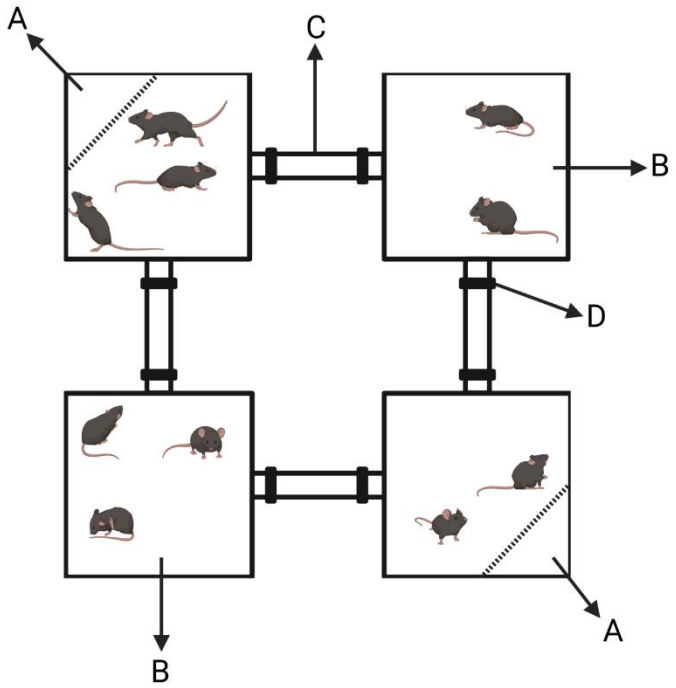


Figure 4. Schematic of the Eco-HAB system. A - olfactory stimuli were presented behind the perforated separator, allowing for extensive sensory exploration but preventing spreading the scents throughout the territory, B – home cages with unlimited access to food and water, C – a tube-shaped corridor connecting Eco-HAB compartments, D – RFID antenna

### 5.6.2 Behavioral measures and data processing algorithms

In the presented experiments we assessed the following behavioral aspects: activity, approach to social odor, consumption from the preferred bottle.

Namely, activity was measured as a total number of visits to all of the Eco-HAB compartments during the testing phase (12h dark phase after stimulus presentation).

Approach to social odor was calculated to evaluate animals' interest in the scents presented behind the perforated partitions. It was defined as a proportion of visits to the compartment containing social olfactory stimulus, to the visits to the compartment containing non-social (control) olfactory stimulus during the testing phase (12h dark phase after stimulus presentation). To control for the individual preferences in spending time in various parts of the Eco-HAB territory this proportion was then divided by the same proportion from the preceding dark phase of the adaptation phase (when no olfactory stimuli were present in the compartments).

Consumption from the preferred bottle was measured as time spent on drinking from the preferred bottle divided by the total time spent on drinking (from both available bottles) during the 1st hour of the novel environment experiment.

To measure the dynamics of exploration of the presented social odors we calculated the persistence in odor seeking. It was calculated as the proportion of visits to the compartments where odors (indicating reward and neutral, or neutral and neutral in the control condition, please see Figure 4) were presented, during the last 6 hours of the testing phase, divided by the same proportion from the first 6 hours of the testing phase. This measure shows how long the tendency to seek for social information persists after it was first presented.

In the experiments performed in the novel environment persistence in reward seeking was calculated as time spent on drinking from the bottle previously containing 10% sucrose solution, in the second 6h of the testing phase divided by the time spent in the compartment containing that bottle during the same period. The value was then divided by the same proportion from the first 6h of the testing phase.

Both persistence measures were developed to assess the dynamics of the subjects' interest in exploring a potential source of the reward, as indicated by the social cues left by the conspecifics. Moreover, an algorithmic solution similar to that used to calculate approach to social odor was implemented to account for the potential preference for specific Eco-HAB compartments/drinking bottles, that might have otherwise confounded the interpretation of the data.

To assess how animals trail one another within the Eco-HAB territory we measured the number of events when mice followed one another through the corridors of the system. Specifically, following was defined as an event when one mouse (leader) entered a corridor, another mouse (follower) trailed in it into the corridor, before the leader left the tube, and both mice left the corridor in the same order and in the same direction (Figure 5).

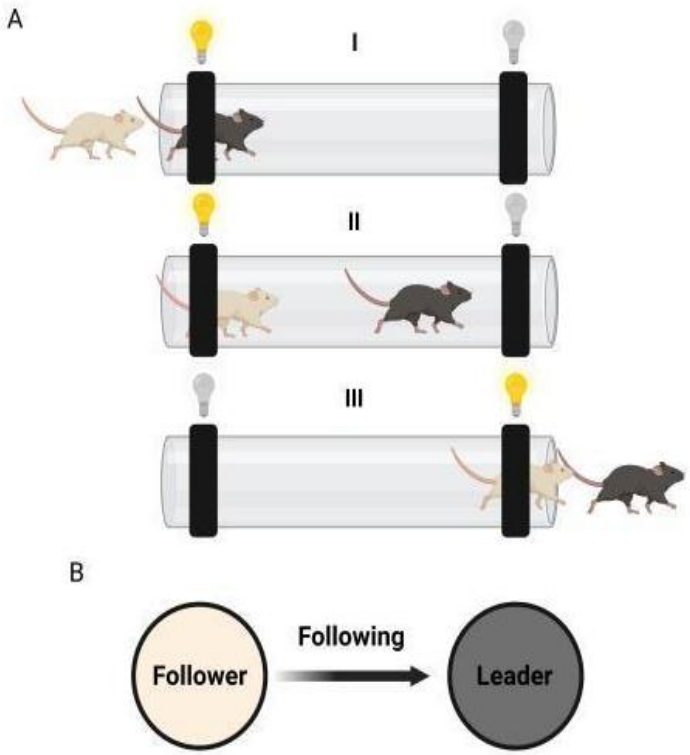


Figure 5. Schematic of the following event measured in Eco-HAB. I – A leader mouse enters the corridor tube (trigger first antenna), II – A follower mouse enters the tube, from the same end and going in the same direction as a leader mouse; a leader is still in the tube, III - both mice leave the corridor on the opposite side of the tube in the same order they entered ( triggering the second antenna, B - representation of followings by graph, nodes represented mice, edges direction and intensity of followings in time)

To assess the significance of the level of following performed by each mouse in relation to its position as an element of the social network (group), we calculated PageRank centrality for the inverted weighted directed graph of followings, in which each directed edge carries a weight equal to the number of respective events. PageRank analyses have been previously shown useful in identifying leaders within social groups (Wang et al. 2013). For the purpose of between-group comparisons to control for the individual variability in locomotor activity we summed all the following events of each mouse and divided them by its locomotor activity (total number of its visits to all Eco-HAB compartments) during the analyzed time bin. For the analysis of within-cohort changes in following patterns raw values were used.

To evaluate the tendency of mice to voluntarily spend time together, we measured in-cohort sociability. For a particular pair of subjects, animal a and animal b, we first calculated the times spent by the mice in each of the four compartments during a chosen experimental time bin: $t_{a1}$, $t_{a2}$, $t_{a3}$, $t_{a4}$ for animal a, and $t_{b1}$, $t_{b2}$, $t_{b3}$, $t_{b4}$ for animal b. The total time spent by the pair together in each of the cages was then calculated: $t_{ab} = t_{ab1} + ;t_{ab2} + t_{ab3} + t_{ab4}$.

All times were normalized by the total time of the analyzed time bin, so that each of the quantities fell between 0 and 1. The in-cohort sociability was then defined as $t_{ab}$ - ($t_{a1}$*$t_{b1}$ + $t_{a2}$*$t_{b2}$ + $t_{a3}$*$t_{b3}$ + $t_{a4}$*$t_{b4}$), which is the total time spent together minus the time animals would spend together assuming independent exploration of the apparatus. The measure was calculated for each pair of the subjects within a testing cohort of animals.

For the details of the implemented algorithms please refer to the freely available source code on https://github.com/Neuroinflab/pyEcoHAB.

## 5.7 Assessment of the behavioral response to social olfactory cues indicating reward presented in a familiar environment

The design of the experiment on socially transmitted information about the reward (cohort I, n = 13, one mouse was excluded from the experiment due to anatomical dysfunction that could have affected its behavior) was performed as follows. The experiment lasted 4 days. For the first 48 hour animals were undergoing the adaptation phase, when they freely explored the Eco-HAB system, habituated to the environmental conditions and stabilized groups' social hierarchy. After this period, 2 randomly chosen mice were removed from the Eco-HAB system and subsequently housed in the individual cages (17 cm x 23 cm x 13 cm) for the next 24h (isolation phase). One of the isolated subjects were given access to tap water, the other to a highly rewarding 10% sucrose solution, food was available *at libitum*. In the control condition both mice were given tap water. Separated animals stayed on the opposite sides of the experimental room to eliminate the possibility of information exchange. Furthermore, the rewarded mouse had access to an additional bottle with tap water. At the beginning of the next dark phase (testing phase) the samples of bedding from the individual cages of the isolated subjects were collected and presented to the rest of the cohort that stayed in Eco-HAB. To avoid spreading of the scent throughout the territory while maintaining unrestricted access, bedding samples were placed behind the perforated partitions in the opposite cages of the system (see Figure 3 and 4).

The animals were tested twice, in the first, control trial (CTRL) both separated mice had access to tap water. After the control trial all mice from the cohort (2 isolated subjects and 10 subjects still housed in the Eco-HAB system) were put together in a home cage. The Eco-HAB system was cleaned and after 24h the second, reward trial was conducted. The only difference between the control and reward conditions was that in the latter one

of the separated mice had access to 10% sucrose solution, while the other to tap water. One mouse from this cohort was excluded from the experiment due to health problems with foretooth overgrowth that might have affected its social behavior.

Further, the described protocol was then adapted to perform experiments examining the effects of manipulating neuronal plasticity in the PL on the response to social olfactory cues indicating reward. To disrupt neuronal plasticity we injected NPs loaded with control BSA (cohort II, n = 12), or TIMP1 (cohort III, n = 13), to the PL of all experimental subjects, except the ones that were isolated.

To study the effects of TIMP1 injection to the PL and allow for within-subject analysis, experiments were performed twice, before and after treatment. The first trial (before treatment) contained all 3 previously described stages (adaptation, isolation, test). After the experiment we subjected animals to the TIMP1/BSA NPs injections. After surgery, mice were placed in the individual cages and taken to the experimental room for 5 days of recovery. Then animals were put back into the Eco-HAB and the experiment was repeated.

Despite due diligence given during and after the surgical procedures, 2 mice from cohort II (BSA-experiment) were excluded from the experiment because of the postoperative complications that could have affected their social behavior.

## 5.8 Assessment of the behavioral response to social olfactory cues indicating reward presented in a novel environment

Experimental protocols similar to those previously described were designed to test animals' response to socially transmitted information about reward presented in a novel, unknown environment. In this set of experiments however, the two opposing Eco-HAB compartments (the ones that usually contained built-in perforated separators) were modified to offer access to the additional drinking bottles (1 per each of the two compartments). To be able to drink from the bottles animals had to poke into a short (8cm) tube, equipped with an RFID antenna, registering each animal's individual tag and drinking time.

Two independent Eco-HAB systems were used during this protocol. Systems were fully isolated and working on different levels of the designer rack (Figure 3). As in the previous experiments, the mice were put into the Eco-HAB system (Eco-HAB I) at the beginning of the dark phase. They were adapting to the environment for the next 72 hours (Adaptation

phase). During this time a second Eco-HAB system (Eco-HAB II) stayed empty (without any mice inside). Following the adaptation phase, 2 randomly chosen subjects (scouts) were moved into a new, unknown Eco-HAB II environment, in which the only drinking bottles available were the ones with the antennas monitoring drinking behavior (with *at libitum* access to food in the standard feeders).

In the reward (REW) trial the separated mice had access to tap water in one compartment and to 10% sucrose solution in the opposite compartment of the Eco-HAB II. In the control (CTRL) trial both bottles were filled with tap water. After 24h of the isolation phase, the two scout mice were removed from the Eco-HAB II and put out of the experimental room. Both bottles in the Eco-HAB II were cleaned and refilled with fresh tap water, however bedding soaked with scents left by the scout mice remained. Then the rest of the cohort, which until now had inhabited the original Eco-HAB I, was transferred to the Eco-HAB II for 12 h starting at the beginning of the dark phase (testing phase).

Three experimental trials were conducted in mice injected with either TIMP1 or BSA-loaded NPs to assess the effects of the neuronal plasticity manipulation on the behavioral response to social olfactory cues indicating reward presented in a novel environment. Namely, we performed the following experiments: the control trial in the BSA-treated mice (NP-BSA-CTR, cohort IV, n = 12, one mouse had to be excluded from the experiment, and subsequently from the analysis, because it stopped drinking, indicating health issues), the reward trial in the BSA-treated mice (NP-BSA-REW, cohort V, n = 12), and the reward trial in the TIMP1-treated mice (NP-TIMP1-REW, cohort VI, n = 12, 2 mice died after the surgeries). All mice (except for the isolated scout animals, who were sham-operated) were subjected to injections of the NPs containing either TIMP1 or BSA (depending on a given experimental condition) 5 days before the start of the behavioral testing.

## 5.9 Reward preference test

Cohorts V and VI were subjected to a reward preference test, to measure their propensity for 10% sucrose consumption. To that end, 24h after the Eco-HAB experiments in a novel environment, mice were placed in a clean Eco-HAB system with tap water-filled drinking bottles in the opposite compartments, placed as in the preceding experiments. Mice were subjected to the standard adaptation phase, followed by the testing phase, when bottles were removed, washed and refiled: one with tap water, the other with 10% sucrose solution.

Consumption from the preferred bottle was calculated as described in the Behavioral measures and data processing algorithms section.

## 5.10 Measuring formation and stability of social structure in the Eco-HAB

To observe how social structure was formed and maintained in the Eco-HAB system, and how it was affected by the TIMP1 release in the PL we tested voluntary behavior of mice in a series of the longitudinal experiments, in which the animals inhabited the Eco-HAB system without any additional changes to the testing environment. First, the mice (cohort VII, n = 15) were tested for 4 days. Next, they were subjected to the stereotaxic injections with TIMP1-loaded NPs. After recovery the mice were placed back into the Eco-HAB system and their behavior was re-measured for another 4 days.

## 5.11 Social dominance tests

To investigate the relationship between animal's position in social networks based on the followings measured in Eco-HAB and social dominance (hierarchy) we tested a new, naive cohort of mice (cohort VIII, n =12) in the Eco-HAB system and compared the results with the scores from the U-tube social dominance test. Two-staged experiment was designed. In the first stage mice were tested in a classical Eco-HAB environment for 10 days, without any additional manipulations, to observe formation and dynamic changes of social structure. Following this part, U-tube dominance test was conducted. For that purpose mice were placed in the individual cages and tested in a round robin system, in all the possible pairwise combinations. Specifically, the subjects from each tested pair were placed at the entrances, at the opposite sides of the u-shaped tube (1m length, 42mm diameter). Then animals were allowed to interact in the apparatus, until one animal pushed the other out of the tube. A mouse who pushed the partner out of the tube was declared a winner of a given bout. All pairs were tested and dominance score was measured as a number of wins each mouse collected during the experiment.

## 5.12 Statistical analyses

For statistical analysis GraphPad Prism7 software was used. The normality of data distributions was assessed with the D'Agostino-Pearson omnibus normality test. Data sets that passed the normality tests were further analyzed using Student's t-test for the independent or paired samples, depending on the particular type of the comparison. For the data sets that did not pass the criterion of normality required for performing parametric analyses, the Mann-Whitney or Wilcoxon matched-pairs signed-rank tests were used. For the comparisons of the data with the theoretical value (e.g. no-change level) we used one sample t-test for parametric data. Correlations between various measures of social dominance were calculated with a use of the Pearson correlation test. Calculations were performed with the use of Wolfram Mathematica 13.0. The weights are given in percent and rounded to the nearest integer number. The criterion for statistical significance in all performed analysis was a probability level of $p<0.05$.

# 6 Results

## 6.1 Scent of a rewarded mouse attracts other mice and changes the pattern of social interactions

The main goal of the first set of experiments was to test how information about the potential presence of a reward in the environment changes the exploration and social behavior of the tested mice. Briefly, as described in detail in the Material and Methods section 5.7, familiar group of animals was housed in the Eco-HAB system (Figure 6). After the adaptation period two mice were separated to single cages for 24h. One of them was given access to reward (10% sucrose solution) and the other to a neutral stimulus (water). Bedding carrying social scents was collected and presented in two opposite ends of the Eco-HAB territory behind the perforated partitions, so that it did not get spread throughout the rest of the habitat. In the reward (REW) trial, social information about the reward was introduced by the scent from a rewarded familiar mouse. To control for the presence of social odor, scent from the non-rewarded mouse was also placed in the experimental environment. In the control (CTRL) experiments both isolated animals were given access to the neutral stimulus (water). The same cohort of mice was subjected to two rounds of experimental procedures, first to the CTRL and then to REW trial.

Interest in the presented stimuli (approach to odor signaling reward) was measured as a proportion of visits to the Eco-HAB compartments where odors were presented (rewarded vs neutral in the REW trial and neutral vs neutral in the CTRL trial) divided by the same proportion from the last adaptation dark phase (to control for the reward-unrelated individual preferences for visiting space)**.** As attraction to the newly presented odors usually decreases over time to measure how enticing the social reward information is I assessed the persistence in its exploration. To that end, the proportion of visits to Eco-HAB compartments containing the social odors in the second half (6h) of the testing phase was divided by the proportion of visits from the first half of the testing phase (6h, Persistence in odor seeking). During all phases of the experiment mice had unrestricted access to all compartments and could freely explore the Eco-HAB environment. The activity was measured to control for the possibility that the observed responses to social information were, at least partially, due to the changes in locomotor behavior.

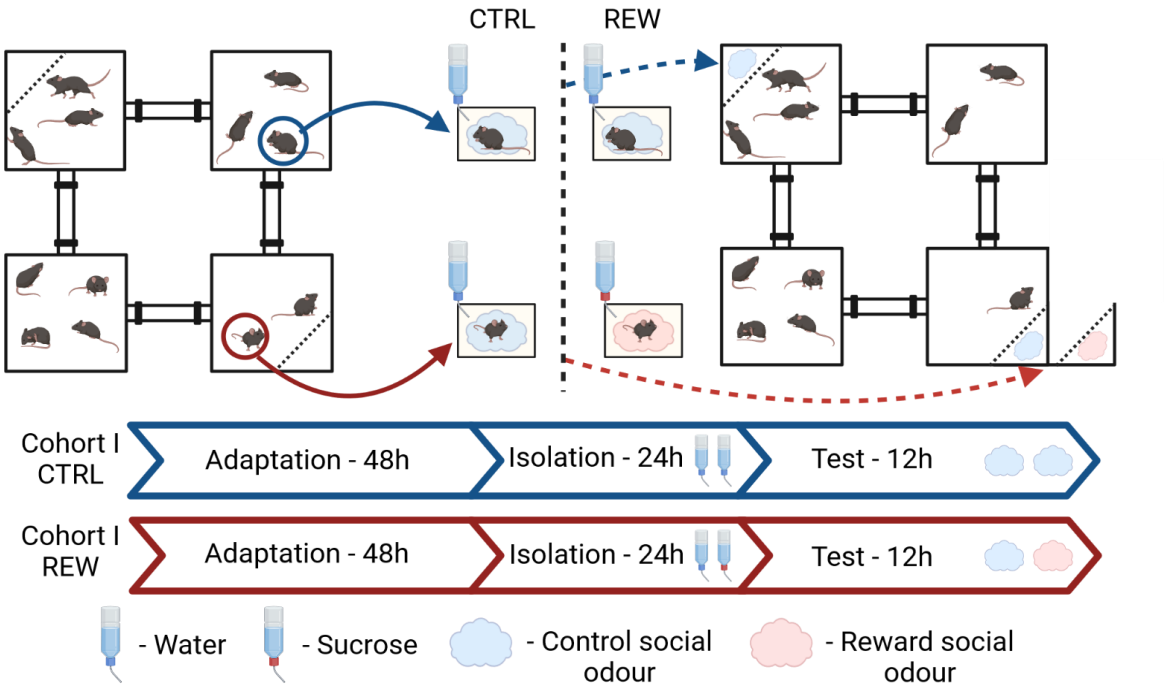


Figure 6. Design of the experiment on social transfer of information conducted in a familiar environment. During the adaptation phase mice had unrestricted access to all Eco-HAB compartments and habituated to the experimental environment. In the next step (isolation phase) 2 randomly selected mice were taken out of the Eco-HAB and placed in the separate cages. In the control condition (CTRL, first trial) each separated animal had access to the bottle with water. In the reward condition (REW, second trial) one from the isolated subjects had access to the bottle with highly rewarding 10% sucrose solution and the other to the bottle with water. In the final phase of the experiment (Test phase) bedding soaked with social scents were collected from the individual cages of the separated animals and presented to the rest of the cohort inhabiting the Eco-HAB and the behavioral response of mice to the stimuli were measured

When bedding from a rewarded mouse was presented in the Eco-HAB animals displayed a strong preference to its scent in relation to the scent of a mouse having access to the neutral stimulus, as opposed to the control condition (both scents came from the mice having access to water) in which they did not prefer any of the presented social scents (Figure 7A, CTRL vs REW as the same cohort of mice was tested twice, paired t-test was used: $t = 3.559$; $p = 0.0061$, both datasets passed the D'Agostino & Pearson normality test CTRL: $K2 = 0.5342$; $p = 0.7656$ REW: $K2 = 2.499$; $p = 0.2866$). Persistence in odor seeking was significantly higher when mice were tested in the REW trial compared to the CTRL trial (Figure 7 B, CTRL vs REW paired t-test: $t = 2.335$; $p = 0.0444$, both datasets passed the D'Agostino & Pearson normality test CTRL: $K2 = 4.868$; $p = 0.0877$ REW: $K2 = 1.58$; $p = 0.453$). Importantly, despite the above mentioned differences, during both the CTRL and REW trials mice showed similar level of activity (Figure 7 C, CTRL vs REW paired t-test,

t = 1.753; p = 0.1134, both datasets passed the D'Agostino & Pearson normality test CTRL: K2 = 4.916; p = 0.856 REW: K2 = 4.729; p = 0.094. Approach to odor signaling reward (Figure 7A) and persistence (Figure 7B) is showed as natural logarithm of the raw values, to improve the readability of results; statistical tests were performed on the non-processed data.

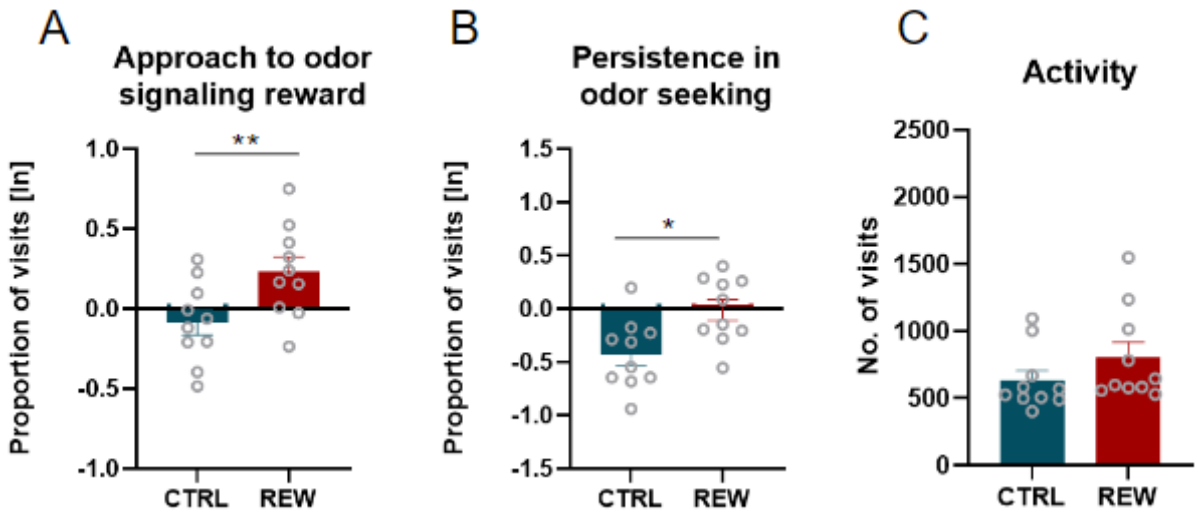


Figure 7. Socially-transferred information about reward attracts mice. A – Approach to odor signaling reward. In the REW trial mice displayed a preference towards visiting the compartment with social scent indicating reward in relation to the scent of a mouse having access to the neutral stimulus. In the CTRL trial animals were equally inclined to approach both social scents. B – Persistence in odor seeking. In the REW trial exploration of the social olfactory cues persisted for the whole testing phase, while in the CTRL trial it diminished over time. C – Locomotor activity during the testing phase of experiment. In both, REW and CTRL trials mice showed similar level of activity.

Introduction of the social information about the reward also influenced social behavior of the tested animals. Namely, it changed the intensity with which animals followed one another through the tubes of the Eco-HAB system (Figure 8A) and the level of in-cohort sociability (Figure 8B). During following episodes one mouse (follower) is closely tracking another (leader). It is noteworthy that following behavior gives access to olfactory cues coming directly from the mouse being followed, which can be an important source of information. In-cohort sociability is based on the time each pair of mice from the tested cohort voluntarily spends together. Thus, this measure is a notable aspect of social bonding.

Presence of the social cues containing information about the reward significantly increased the number of followings as compared to the CTRL trial (Figure 8A, CTRL vs REW paired t-test, t = 4.746; p = 0.0011, both data sets passed the normality test CTRL: K2 = 0.5638; p = 0.7543 REW: K2 = 1.795; p = 0.4076). However, it did not influence the level of in-cohort

sociability, as there were no differences between the CTRL and REW trials (Figure 8B, CTRL vs REW Kolmogorov-Smirnov: D = 0.2; p = 0.3291, both groups passed the D'Agostino & Pearson normality test CTRL: K2=3.222; p = 0.1996 REW: K2 = 0.9165; p = 0.6324).

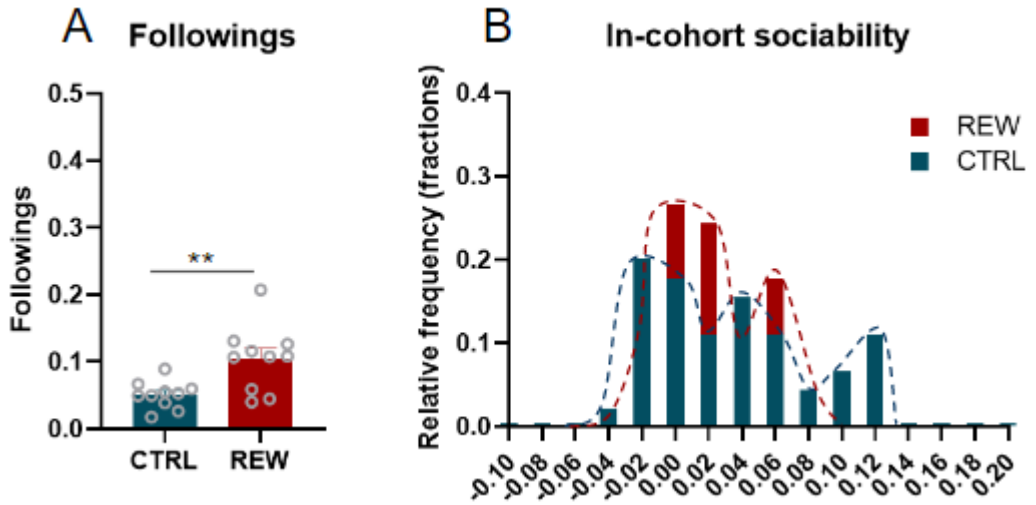


Figure 8. Changes in social behavior in response to introduction of the social cues indicating reward to the testing environment. A – The number of following events normalized to the activity level. Mice followed each other more frequently when information about the reward was presented in the environment. B – In-cohort sociability, a measure of voluntary social bonding, did not change in response to the presence of social information about the reward.

## 6.2 Disrupting synaptic plasticity in the prelimbic cortex impairs response to the scent of a rewarded mouse

The next set of experiments was designed to explore the role of the prelimbic part of the prefrontal cortex in the previously observed effects. The experiments were performed as the within subject trials, as described in the Materials and Methods section 5.7 and presented in Figure 9. Specifically, mice were tested two times in accordance with the protocol in which after the period of adaptation two conspecifics were isolated. As previously, one of them was exposed to the reward and the other to neutral stimulus. Before the second trial, synaptic plasticity in the PL part of the PFC was affected by stereotaxic injection of TIMP1-loaded nanoparticles. After 5 days of recovery mice were re-tested under the same experimental conditions. Control cohort of mice was tested under the same protocol but injected with nanoparticles loaded with BSA. The tested behaviors were identical to the ones reported in the previous section 6.1.

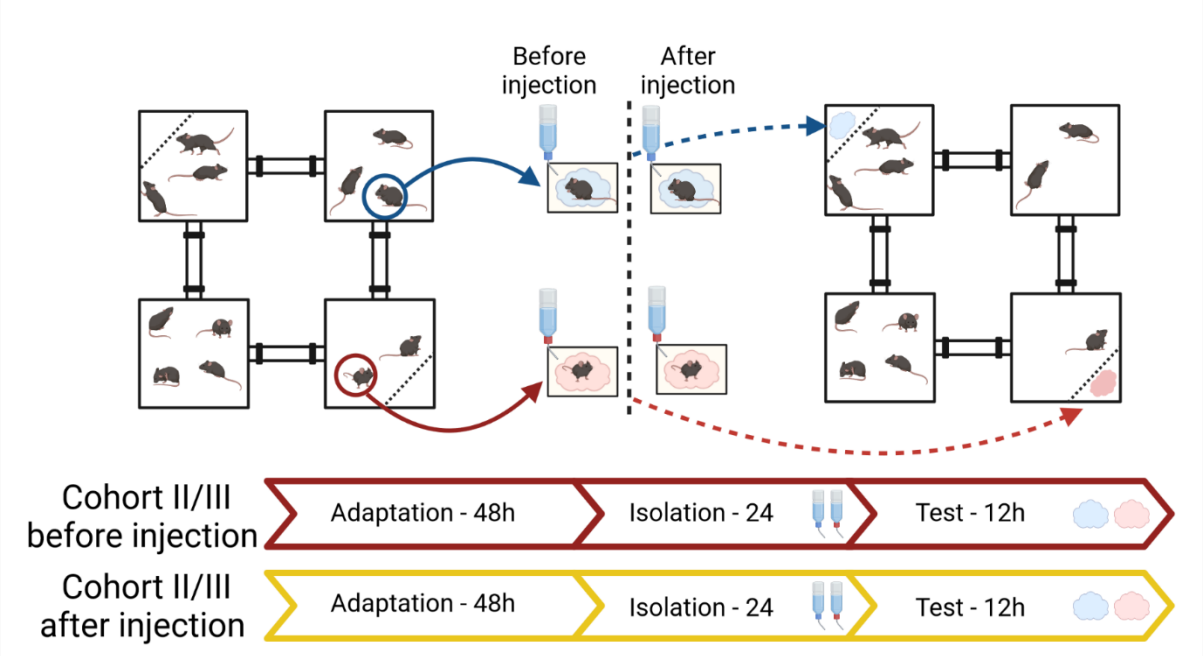


Figure 9. Design of the experiment on the influence of TIMP1-induced disruption of neuronal plasticity in the PL on social transfer of information in a familiar environment. The behavioral experiments were similar to the REW trial described in Figure 6. However, this time procedures were conducted before, and then again after the injection of the nanoparticles loaded with either BSA (vehicle) or TIMP1 into the PL of the tested animals.

In both tested groups (vehicle and TIMP1) approach to the odor signaling reward after the surgical injection of the nanoparticles into the PL was not significantly different when compared to the same observation from the naïve trial (before surgery) (Figure 10A, both cohorts were tested twice and results were compared within subject REW vs REW – NP-BSA: Wilcoxon matched-pairs signed rank test, W = -16; p = 0.3125, only the data from REW trial passed the D'Agostino & Pearson normality test, REW: K2 = 0.0562; p = 0.9723 REW – NP-BSA: K2 = 9.168; p = 0.0102; Figure 10B, both cohorts were tested twice and the results were compared within subject REW vs REW – NP-TIMP1: Paired t test, p = 0.3566, t = 0.9666, tested cohort passed the D'Agostino & Pearson normality test in both trials, REW:K2 = 1.777, p = 0.4112; REW – NP-TIMP1:K2 = 0.1008, p = 0.9509). However, persistence in odor seeking significantly decreased after injection of the nanoparticles loaded with TIMP1. The effect was absent in the vehicle (BSA) condition (Figure 10C, both cohorts were tested twice and results were compared within subject REW vs REW – NP-BSA: Paired t test was used, t = 1.556; p = 0.1637, results passed the D'Agostino & Pearson normality test in both trials, REW: K2 = 3.186, p = 0.2033 REW – NP-BSA:K2 = 4.983, p = 0.0828; Figure 10D, both cohorts were tested twice and results were compared within subject REW vs REW – NP-TIMP1: Wilcoxon matched-pairs signed rank test W = -52, p = 0.0186, tested cohort passed

the D'Agostino & Pearson normality test only in REW – NP-TIMP1 trial, REW:K2 = 3.186; p<0.0001, REW – NP-TIMP1: K2 = 1.213, p = 0.5452). As previously, approach to the odor signaling reward (Figure 10A, 10B) and persistence in odor seeking (Figure 10C, 10D) are showed as natural logarithm of the raw values.

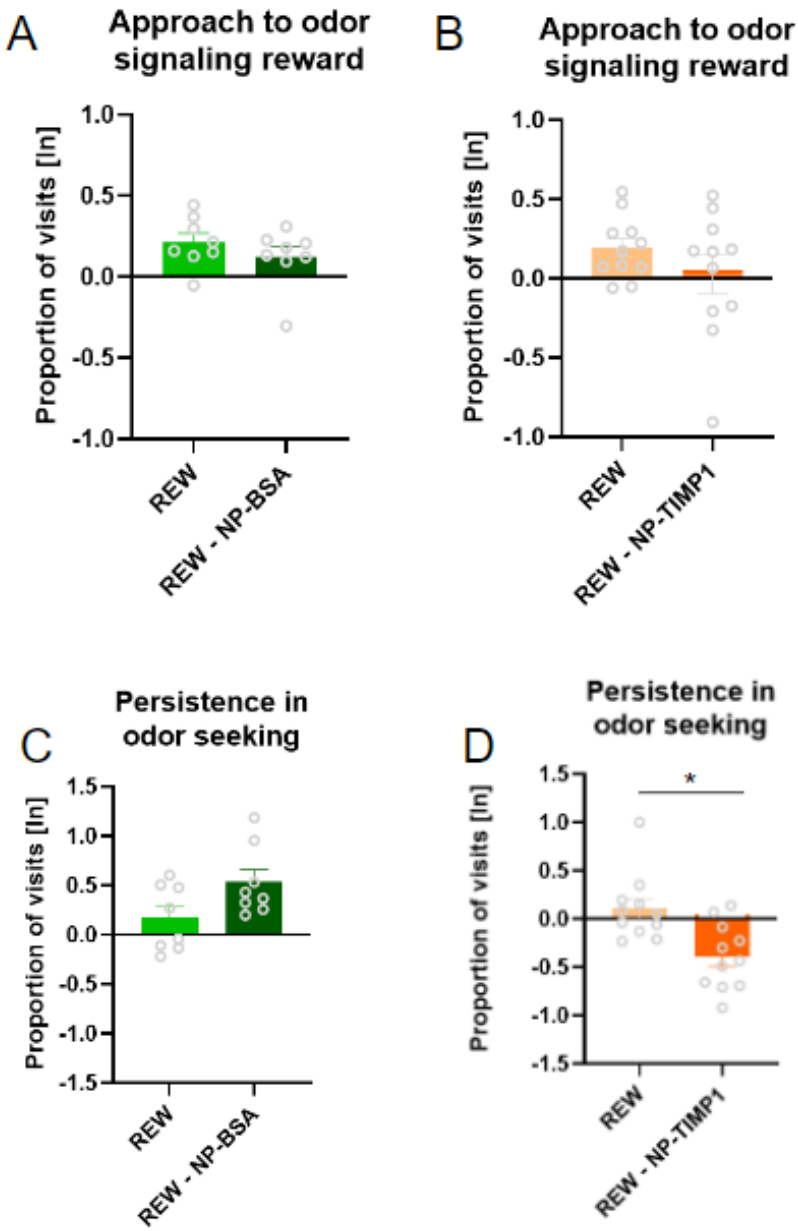


Figure 10. Effects of synaptic plasticity disruption in the prelimbic part of the prefrontal cortex on behavior affected by the socially-transferred information about reward. A –Approach to odor signaling reward in control trial, no difference was observed between the naïve condition and re-testing done after surgery. B – Approach to odor signaling reward in a trial where nanoparticles were loaded with TIMP1, also no significant difference was observed. C – Persistence in odor seeking in the NP-BSA trial, injection of nanoparticles did not significantly affect this behavior. D – Persistence in odor seeking in NP-TIMP 1 trial, after surgery this behavior decreased significantly.

Moreover, disruption of synaptic plasticity induced by the injection of TIMP1-loaded nanoparticles significantly decreased the number of followings. Such effect was not observed in the BSA group (Figure 11A, both cohorts were tested twice and results were compared within subject REW vs REW – NP-BSA: Wilcoxon matched-pairs signed rank test, W = 0; p>0.9999, results passed the D'Agostino & Pearson normality test only in REW – NP-BSA trial, REW:K2 = 7.842; p = 0.0198; REW – NP-BSA:K2 = 1.97; p = 0.3734; Figure 11B, both cohorts were tested twice and results were compared within subject REW vs REW – TIMP1: Wilcoxon matched-pairs signed rank test, p = 0.0010, W = -66, results passed the normality test only in REW trial, REW:K2 = 0.8086, p = 0.6675; REW – NP-TIMP1:K2 = 13.14, p = 0.0014). Notably, in both tested groups mice showed significantly higher in-cohort sociability after surgery (Figure 11C, both cohorts were tested twice and results were compared within subject REW vs REW – NP-BSA: Kolmogorov-Smirnov D = 0.5; p = 0.0018, both datasets passed the D'Agostino & Pearson normality test REW: K2 = 1.348; p = 0.5097 REW – NP-BSA: K2 = 2.481; p = 0.2893; Figure 11D, both cohorts were tested twice and results were compared within subject REW vs REW – NP-TIMP1: Kolmogorov-Smirnov D = 0.3091; p = 0.0104, both datasets passed the D'Agostino & Pearson normality test REW: K2 = 0.8028; p = 0.6694 REW – NP-TIMP1: K2 = 1.333;p = 0.5135).

Additionally, locomotor activity was measured to control for its potential influence on the observed changes in social learning and other social behaviors. The results show that neither TIMP1, nor vehicle injections changed the activity of the tested animals, thus excluding the possibility that changed activity was impacting the reported effects of social learning (Figure 12A, both cohorts were tested twice and results were compared within subject REW vs REW – NP-BSA: Wilcoxon matched-pairs signed rank test, W = 2; p = 0.9453, only the REW data passed the D'Agostino & Pearson normality test, REW:K2 = 1.545; p = 0.4619, REW – NP-BSA:K28.34; p = 0.0155; Figure 12B, both cohorts were tested twice and results were compared within subject REW vs REW – NP-TIMP1: Paired t test, t = 0.143; p = 0.8891, in both trials data passed the D'Agostino & Pearson normality test, REW :K2 = 1.482; p = 0.4767, REW– NP-TIMP1 :K2 = 5.78; p = 0.0556).

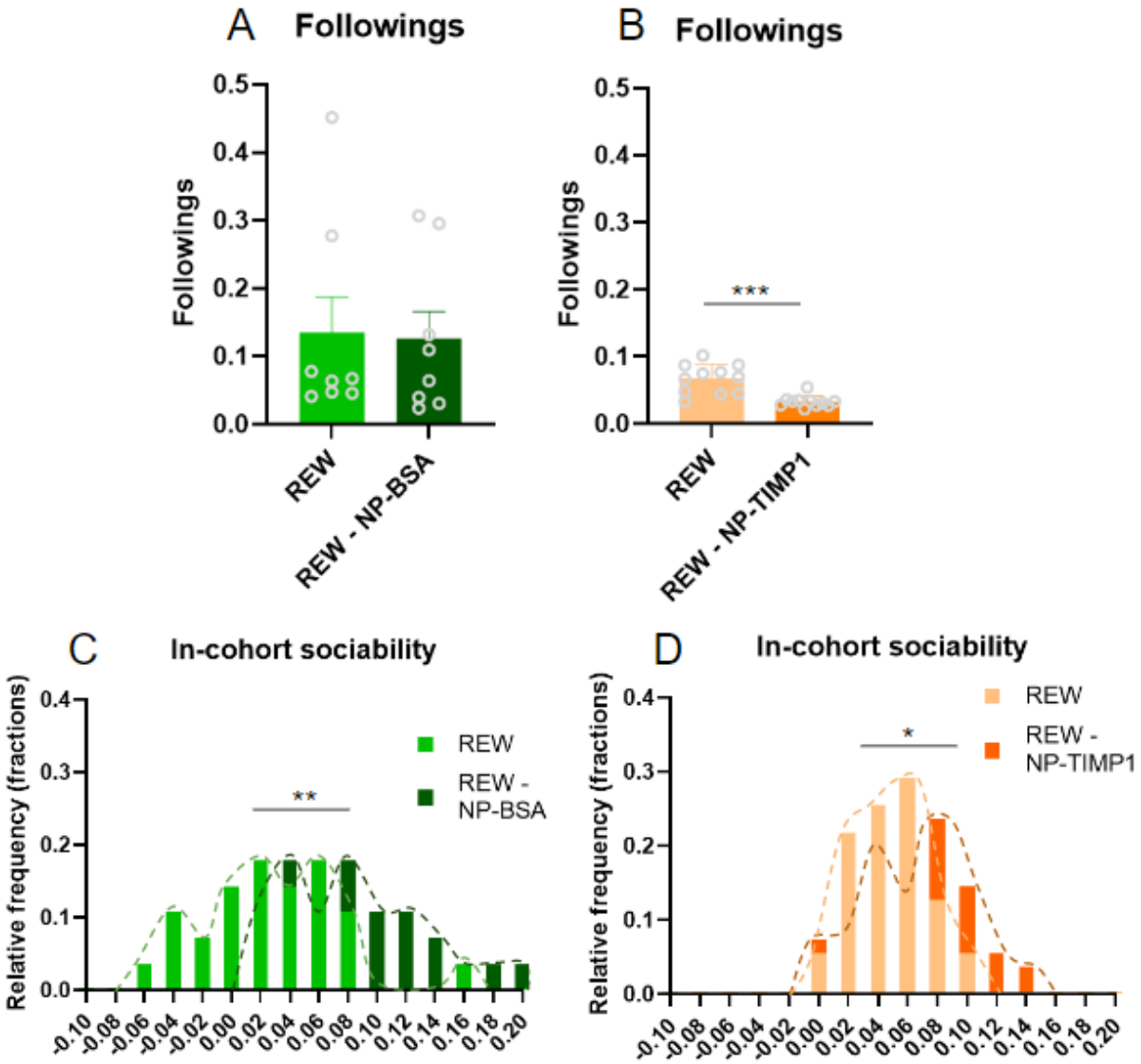


Figure 11. Effects of synaptic plasticity disruption in the prelimbic part of the prefrontal cortex on social behavior affected by the socially-transferred information about reward. A – There were no changes in followings after injection of the nanoparticles loaded with BSA. B – Changes in followings after injection of nanoparticles loaded with TIMP1 – the level of following decreased. C – Changes in in-cohort sociability after injection of the BSA-loaded nanoparticles, distribution was significantly shifted to the right, indicating higher level of in-cohort sociability in comparison to the first trial, D – Changes in in-cohort sociability after injection of TIMP1-loaded nanoparticles, as in the control group, in-cohort sociability increased.

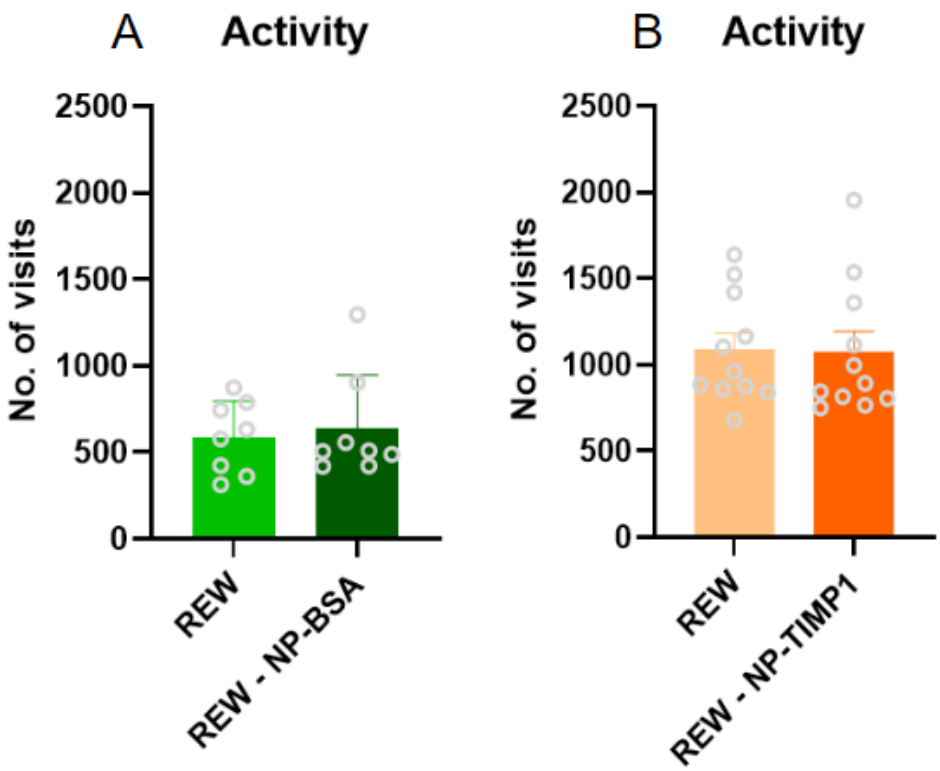


Figure 12. Activity was not affected by the injections of nanoparticles containing, either TIMP1, nor BSA (vehicle). A – Activity of the control (BSA) group. B – Activity of the TIMP1-treated group.

## 6.3 Social olfactory information helps to find the reward in a novel environment, which requires an intact prelimbic cortex

Previously described experiments were conducted in the environment familiar to the tested mice. To investigate the role of social information about the reward in the novel, unfamiliar environment, another set of experiments using two different Eco-HAB systems was performed (Figure 13). The detailed design of the experiments was described in the Material and methods section 5.8. Briefly, the experiment started with all animals being housed in the Eco-HAB I, where adaptation phase took place (Figure 13 Eco-HAB I). During the adaptation period mice habituated to the environment and learned how to drink from the bottles whose tips were placed in a short tube equipped with an RFID antenna. This design allowed for (a) measuring individual drinking behavior of the subjects and (b) limiting access to the bottle to only one animal at the time. In the second experimental phase (isolation) two mice from the tested cohort, referred to as scouts, were moved from Eco-HAB I to novel Eco-HAB environment (Figure 13 Eco-HAB II). During that phase scouts explored the Eco-HAB II, where - as in the Eco-HAB I - additional bottles were accessible in the corners of the two

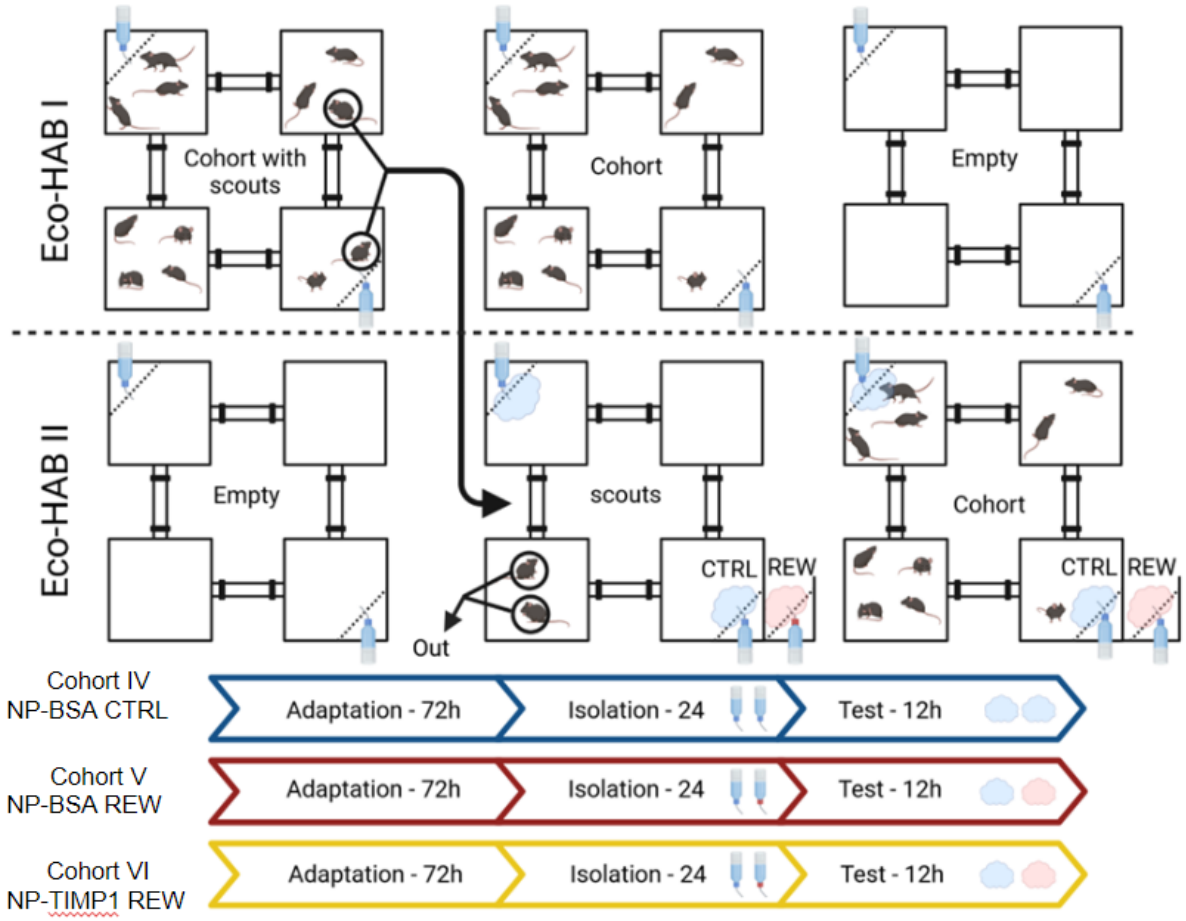


Figure 13. Design of the experiment on the influence of TIMP-induced disruption of neuronal plasticity in the PL on social transfer of information in a novel, unfamiliar environment. At first all mice were put in one Eco-HAB system (Eco-HAB I). In the following phase (Isolation) two scout mice were taken out of the Eco-HAB I and moved to the new Eco-HAB II. In the new apparatus scout animals had access to either two bottles filled with water (in the control condition, CTRL), or to one bottle with water and one bottle with 10% sucrose solution (in the reward condition, REW). The bottles were always placed on the opposite sides of the territory, as was during the adaptation phase. In the process of the exploration of the environment and drinking the scouts have left social scents in the soaked bedding near the tips of the bottles. After the Isolation phase, scouts were removed from the experiment, bottles from Eco-HAB II were washed and refilled with tap water. However, the bedding with social scents was left untouched. Then, the rest of the cohort from the Eco-HAB I was moved to Eco-HAB II and their behavior in response to social cues left by the scouts was measured.

opposite compartments for 24h. As a result of inhabiting the new territory scout animals left social cues (the scents spread through the compartments). On the next day after isolation phase the scouts were removed from the Eco-HAB II and the rest of the cohort was moved from the Eco-HAB I to the Eco-HAB II. In the REW trial scouts had access to the highly rewarding 10% sucrose solution in one of the presented bottles and water in the other. The CTRL group's scouts had access to two water bottles. In this set of experiments nanoparticles containing either

TIMP1 or BSA were injected 5 days before the start of the experiments and the between-group comparisons were conducted to analyze the data.

The ability to use social cues in searching for potential reward in the novel environment was measured as relative time spent drinking from the bottle preferred by the scouts during the isolation phase within the 1$^{st}$ hour of testing (Figure 14A). Disruption of synaptic plasticity in the PL by the injection of TIMP1 decreased the scout-favored bottle preference when compared to the BSA-treated group exposed to social cues indicating the reward. Notably, TIMP1 group level of performance did not differ from the BSA-treated animals from the CTRL group, where scents were left by the scouts only exposed to water. It is noteworthy, that the difference between the REW – NP-BSA and the CTRL – NP-BSA in preference to the bottle preferred by the scouts also was not significant (Figure 14A REW – NP-TIMP1 vs REW – NP-BSA: Unpaired t test, t = 2.795; p = 0.0130, REW – NP-TIMP1 vs CTRL – NP-BSA: Unpaired t test, t = 1.072; p = 0.3005, REW – NP-BSA vs CTRL – NP-BSA: Unpaired t test, t = 1.246, p = 0.2297, all the data sets passed the D'Agostino & Pearson normality test, REW – NP-TIMP1:K2 = 0.2488; p = 0.8830, REW – NP-BSA: K2 = 2.81; p = 0.2454, CTRL-NP-BSA: K2 = 2.322; p = 0.3132). Persistence in reward seeking, (Figure 14B) in the REW NP – TIMP1 group was lower than in both control groups. Furthermore, it was higher in the REW NP-BSA than in CTRL NP-BSA group, indicating that social cues about the reward increased the tenacity of bottle-specific exploration (Figure 14B, REW NP-TIMP1 vs REW NP-BSA: Unpaired t test, t = 3.933;p = 0.0012, REW NP-TIMP1 vs CTRL NP-BSA: Unpaired t test, t = 3.437; p = 0.0037, REW NP-BSA vs CTRL NP-BSA: Unpaired t test, t = 2.651; p = 0.0168, all data sets passed the D'Agostino & Pearson normality tests, CTRL NP-BSA:K2 = 1.503; p = 0.4717, REW NP-BSA:K2 = 2.642; p = 0.2669, REW NP-TIMP1:K2 = 2.969; p = 0.2266).

Similarly to the experiments in the familiar environment, social behavior was also impacted by the presence of social cues about the reward. Specifically, following of mice in the Eco-HAB was higher in REW NP-BSA group than in CTRL NP-BSA group. Disruption of the PL plasticity lead to the following in the REW NP-TIMP1 group being lower than in the REW NP-BSA group, and it did not differ from the level of CTRL NP-BSA group. Similarly, in-cohort sociability representing the time animals voluntarily spend together, was lower in REW NP-BSA group than in the REW NP-TIMP1 and CTRL NP-BSA.

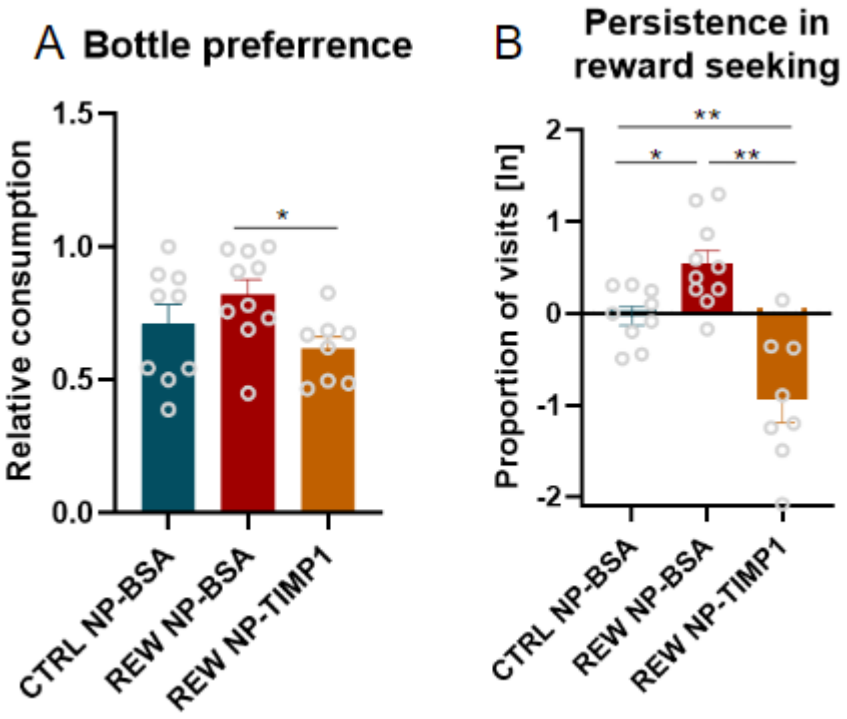


Figure 14. Effects of social information about the reward in the new territory on the behaviors related to exploration of the environment are disrupted by the TIMP1 injection into the PL. A – Bottle preference in the new environment, NP-TIMP1 injection into the PL decreased the consumption from the preferred bottle as compared to the REW NP-BSA group, to the level characterizing the CTRL NP-BSA; difference between the CTRL NP-BSA and REW NP-BSA was not significant. B – Persistence in reward seeking decreased in the group injected with the NP-TIMP1, when compared to REW NP-BSA and CTRL NP-BSA groups. Also, it was higher in the REW NP-BSA than in the CTRL NP-BSA group.

Thus again, the effect of social information about the reward impacting this aspect of social behavior was disrupted by the TIMP1 injection (Figure 15A, REW NP-BSA vs. CTRL NP-BSA: Unpaired t test, $p = 0.0168$, $t = 2.65$; REW NP-BSA vs. REW NP-TIMP1: Unpaired t test, $p = 0.0007$, $t = 4.198$, CTRL NP-BSA vs REW NP-TIMP1 Unpaired t test, $p = 0.056$, $t = 2.071$, all data sets passed the D'Agostino & Pearson normality test CTRL NP-BSA: $K2 = 3.204$, $p = 0.2015$; REW NP-BSA:$K2 = 1.133$, $p = 0.5675$; REW NP-TIMP1:$K2 = 2.188$, $p = 0.3349$; Figure 15B REW NP-BSA vs REW NP-TIMP1 $p<0.0001$, Kolmogorov-Smirnov $D = 0.8667$, REW NP-BSA vs CTRL NP-BSA $p<0.0001$, Kolmogorov-Smirnov $D = 0.65$, CTRL NP-BSA vs REW NP-TIMP1 $p<0.0772$, Kolmogorov-Smirnov $D = 0.3214$, the data for the REW NP-TIMP1 group did not pass the D'Agostino & Pearson normality test, CTRL NP-BSA: $K2 = 3.864$; $p = 0.1449$, REW NP-BSA: $K2 = 3.288$; $p = 0.1933$, REW NP-TIMP1: $K2 = 7.48$, $p = 0.0238$).

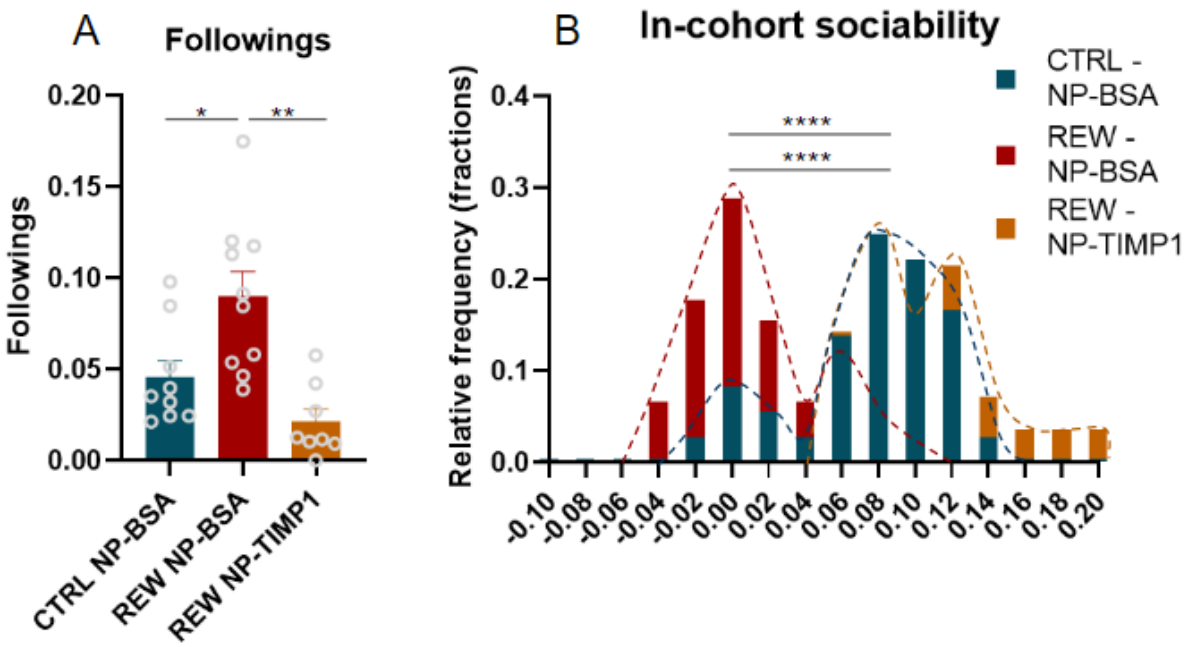


Figure 15. Effects of TIMP1 treatment in the PL on social behavior in novel environment with social cues about the reward. A – Following among mice exposed to the social cues about the reward (REW NP-BSA) was higher than in mice from the control group (CTRL NP-BSA). This effect was absent after the injection of NP-TIMP1 into the PL (REW NP-TIMP1). No difference was found between the CTRL NP-BSA and the REW NP-TIMP1 groups. B - In-cohort sociability decreased in mice exposed to social cues about the reward (REW NP-BSA), as compared with the control group (CTRL NP-BSA). TIMP1 injections in the PL abolished this effect; the animals showed the level of in-cohort sociability lower than REW NP-BSA group and did not differ from the CTRL NP-BSA group.

Notably, TIMP1 injections into the PL disrupted also the level of locomotor activity. Specifically, activity measured in the REW NP-TIMP1 group was lower than in both CTRL NP-BSA and REW NP-BSA groups, which did not differ from one another in this parameter (Figure 16 REW NP-TIMP1 vs CTRL NP-BSA: Unpaired t test, $p = 0.1570$, $t = 1.481$; REW NP-TIMP1 vs. CTRL NP-BSA: Unpaired t test, $p = 0.0004$, $t = 4.1481$; REW NP-TIMP1 vs REW NP-BSA: Unpaired t test, $p = 0.0003$, $t = 4.4524$, all data sets passed the D'Agostino & Pearson normality test CTRL NP-BSA:$K2 = 1.03$, $p = 0.5975$; REW NP-BSA:$K2 = 1.105$, $p = 0.5756$; REW NP-TIMP1:$K2 = 4.497$, $p = 0.1056$). This result requires further studies since it is feasible that the effects of TIMP1 on social behavior in novel environment may be, at least to some degree, attributable to the disrupted locomotor activity.

To exclude the possibility that the observed impairments of social learning in the novel environment caused by the TIMP1 treatment might have been a result of the disrupted reward propensity, REW NP-TIMP1 and REW NP-BSA groups were additionally subjected to the reward propensity test (Fig. 17, see the Materials and methods section 5.9. When Eco-HAB

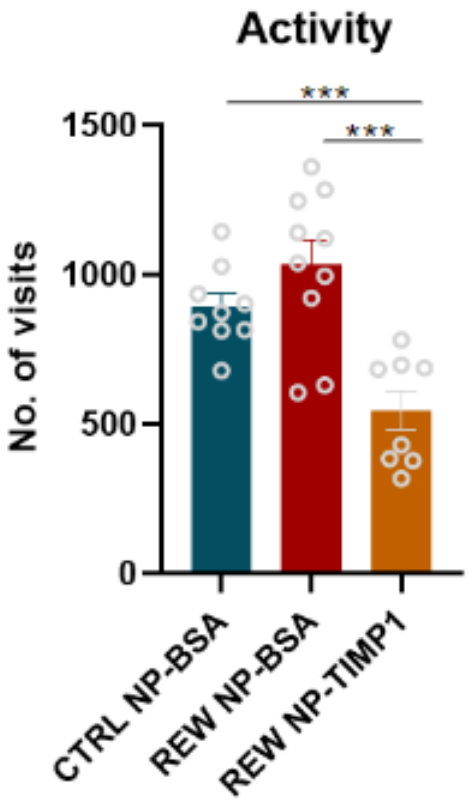


Figure 16. Activity in novel environment was affected by the TIMP1 injections into the PL. NP-TIMP1group showed the reduced exploration of the environment, as compared to CTRL NP-BSA and REW NP-BSA, difference between CTRL NP-BSA and REW NP-BSA was not significant.

testing of social learning was concluded the groups were placed in the new Eco-HAB experiment with access to 10% sucrose solution and water. The consumption of the 10% sucrose solution in the REW NP-TIMP1 and REW NP-BSA did not differ, thus animals from both groups displayed similar reward propensity (Figure 18 REW NP-TIMP1 vs REW NP-BSA: Unpaired t-test, $p = 0.6403$, $t = 0.477$, all results passed the D'Agostino & Pearson normality test, REW NP-BSA:K2 = 0.4368, $p = 0.8038$; REW NP-TIMP1:K2 = 4.124, $p = 0.1272$).

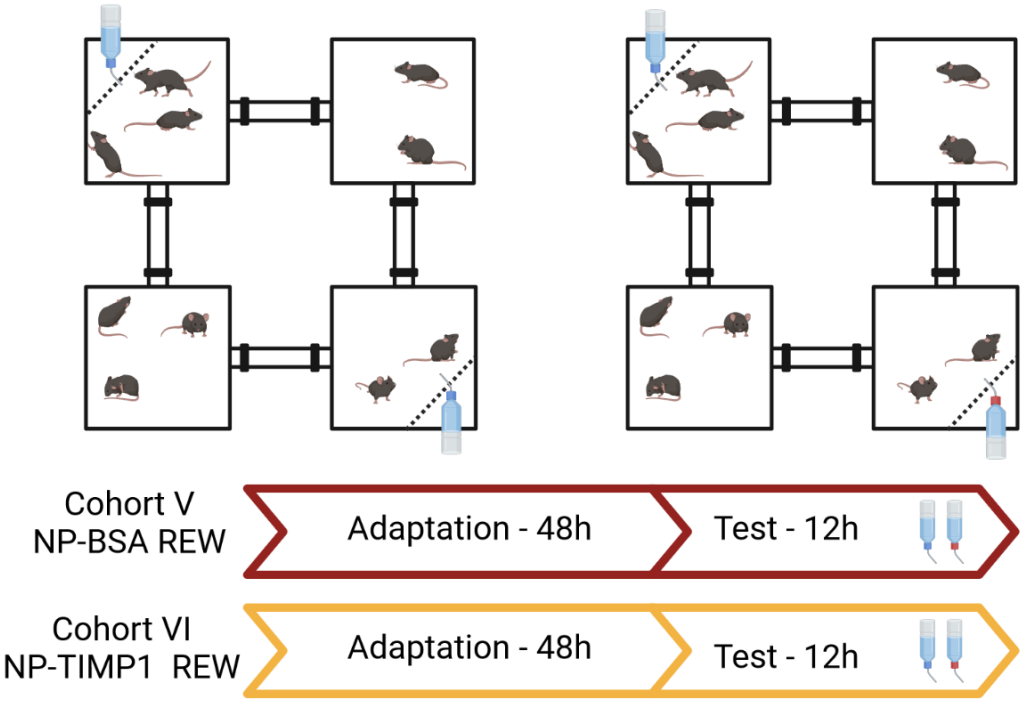


Figure 17. Design of the reward preference test. Mice were tested in the standard Eco-HAB environment with bottles equipped with the RFID antennas near the bottle tips. During the adaptation phase mice habituated to the experimental environment and had unlimited access to the bottles, which were at the time filled with water. Then, at the beginning of the Test phase both bottles were washed and one of them was filled with 10% sucrose solution. We measured the time of drinking from each bottle.

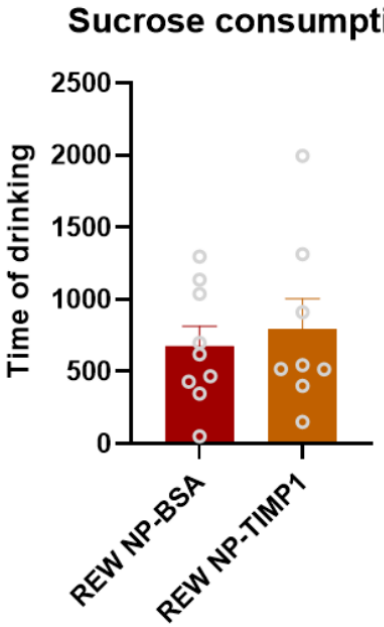


Figure 18. Consumption of 10% sucrose solution tested in the free-access in Eco-HAB experiment. Time spent drinking from the bottle with sucrose was not affected by the injection of REW NP-TIMP1 into the PL in comparison to the REW NP-BSA.

## 6.4 Mice form stable social networks; position in the social network affects responding to social information about the reward

One of the goals of the presented work was to examine the effects of socially transmitted information about the reward on social structure. The olfactory cues from the familiar individuals from the cohort play a key role in getting information about the pertinent factors in the environment. To measure the social networks within the groups and their relation to social learning I assessed how animals follow one another within the Eco-HAB territory. Following is a spontaneously occurring natural social behavior and due to its dynamic characteristics can be used to build social network graphs, similar to the ones used in human and primate research (McCowan et al., 2022; Redhead and Power, 2022). In such graphs the nodes represent individual subjects from the tested group and the edges represent the number and direction of following between pairs of mice.

I conducted the experiment to examine the link between the neuronal plasticity in the PL and social networks (Figure 19, please see the detailed description in Materials and methods section 5.10). Mice were tested for 4 days in Eco-HAB. Then they were subjected to the injections of TIMP1 into the PL and retested after 5 days of recovery, as in the previously described experiments.

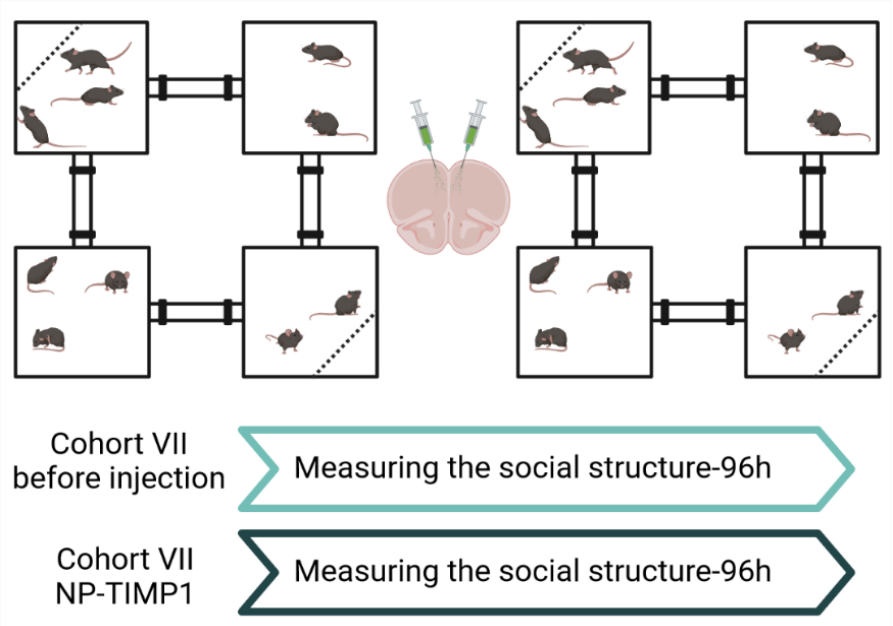


Figure 19. Design of the experiment measuring formation and stabilization of social structure in the Eco-HAB. Subjects were put into the Eco-HAB and were allowed to freely explore the testing environment without any

manipulation for 96h. In the course of the experiment mice performed multiple social interactions and established social hierarchy. After the first trial, the subjects were injected with NP-TIMP1 into the PL and after 5 days retested under the same conditions allowing me to study influence of such manipulation on social behavior and group structure.

We observed that non-treated, naïve mice (cohort VII, Figure 20A, 20C) formed gradually stabilizing social network over days. Specifically, as the social network represented by the distribution of following behavior differed between days 1 and 2, as well as 2 and 3, it stabilized between days 3 and 4 (Figure 20A, 20C – different representation of the same data, day 1 vs day 2: Kolmogorov–Smirnov test, $D = 0.6515$, $p < 0.0001$; day 2 vs day 3: Kolmogorov–Smirnov test, $D = 0.1742$, $p = 0.0142$; day 3 vs day 4: Kolmogorov–Smirnov test, $D = 0.1136$, $p = 0.2128$). At the same time, animals injected with NP-TIMP1 into the PL (Figure 20B, 20D) did not show this pattern of progressive stabilization of the social network. Instead, distribution of the following behavior and the resulting network did not differ between day 1 and 2, than differed between day 2 and 3, and did not differ again between days 3 and 4. Additionally, the histograms of the following behavior of the TIMP1-treated mice illustrate the notable variability of this behavior in the subsequent days of the experiment relative to the naïve animals. (Figure 20B, 20D – different representation of the same data, day 1 vs day 2: Kolmogorov–Smirnov test, $D = 0.0714$, $p = 0.3089$; day 2 vs day 3: Kolmogorov–Smirnov test, $D = 0.1142$, $p = 0.0417$; day 3 vs day 4: Kolmogorov–Smirnov test, $D = 0.1095$, $p = 0.0584$). Thus, TIMP1 caused the disruption of the pattern observed in the control animals, where network continuously and consequently settled into a stable state.

To examine the relationship between the place individual animals occupy within the social network and their dominance status another experiment was performed, where following was correlated with social dominance measured with a used of the U-tube test (Figure 21, please see the detailed description in Materials and methods section 5.11). Mice were housed in the Eco-HAB for 10 days with no modifications to the testing environment or external stimuli being used. After this period, during which social group was consolidated, U-tube test was performed and winning score was calculated. The subjects were tested in pairs; mice from each pair were placed at the entrances, at the opposite sides of the u-shaped tube. Then animals were allowed to interact in the apparatus, until one animal pushed the other out of the tube. A mouse who pushed the partner out of the tube was declared a winner of a given bout. Then I correlated to the level of following behavior from the last dark phase of the Eco-HAB experiment (directly preceding the dominance measurement) with the winning scores.

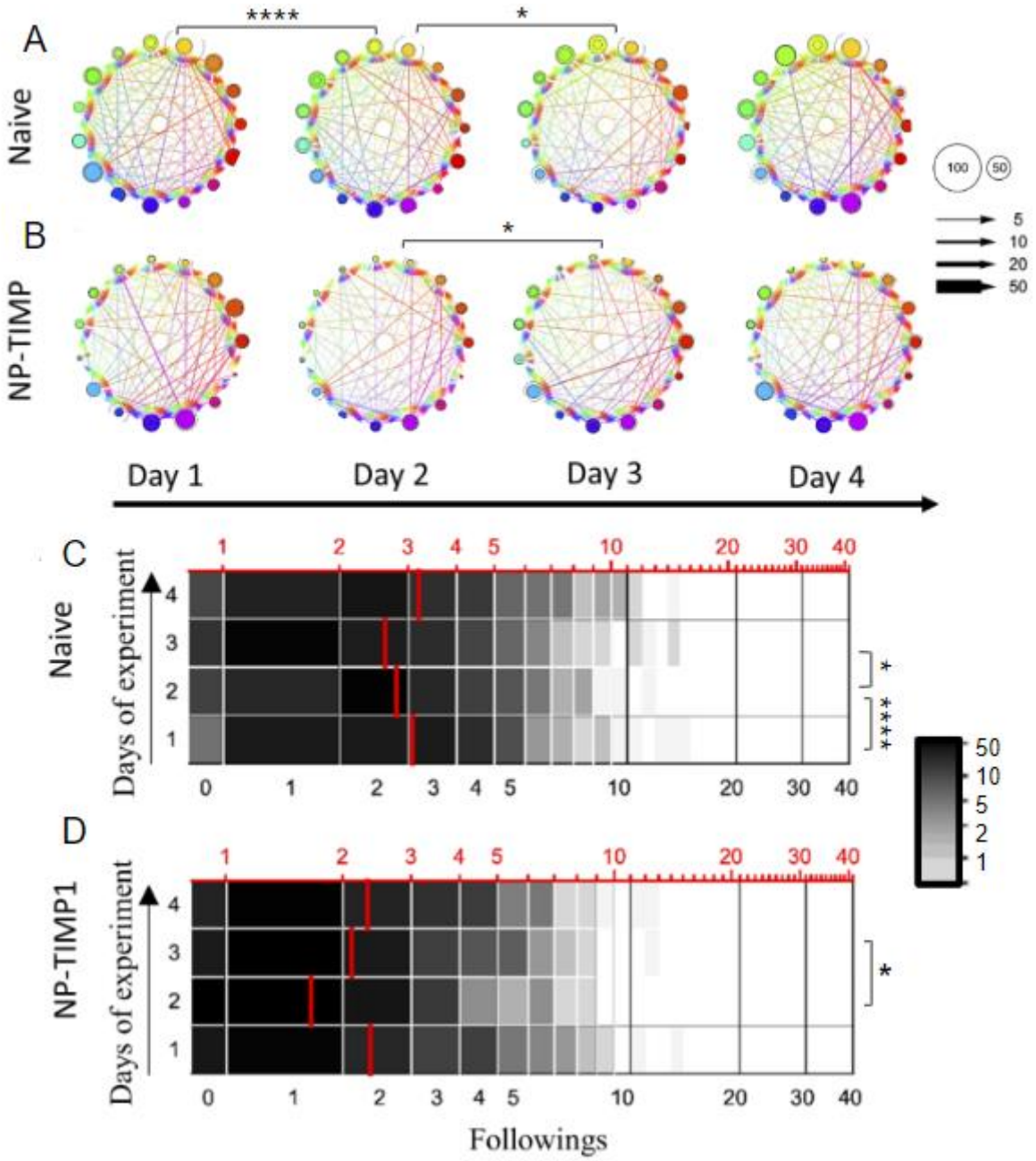


Figure 20. Observation of the social network in the naïve animals shows that it gradually stabilizes over days and social structure stops fluctuating between days 3 and 4 (A, C). The same cohort was then subjected to the injection of TIMP1-carrying NPs into the PL and reintroduced to the Eco-HAB environment for another 4 days. In the TIMP1-treated animals the gradual pattern of social network stabilization is disrupted (B, D). The social network graphs and the respective horizontal histograms of the following (A, B, corresponding to C,D). Pattern of followings between individuals form group's social network represented as a weighted, directed graph with nodes corresponding to individual mice and edges to interactions between them. Different colors represent the followings of each individual mouse. The radius of the colored circle at a given node is proportional to the number of followings performed by the corresponding mouse, while the radius of the dashed circle is proportional to the number of leadings performed by that mouse. The arrows are directed from a follower to a leader; the thickness of an arrow is proportional to the number of followings a given follower performed after a given leader. Histogram segments (C, D) correspond to the distribution of the number of following events in all

pairs of mice within cohort VII. in the subsequent dark phases of the experiment (1-4). Subsequent days of the experiment correspond to respective rows, from bottom to top (pointed on left y-axis). Rectangles running from left to right reflect the number of followings. The intensity of the shading represents the number of occurrences of a given number of followings in all pairs of mice. Additionally, the mean number of followings for all pairs of mice during a given experimental phase, calculated for this distribution, is marked as a red line at the position corresponding to the red scale at the upper edge of the plot.

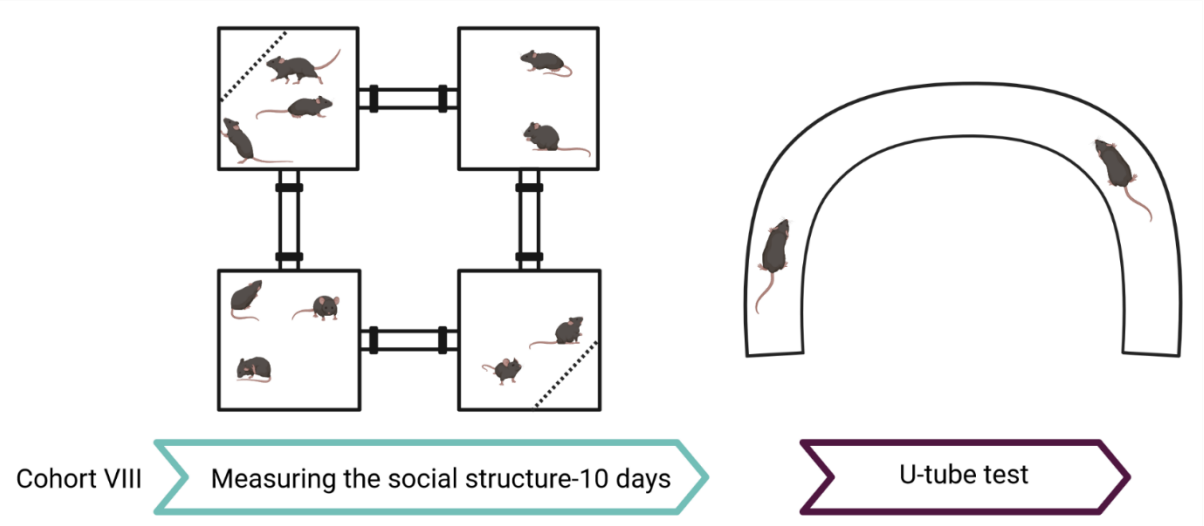


Figure 21. Social dominance tests. Mice were put in the Eco-HAB for 10 days and during that time the formation and stabilization of the social structure was measured. The procedure was followed by a classical dominance U-tube test. The number of wins was recorded as a dominance score.

Data analysis revealed a positive correlation between the winning score in the U-tube test and the number of followings for individual mice (Figure 22, $R2 = 0.3363$, $p = 0.0481$). The result suggests that social dominance may correspond to the place animal occupies within the social network formed by the group.

To further investigate the effects of the socially-transferred information about the reward on social structure, I calculated the following behavior from the experiment performed in the familiar environment and based on that data constructed the social networks (cohort I, experiment described in the Materials and methods section 5.7 and Figure 6). To that end, the level of following from the dark phase preceding the introduction of the social olfactory cues (baseline, marked in the histogram as b) was compared with the level of following from the Test phase (test, marked in the histogram as t), when the social cues indicating water (Control cohort 1), or water and reward (Reward cohort 1) were presented in the environment. No changes in the distribution of the following or social network were

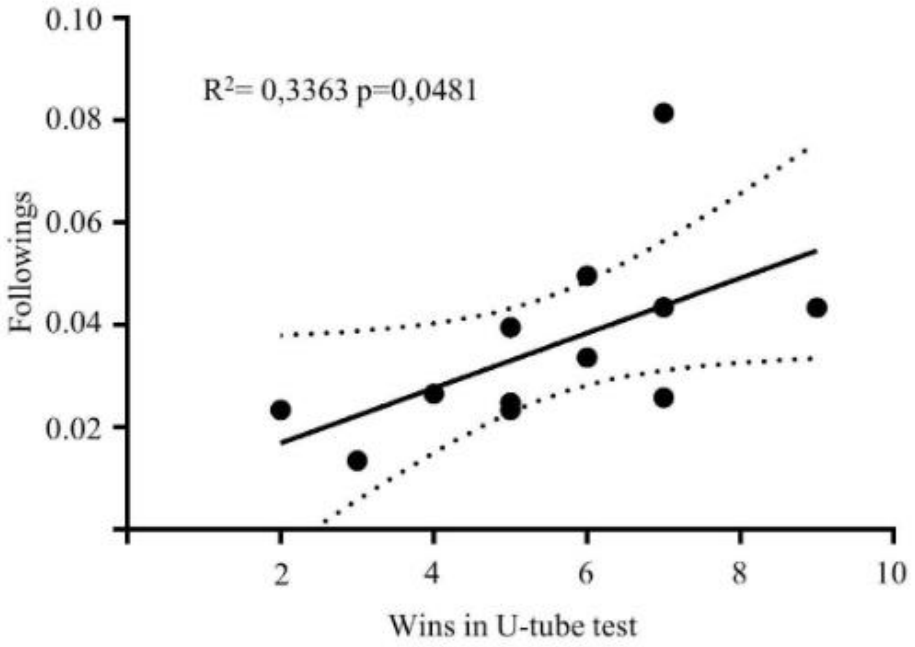


Figure 22. Number of followings performed by the individual mice corresponds with their social status. Positive correlation between the number of followings performed in the Eco-HAB experiment and the win scores from the U-tube social dominance test.

observed in the Control group, where social cues came from the conspecifics consuming water (Figure 23 A,C – different representation of the same data, baseline vs test: Mann-Whitney U test, $p = 0.1945$, all data sets passed the D'Agostino & Pearson normality test, baseline: $K2 = 2.550$, $p = 0.2795$; test:$K2 = 0.5638$ $p = 0.7543$). At the same time, I observed an increase in the following behavior in the Test phase in the reward condition, that is in response to the placement of social cues about the reward within the territory. The same increase was represented by the changes in the social network as illustrated by the bigger sizes of some of its nodes and the thicker edges (Figure 23 B,D – different representation of the same data, baseline vs test: Mann-Whitney U test, $p < 0.0001$, only the data from the Test phase passed the D'Agostino & Pearson normality test, baseline:$K2 = 7.647$, $p = 0.0219$; test:$K2 = 1.795$, $p = 0.4076$). It is noteworthy that the increase in the following observed in the Reward trial (Figure 23 Reward cohort 1) was not homogenous, as illustrated by the social network, in which some nodes grew more notably than other, showing that some mice intensify their following behavior more notably than others.

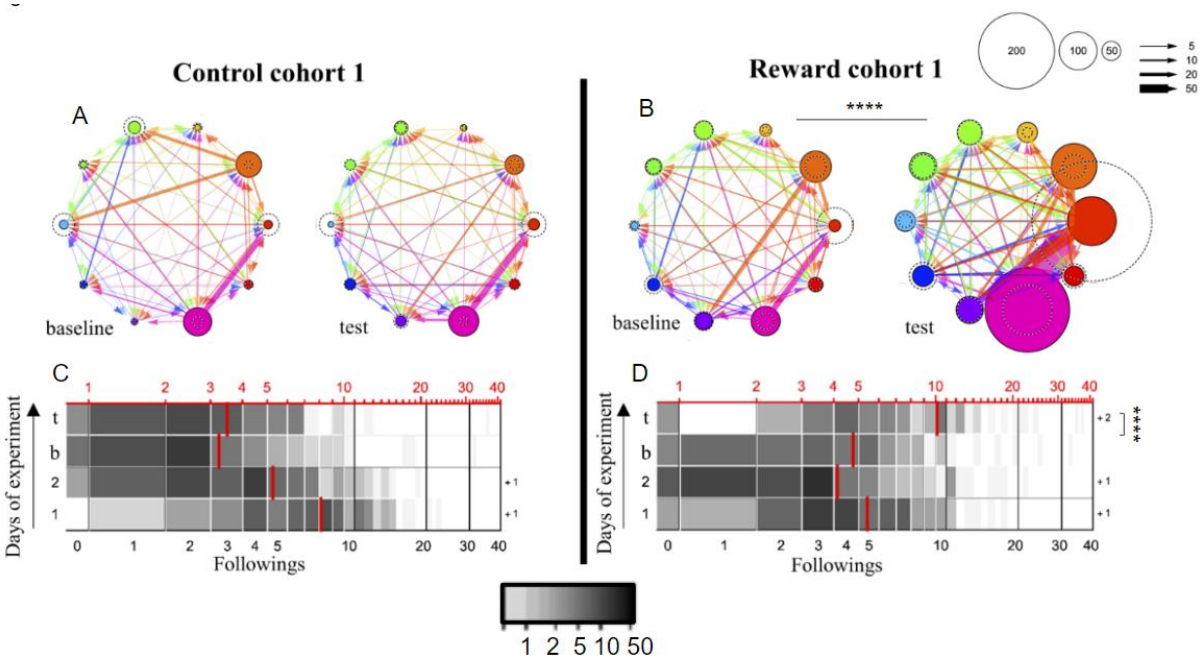


Figure 23. Social network of cohort 1. observed during baseline period and after the presentation of social cues carrying information about either the neutral stimulus (A, C) or the neutral stimulus and reward (B, D). Graphs show an increase in the following resulting from the presentation of the social cue indicating reward (B, D) and its absence in the control condition (A, C). Horizontal segments (C, D) correspond to the distribution of the number of following events in all pairs of mice within the Cohort 1 in each trial in the subsequent dark phases of the experiment (on days 1-4, where day 3. represents the baseline period (b) and day 4. the period of test (t) when stimuli carrying social information were presented in the environment. Subsequent days of the experiment correspond to respective rows, from bottom to top. Rectangles running from left to right reflect the number of followings. The intensity of the shading represents the number of occurrences of a given number of followings in all pairs of mice. In cases when there were pairs of mice with over 40 followings, the number of such pairs was shown with a plus sign to the right of a respective row. Additionally, the mean number of followings for all pairs of mice during a given experimental phase, calculated for this distribution, is marked as a red line at the position corresponding to the red scale at the upper edge of the plot.

# 7 Discussion

## 7.1 Information about the presence of rewards in the environment is encoded in social olfactory cues

In the presented work I focused on the social appetitive learning and its neural underpinnings. Social appetitive learning is a process through which subjects adjust their behavior to the pertinent changes in their environment based on socially transferred information. Namely, I investigated how such information affects murine exploratory patterns and social behavior towards other members of the group. To that end, I used the Eco-HAB - a fully automated assay for behavioral testing of the group-housed mice. Under laboratory conditions appetitive social learning is most commonly tested in the food preference experiments, designed by Galef (Galef, 1977). However, taking under consideration the specific characteristics of the Eco-HAB system, such as feasibility of long-term testing and experimenting on groups of mice, the direct application of the Galef's protocol would not be advisable. Further, many experiments, including those using the Galef's protocol, showed that important aspects of social information gained during the interaction with another conspecific are transferred via chemical (olfactory) signaling (Arakawa et al., 2013; Beauchamp and Yamazaki, 2003; Broad and Keverne, 2008; Galef, 1977; Galef and Heiber, 1976). Such olfactory cues may be obtained by sniffing either a conspecific – especially its anogenital area - or olfactory cues left in the environment by other mice (Bowers and Alexander, 1967; Harrington, 1976; Ryan et al., 2008). Moreover, studies in mice showed that naive mice are attracted to the odor of another conspecific (Yang et al., 2011). Notably, deprivation of the olfactory system in mice leads to social anxiety (Beny and Kimchi, 2016), which shows the importance of the olfactory channel for social communication. Thus, in the presented studies I used bedding soaked with social odors as a source of social information. The effectiveness of using bedding soaked with social cues in the Eco-HAB experiments was previously reported by Puscian et al. (Puścian et al., 2022b, 2016). In my work, I modified the original protocol, and presented subjects with social cues obtained from conspecifics exposed to reward (10% sucrose solution) or neutral stimuli (tap water). This protocol enabled me to test if mice are able to encode the information about potential

rewards in social olfactory stimuli and if so, how such information changes the behavior of its recipient.

My first discovery was that the bedding soaked with urine of a mouse consuming 10% sucrose solution contains information about reward. The bedding was more attractive than the one containing social odor from a conspecific exposed to a neutral stimulus (tap water, Figure 7). The result, although novel, is in line with classic appetitive conditioning tests showing that sucrose is very effective as a rewarding stimulus (Sclafani et al., 2014). Furthermore, results from experiments conducted in the IntelliCage, an alternative assay for automated group-housed testing, showed that mice easily learn the position of sucrose rewards in the environment and are highly motivated to access it (Endo et al., 2011; Kiryk et al., 2020; Mechan et al., 2009; Puścian and Knapska, 2022). My data go a step further and show that the scent of a sucrose-rewarded mouse is an incentivizing stimulus in and of its own. As expected, the results from the control experiment, in which both animals whose scents were presented to the group were exposed to a neutral stimulus (water), show that there was no preference to either (both were equally often visited).

The results were quantified based on the data collected during the 12h-long dark phases of the dark/light cycles of a 24/7 experiment, which gave me the possibility to observe the spontaneous and voluntary behavior during the periods when mice, nocturnal animals, are naturally active. Also, such long measurement periods provided substantial amount of data thus boosting the reliability of the results. On the other hand, taking under consideration 12h-long time bins made the information about the dynamics of tested responses unavailable. Thus, to better understand how the interest in presented social odors changed over time I proposed a variable called persistence in odor seeking, which reflected how interest in exploration of olfactory cues changed over time. In the control experiments, with time passing by the animals explored social cues less and less. However, in the experiments in which a scent of a rewarded mouse was presented, the interest in social olfactory cues was stable throughout the whole dark phase, which may reflect how enticing social cues about the rewards are in comparison to social cues not conveying any pertinent information about the environment.

Moreover, introducing olfactory cues about rewards into the experimental environment influenced social behavior of the tested individuals in a noteworthy way. Specifically, mice started to follow each other more when the social cue about the reward was present, in comparison to the control condition (Figure 8A, Figure 23A, C). I argue, that tracing other mice within the territory may be adaptive from the point of view of gathering additional

information. Such behavior is then understandably boosted when essential information about the potential presence of a reward becomes available. In line with my hypothesis, an increase of social interactions between the rewarded mice was described in classic behavioral protocols (Kummer et al., 2014; Wrenn, 2004). Mice during the food preference tests were highly interested in the conspecific that had just ate. and intensified the social interactions with the food-rewarded mouse. In the presented protocol, in which only olfactory information from a mouse that got a reward elsewhere was available in one of the Eco-HAB's corners, the information about food location was more ambiguous. This ambiguity likely motivated the mice to search for more information through direct social contact with others in the cage. The following behavior offers an access to olfactory information coded in the scents secreted by the anogenital area of the preceding mouse. Such effects were reported earlier. When self-gained information about reward was ambiguous, the animals relied more on information gained from other conspecifics (Bhanji and Delgado, 2014; Smolla et al., 2016).

One of the key evolutionary advantages of social learning is the ability to gain information about the environment without the need for first-hand experience, which helps to avoid unnecessary dangers (Kaplan et al., 2009). Thus, I aimed at developing a new experimental protocol enabling to test how social information helps to navigate in a novel, unfamiliar environment. Specifically, in the protocol I developed two mice out of a cohort of 10 housed together (in Eco-HAB I), referred to as the scouts, explore a new territory (Eco-HAB II) for 24 hours. Therein they get access to two bottles placed in two opposite cages of the Eco-HAB II, and as they explore them they leave olfactory social cues in the close proximity of the bottles' tips. After that period the scout animals are removed from the new environment, bottles are emptied and refiled with water. Then the rest of the cohort moves in and is thus exposed to the olfactory social cues left by the scouts. The results of the experiment showed that the rest of the cohort drank more from the bottle preferred by the scouts (Figure 15A CTRL NP-BSA). Notably, it was previously shown that mice subjected to naturalistic testing environments naturally develop preference to a specific bottle, even if all available bottles contain the same liquids (Kiryk et al., 2020; Knapska et al., 2013, 2006b; Puścian et al., 2022b). Field experiments also showed that mice use social cues left by other mice to navigate in the environment (Andrzejewski et al., 2011; Knapska et al., 2006a; Łopucki, 2007; Puścian et al., 2022b). Similarly to our results, in the food preference tests mice favor food that was eaten by the demonstrator (Galef, 2012). The presented discovery makes a strong argument that social information plays a crucial role in the navigation in the new environment.

It is noteworthy, that preferring a given bottle by the scouts was a factor sufficient to evoke preference in the rest of the cohort, regardless of whether or not the bottle has previously contained the reward (10% sucrose solution) or neutral stimulus (water, Figure 15A CTRL NP-BSA). That is, in the control experiments, in which both scents were obtained from mice drinking water, there was a preference of the scout animals for one of the bottles, which affected the preference of other animals that moved in to the environment. Nevertheless, the animals moving in showed higher persistence in exploring the scout-preferred bottle when it had previously contained the reward (Figure 15A REW NP-BSA), which shows that they distinguished between the smells of the scouts drinking the sucrose solution and water. Taken together, these results strongly suggest that social cues carry information which affects navigation and exploratory preferences.

Interestingly, social behavior was affected differently by the presence of social olfactory cues about reward in the novel and familiar environments. In the case of the former, both, in-cohort sociability and followings were influenced when scouts had access to the bottle with highly rewarding sucrose solution (Figure 15A, 15B).

In line with my results, mice have been shown to use social information to seek the sources of safe food (Loureiro et al., 2019). Such effects were also reported in the species from different phylogenetic levels, i.e., insects (Worden and Papaj, 2005), fish (Brown and Laland, 2003), monkeys (Fragaszy and Visalberghi, 2004), and humans (Rademacher et al., 2017). For instance, bumblebees use social navigation to find sources with better reward quality (Jones et al., 2015). Interestingly, transfer of information about the reward via social cues can also be observed between individuals from different species, for example, dingo dogs use olfactory cues left by humans to find the source of rewarding food (Smith and Litchfield, 2010).

In summary, the presented results show that mice are able to use social information from conspecifics to adjust their behavior in both, novel and familiar territories. Furthermore, they change their social behavior to accommodate to changing environment.

## 7.2 Role of social hierarchy in transmission of social information

Social hierarchy is a natural phenomenon occurring in group-living organisms and has a significant impact on behavior of individuals and the group itself (Dubois and Ordabayeva, 2015; Witkower et al., 2020). Nevertheless, in nature, the process of establishing hierarchy is very complex and species-specific (Zhou et al., 2018). In naturally formed animal societies,

social status is a crucial factor regulating access to food (Qu et al., 2017), reproduction success (Bercovitch and Clarke, 1995), prosocial behaviors (Gachomba et al., 2022), and affecting health (Sapolsky, 2005). The noteworthy role of high social status is its critical value in winning social conflicts (Hand, 1986).

One way of establishing social status in Animalia kingdom is the physical conflict with direct confrontation. However, energy costs of such strategy are high and it can be dangerous for all involved individuals (Zhou et al., 2018). Notably, stable social hierarchy reduces the unnecessary fights (Hobson, 2020). In the laboratory experiments the tube domination test is considered the most classical way to examine social hierarchy in mice. Therefore, I decided to compare the Eco-HAB results on social status indicated by the following behavior of animals with the tube test data. A large increase in followings in response to social information about the reward in both, novel and familiar environments while the locomotor activity levels remained stable, suggest that the former behavior plays an important role in spreading the information within the group and could be related to competition to reach that reward. Followings measured in the Eco-HAB system positively correlated with the tube test score (Figure 22), suggesting that intensity of following behavior may be related to social rank of an individual. It is noteworthy that the tube test was conducted right after the end of the Eco-HAB experiments to preserve the most accurate measure of social status. Since following behavior is by definition a directed one (one animal follows and the other one is followed) it reflects an asymmetric relationship. Indeed, it is very rare that two animals follow one another equally (Figure 20 and 21).

Social hierarchy and social networks are highly related to one another (Gupte et al., 2011; Maiya and Berger-Wolf, 2009). The dominant chimpanzees had the highest centrality score in the social network of their group (Funkhouser et al., 2018). Moreover, mice with higher social status are more motivated for social interaction than mice from the bottom of social hierarchy (Kunkel and Wang, 2018).

Further, social networks can change over time - the effect previously described in humans (Cornwell et al., 2014). The developed experimental protocol and the related analytical tools of following behavior in the Eco-HAB offer the possibility of observing how social networks change over time. Firstly, the level of following in the experiments conducted in the Eco-HAB without any additional stimulation stabilized between the 3$^{rd}$ and 4$^{th}$ day of adaptation, which, I argue, may be related to the process of habituation to experimental conditions (Figure 20). Formation and stabilization of social relations are continuous processes, requiring constant updating (Wei et al., 2015). The process of learning of the social status

of other animals was described by Zhou et al. (2017). In this study, the scientists used the tube tests and optogenetics to manipulate the neuronal circuits engaged in learning associated with social hierarchy (Zhou et al., 2017). They discovered that activation of the dmPFC circuits induces winning in the tube test. Moreover, in vivo experiments showed that mediodorsal thalamic input to the dmPFC is crucial for processing information about social hierarchy (Zhou et al., 2017). In my work it was shown that a similar hierarchy learning process can be observed in semi-natural environments.

Dominant mice can be easily identified in the social network graphs even after the habituation period, when the network stabilizes. In other words, social equilibrium does not lead to "silencing" of the following interactions but rather to establishing stable asymmetric relations of tracing one another (Figure 20). Asymmetry of social networks is commonly observed and described in literature (Labianca and Brass, 2006; Meng et al., 2018). Interestingly, introduction of the odor from the mice exposed to water (neutral stimulus) has no effect on social networks (Figure 23 Control cohort 1), while social information about the reward leads to its significant boost (Figure 23 Reward cohort 1). This may mean that socially transferred information must be sufficiently pertinent to influence social network. Further, analysis of social networks showed that the increase in followings upon presentation of social odors indicating reward was not homogenous (Figure 23 Reward cohort 1). The impact of potential reward availability on social networks was previously described in humans (Fareri et al., 2012; Mandefro Messele, 2020). The presented work shows that this phenomenon can be successfully tested also in mice under laboratory conditions, which presents great opportunities for exploring its brain mechanisms.

## 7.3 Increased TIMP1 activity in the PL affects social behavior

Processes of neuronal plasticity in the PL and their key role in modulating social behavior were previously reported in a number of studies (Christoffel et al., 2011; Djordjevic et al., 2012; Wang et al., 2018). The main techniques used to manipulate neuronal activity in the PL are based on the application of optogenetics (Stefanik et al., 2013), chemogenetics (Shipman et al., 2019), or electrical stimulation (Yamada and Sakurai, 2022). Indeed, such manipulation approaches are well-suited for classic behavioral assays, where animals are tested in short periods and the experimental environment can be relatively easily adapted to accommodate the experimental requirements. The Eco-HAB is a very flexible and customization-friendly assay. However, due to the longitudinal character of the conducted

experiments - one of the main advantages of the system - typical neuronal manipulations methods may not always work in an optimal way. To meet the requirement of the longitudinal manipulation of neuronal plasticity in the PL, targeted at a specific molecular mechanism, in my work I used designer nanoparticles loaded with TIMP1. Nanoparticles described by Chaturvedi et al. (Chaturvedi et al., 2014) can carry large molecules, such as TIMP1, and release the cargo gradually over time. In case of the herein used tool, the pick of the TIMP1 release described by the authors is reached around the 5th day, which in my experiments related to the first day of the experiment (after recovery from the surgical procedures). Nanoparticles were criticized for their potential neurotoxicity (Buzea and Pacheco, 2019). However, the data presented in this work, as well as previous research conducted with their use, show that polylactic nanoparticles can be successfully used in longitudinal behavioral paradigms without adverse side effects (Puścian et al., 2022b). Another advantage is the possibility to easily combine nanoparticles with fluorescent dye and thus test the injection site and the protein distribution in the brain tissue. Unfortunately, the mechanism of protein storage in the nanoparticles and its release is not yet fully understood, which is the commonly used argument against this method (Buzea and Pacheco, 2019). Another issue with nanoparticle usage is their size and resulting density of the solution in which they are stored, which leads to the necessity of using a relatively large injection needle. It is especially problematic when targeting the neuronal circuits in the PL, because of the risk of damaging the nearby sinuse (a large blood vessel).

BSA-loaded nanoparticles were used in the control experiments, as BSA is an inactive compound, having no impact on neuronal plasticity. Results from the BSA-injected mice are similar to those recorded in non-operated animals (cohort I). This result confirms that in the conduced experiments the surgery and recovery had no effect on the reported behavior related to the presence of the social olfactory cues indicating reward.

TIMP1 is well known for its impact on neuronal plasticity (Dziembowska and Wlodarczyk, 2012; Jourquin et al., 2005; Trofimov et al., 2017), reported also in the prefrontal cortex (Okulski et al., 2007). The main role of TIMP1 is inhibiting the activity of matrix metalloproteinase 9 (MMP9), the enzyme crucial for dendritic spines maturation (Michaluk et al., 2011; Puścian et al., 2022b). MMP9 was described as the key factor necessary for proper learning about the reward (Knapska et al., 2013; Puścian et al., 2022b). However, TIMP1 is not an inhibitor specific only to MMP9, in the literature it is described also as inhibitor of MMP2 and the proteins from ADAM family (Amour et al., 2000). Interestingly, mice with deficits of TIMP1 expression do not upregulate the MMP9 and MMP2 in the brain

after seizures (Jourquin et al., 2005). Furthermore, *in vitro* studies show that cytokines with proinflammatory functions like interleukin-1 increase expression of TIMP1 in astroglia cells and induce their proliferation (Ogier et al., 2005). Further, it was shown that TIMP1 inhibits several of MMP proteins except for the MMP9, including MMP2 (Chen et al., 2020), and MMP10 (Batra et al., 2012). Thus, unequivocal linking the observed behavioral effects directly to MMP9 is not possible based on the presented results. However, in the description of the results I refer to MMP9 as it is the most likely synaptic-plasticity-related target of TIMP1 (Michaluk and Kaczmarek, 2007). Thus, the detailed molecular mechanism of TIMP1, by which it affects the social learning after its injection into the PL, requires further studies. Nevertheless, my results show that the proper level of MMP9 activity, even if not exclusively involved, is crucial in social learning about rewards.

The social odor containing information about the reward was used as a vehicle for information storage and spreading. To measure the interest in that odor two metrics were developed: the proportion of visits to the compartment with social odor containing the information about the reward, used in the experiments in the familiar environment, and relative time of drinking from the bottles preferred by the rewarded scouts in the novel environment experiments. In the experiments in the familiar environment, the release of TIMP1 into the PL did not significantly affect the interest in social odor containing information about the reward (Figure 7A). However, when animals were tested in the novel environment drinking from the bottles preferred by the scouts was significantly decreased (Figure 14A). These results confirm that the activity of TIMP1 affects social learning about the reward and that this effect is especially pertinent in the novel environments, where information from conspecifics plays a key role in navigation.

Persistence, on the other hand, is a measure developed to quantify if the motivation to reach the information about the potential reward availability changes over time. I observed that in TIMP1-treated animals persistence was significantly decreased irrespective of the familiarity of the experimental environment, which suggests that MMP9 activity has a significant impact on motivation to find information about the reward. Similar observations were reported by Lebitko et al. (Lebitko et al., 2021). They showed the decreased motivation for obtaining sucrose solution access after TIMP1 was injected to the brain. Also experiments on the alcohol addiction showed that activity of MMP9 plays a key role in motivational tasks performed by the group-housed mice (Stefaniuk et al., 2017).

The effects of TIMP1 injection into the PL on other social behaviors was also notable. Characteristic increase in the following in response to socially transferred information about

the reward was not present in the animals injected with NP-TIMP1, in either familiar or novel environments (Figure 11A, 11B, 16A). Moreover, in-cohort sociability was decreased when information about the reward was present in the novel environment (Figure 15B). The effect is likely due to the fact that the increased level of followings decreases time spent together in one place. In the experiments conducted in the familiar environment locomotor activity was not affected by TIMP1. However, in the novel environment a small but significant decrease in activity was observed (Figure 17A). These changes might have had an impact on other behaviors measured in these experiments. Thus, further studies are needed to better understand the reported effects. Nevertheless, TIMP1 disrupted the pattern of formation of the social networks in the TIMP1-treated animals, which suggests that undisturbed neuronal plasticity in the PL is crucial for establishing stable social group behavior (Figure 21 NP-TIMP1).

These results are in agreement with the previously reported role of the prefrontal cortex in regulating social behavior (Dang et al., 2019, 2019; Denny et al., 2012; Izhar et al., 2022; Levy et al., 2019; Puścian et al., 2022b; Yamada and Sakurai, 2022). Furthermore, they also show that processing information about the reward and social behavior have similar neuronal background and can be – at least to some extent - processed by the same TIMP1-sensitive neuronal circuits in the PL.

## 7.4 Eco-HAB as an environment for testing complex social behavior

The Eco-HAB is a fully automated assay for testing behavior of group-housed mice, originally described by Puścian et al. (Puścian et al., 2016). Its design enables full automatization of social behavior experiments. In the presented work I proposed new experimental protocols enabling testing effects of socially transferred information about the reward. To obtain that goal I adjusted the basic protocol (in the standard Eco-HAB experiments two olfactory stimuli are presented, bedding soaked with social and non-social scents).

In my experiments I used a familiar mouse as a source of information instead of unfamiliar conspecifics. It allowed me to avoid affecting social structure by the external social input. Moreover, presenting social information about the reward by a cage mate is more ecologically relevant, and thus more natural scenario (Kondrakiewicz et al., 2019a; Puścian and Knapska, 2022). I randomly chose two mice from each cohort to be separated. As the results clearly show that mice establish stable and hierarchical social structure,

in my opinion future follow-up research should control for the position of the separated mice in the social hierarchy.

The following behavior measured in the Eco-HAB was used to investigate social networks, which is a unique feature and promising area of development in the field. It opened the avenue for the future studies to focus on the directed and weighted dynamic social interactions. The feasibility of observing individual diversity of social behavior in group-housed mice under laboratory conditions is an interesting approach to further research in the field of social neuroscience. As position in social structure likely affects responses to social stimuli, the developed protocols create an opportunity to study the brain mechanisms underlying such individual differences.

Another new aspect presented in this work is the discovery that mice can be successfully re-tested in the Eco-HAB thus enabling within-subject comparisons. The main advantage of this approach is the reduction of variability in data caused by the individual diversity.

Further, I also show that the Eco-HAB experimental environment can be used as either familiar or novel environment depending on the experimental design, which is a highly useful feature. Furthermore, I also adjusted the original design of the system by including the additional, electronically-monitored bottles, which allowed to quantify the interest in their exploration and drinking. Such upgrade opens novel possibilities that can be incorporated into the existing protocols. For example, cognitive and learning tasks can be designed with the use of the upgraded system. As the Eco-HAB is an open resource and has been developed by a community of users, the proposed adjustments of the original design are a noteworthy alternative for the expensive and oftentimes problematic commercial solutions.

# 8 Conclusions

- I developed new experimental protocols for testing social transfer of appetitive information; those protocols can be used in the future to study social learning under semi-natural conditions.
- I showed that mice are able to effectively discriminate between the social cues indicating neutral stimuli and rewards.
- I discovered that social olfactory information plays a key role in the navigation of both, familiar and novel environments, and that it changes the pattern of social interactions between the members of a social group.
- I established that MMP9-dependent neuronal circuits in the PL play a critical role in social appetitive learning.

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