Ph.D. Thesis

Neurobehavioral Study on Social Transmission of Avoidance Behavior

回避行動の社会的伝達に関する神経行動学的研究

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Chapter 1

Introduction

1.1. A Brief Overview of Social Neuroscience

Social neuroscience is an interdisciplinary research field which studies neurological underpinnings underlying the process of social interactions, social cognition, and social behaviors. Social neuroscience has been rapidly progressed in the past decade, and several international journals (Social Neuroscience; Social Cognitive and Affective Neuroscience etc.) have been published. Present most main technique of social neuroscience is functional imaging, including functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), magnetoencephalogram (MEG), and electroencephalogram, but lesion studies and free-moving neuronal recording in non-human animals are also important in many senses. In this section, we demonstrate representative works in social neuroscience.

1.1.1. Mirror Neurons in Monkeys and Birds

Rizzolatti and his colleagues discovered a particular class of visuomotor neurons, “mirror neurons”, in premotor cortex (area F5). The neurons discharge both when taking a particular action (such as grasping) and when observing another individual (monkey or human) doing a similar action (Di Pellegrino et al. 1992, Gallese et al. 1996, Rizzolatti et al. 1996). The neurons in F5 and ventral premotor areas have reciprocal connections to hand area of the primary motor cortex (Dancause et al. 2006; Godschalk et al. 1984; Matelli et al. 1986; Muakkassa et al. 1979; Dum et al. 2005) and were connected from intraparietal sulcus (anterior intraparietal; AIP) (Luppino et al. 1999), and they are considered a key neurons for specific actions under the cooperation with the connections. Location of area F5 is presented in Fig. 1.1.1.A. Inactivation of F5 produces impairment of grasping (Fogassi et al. 2001). Mirror neurons show generalized responsibility, and widely different visual stimuli, but which all represent the identical action, are equally responsible. For example, a grasping mirror neuron responds to a hand grasping an object and also to grasping action of the

neuron owner monkey.

In addition to visuomotor mirror neurons, auditomotor mirror neurons have been found in forebrain of songbirds. The neurons respond during perception of specific song and also during vocalizing same song (Prather et al. 2008; Keller et al. 2009). High vocal center (HVc) is a nucleus in the neostriatum. HVc is necessary for singing (Nottebohm et al. 1976) and song perception (Gentner et al. 2000) and has two distinct connections; linkages to premotor neurons in the robust nucleus of the arcopallium (RA) and to neurons in avian basal ganglia (Farries et al. 2002) important to song learning and perception (Scharff et al. 1991; Scharff et al. 1998). Neurons in HVc receive projection from primary auditory area, L field (Vates et al. 1996) (Fig.1.1.1.B). The example of responses of mirror neuron is demonstrated in Fig. 1.1.1.C.

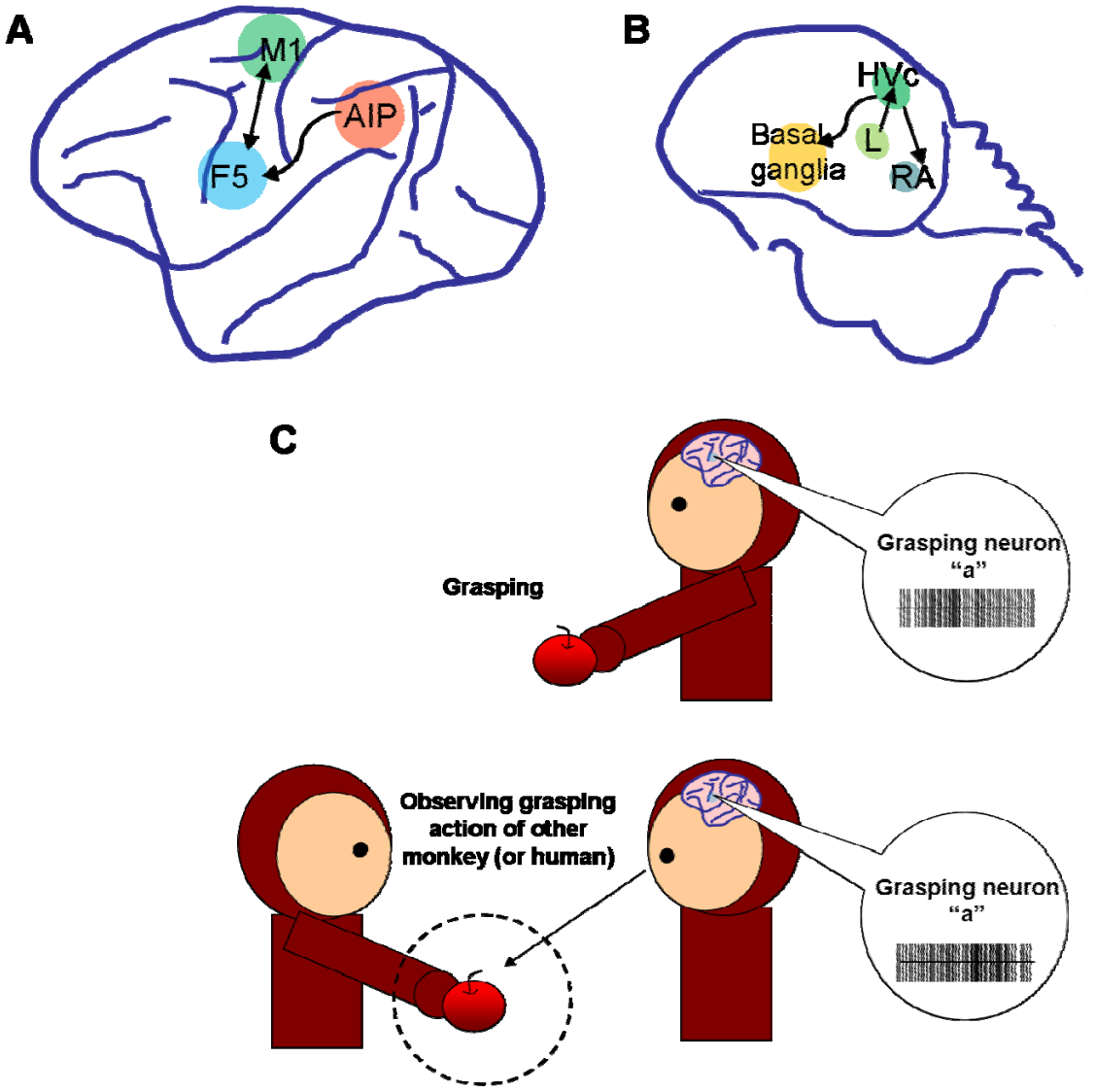

Fig.1.1.1 Areas and selective activity for mirror neurons.

A: Visual/Motor mirror neurons located in F5 of Monkeys' (Macaca mulatta) brain. B: Auditory/Vocal mirror neurons in located in HVC of songbirds' brain. A part of neurons in each area discharge both when behaving a certain action or vocalizing a certain song (output) and when seeing other's identical action or listening other's identical song. C: A grasping mirror neuron, here named "a", (a kind of Visual/Motor mirror neurons) responds when grasping leaded by subject itself and when observing grasping action of others. This does not matter the observed one is human.

1.1.2. Human Patients with Amygdala Damage

A certain nucleus in limbic system, the amygdala, has been implicated to involve in social cognition and behavior in primates. Here, we introduce some examples of the studies reporting the cognitive and behavioral impairment in humans with amygdala damage. There are cognitive difficulties in patients with amygdale damage. Most notable one is a failure to fixate important features of the faces such as strongly opened eyes (Adolphs et al., 2005). Normal humans preferentially fixate onto the eye region of others' faces (Janik et al 1978). This preference appears early in development and may contribute to the social and emotional scene. Subjects with amygdala lesions are impaired in judgment of the emotions shown in photographs of faces (Adolphs et al 1994; Calder et al 1996; Adolphs et al. 1998). Other cognitive and attentional processes are also impaired in patients with amygdale lesion. These include looking different features such as mouth during conversation (Spezio et al. 2007) and incapability to recognize emotion from music (Gosselin et al. 2007).

1.1.3. Proteins for Social Bond and Maternal Behavior

Social animals including humans, form mutual connections among social members. There are many types of social bonds. They include parental bonding, bonding between parent and child, (it can be categorized into maternal bonding and paternal bonding), bonding between male and female, and bonding between mates. How can the animals and their brains form such social bonding? By relatively recent researches, it has been revealed that some neuropeptides regulate social bonding (see for review Young et al. 2004).

Oxytocin (OXT) is composed nine amino acids (Cys–Tyr–Ile–Gln–Asn–Cys–Pro–Leu–GlyNH_2) and regulates a part of social bonding. Uterine-contracting properties (Dale 1906) and the milk ejection property (Ott et al. 1910; Schafer et al. 1911) of OXT have been revealed since long time ago. The neuropeptide was also described as essential part of the hypothalamo-neurohypophysial system in fish (Scharrer 1928). Understanding the role of OXT in neuroendocrinology and physiology raised additional question of behavioral effect of

local OXT release. Central administration of OXT facilitates the partner-preference (to cohabitant male) in female prairie voles, and the selective antagonist abolishes the preference (Williams et al. 1994). Prairie vole (*Microtus ochrogaste*) is a monogramous species of rodents, and has been used as an excellent model for the study of social relationships. Infusion of OXT into lateral ventricle facilitates social recognition, and infusion of antagonist abolishes memory enhancement in males (Benelli et al. 1995). Mother-infant bonding are enhanced (exhibit shorter latency to maternal response) by intracerebroventricular (ICV) infusions of OXT in hormone-primed virgin animals (Pedersen et al. 1979; Pedersen et al. 1982). OXT administration also increased social contact in male rats (Witt et al. 1992) and squirrel monkeys (Winslow et al. 1991). Interstingly, the manipulation of oxytocin systems did not affect sexual behaviour (Insel et al. 1995). OXT is generated mainly in magnocellular neurons in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. OXT are also generated in the bed nucleus of the stria terminalis (BNST), medial preoptic area, and lateral amygdala (LA) (Young et al. 2003), but the amount is small.

Arginine vasopressin (AVP) is also one of the major known neuroptptides regulating social bonds. Compared to OXT, which is well-known to regulate female-typical social behavior including maternal behavior, AVP regulates several male-typical social behavior including aggressive behavior, scent marking, and courtship behavior. For example, infusion of AVP into hypothalamus triggers a type of scent marking used in olfactory communication (Ferris et al. 1984). Central administration of vasopressin facilitates partner preference, and the antagonists block partner preference in male prairie voles (Winslow et al. 1993). As well as OXT, AVP has been largely conserved throughout vertebrate evolution. The structure of AVP is very closed to OXT, and composed of nine amino acids (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH_2). The generation of AVP occurs in hypothalamus (PVN; SON; suprachiasmatic nucleus, SCN), BNST and the medial amygdala (MeA). The AVP acts through activation of specific receptor (V1aR), and administrations of selective V1aR antagonist or antisense V1aR into the lateral septum inhibit social recognition (Landgraf et al. 1995; Everts et al. 1999), whereas infusion of AVP or overexpression of the V1aR in this region enhances social recognition abilities (Landgraf et al. 2003).

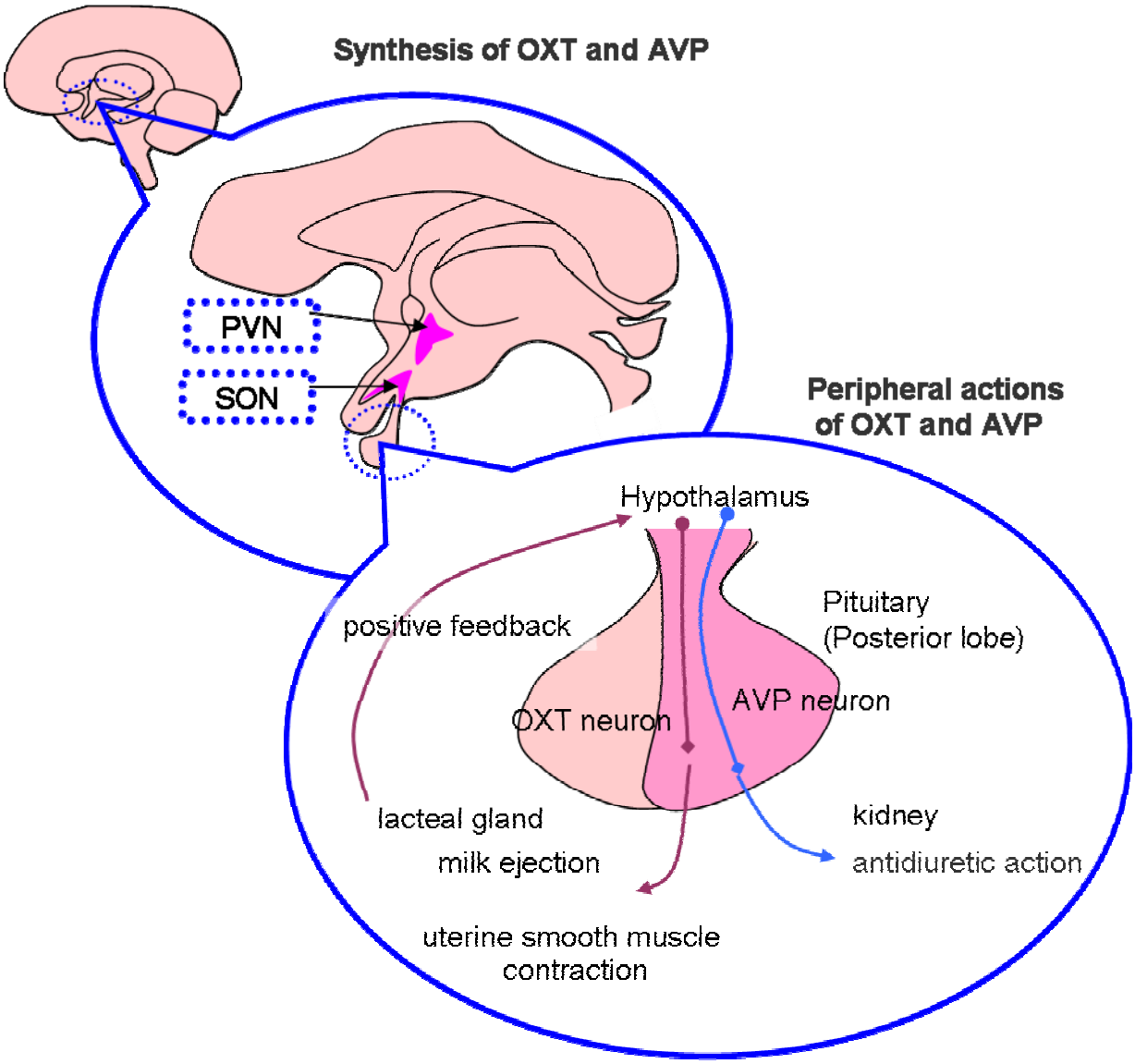

Fig.1.1.2 Fundamental mechanism of OXT and AVP systems.

OXT and AVP are generated in hypothalamus, especially in paraventricular nuclei (PVN) and supraoptic nuclei (SON). Some neurons in PVN or SON contain such neuropeptides and project to posterior lobe of pituitary. Peripheral actions of OXT and SON have been known around 1960s.

Table 1.1.1 Brief summary of central actions of OXT and AVP.

Effect to OXT receptors

Agonist:
partner preference ↑, social recognition ↑, social bond ↑,
social contact (male) ↑, sexual behavior (-)

Antagonist:
partner preference ↓, memory recollection (male) ↓,.

Effect to AVP receptors

Agonist:
scent marking ↑, partner preference ↑, social recognition ↑

Antagonist:
partner preference ↓, social recognition ↓

1.2. Communications in Animals

Communication is a process of transferring information from one entity to another. Generally, the term “communication” includes transferring information in an identical individual such as cell-to-cell communication or organ-to-organ communication. Gap junction and synaptic transmission are examples for the former one, and relationship between endocrines and target organs is an example for latter one. In this thesis, however, communication refers to communication between individuals. Such communication processes are able to be categorized into several aspects. One aspect is sensory type. In both humans and animals, it is possible to divide all communication into visual communication, olfactory communication, vocal communication, and tactile communication. Here, we review the historical findings regarding animal communication, and introduce important researches.

1.2.1. Visual Communication

Visual signals have some limitation. They require a direct line of sight and somehow lighted conditions. In addition, they last during only signaling. Visual images are received only in real-time, and they are able to be said “dynamic signals”. Visual communication is quiet important. For example, humans and primates are strongly dependent on this type of communication.

Tinbergen and his colleagues’ research is a great example for visual communication in gulls (Tinbergen 1951; Tinbergen 1959). Parents of gulls present their bills (beaks) to their chicks in the nest. Typical species of gulls have bright color in their bills. Pecking the parents’ bill is an appropriate response for parental feeding in gulls. The chicks peck all brightly-colored objects which include their parents’ bills and similarly colored plastic or glass. Visual communication (detecting brightly-colored object) is quite important for gull chicks to obtain food from their parents.

More general communication in animal using visual information includes “display”, a presentation of a sequential action. There are many kinds of display in animal communication. One important aspect of display is tool for sexual selection (Anderson 1994) and for fighting behavior (Paker 1974). The former one is categorized as “courtship display”, and the latter one is categorized as “competitive display”. This perspective suggests that visual communication is highly dependent on the evolutional process.

Unlike human language, animal display behaviors are generally ritualized and do not have possibility of reciprocal exchange (Iwata 1987). In another word, it is able to be said that visual communication in animals is one-way communication. Some of the display behaviors enclose information of the transmitter’s intention or emotion. Female avocets (Recurvirostra avosetta) demonstrate receptive display to the males showing courtship display. What type of information is transferred? In this case, transferred information includes intentional component. In a fighting situation, animals often demonstrate display for threatening enemies. That is typical example for emotional display.

1.2.2. Olfactory Communication

Olfaction is a major sensory system. Through olfactory communication, animals may detect and identify other animals as predators or mates and so on. This function has been known for quite long time. According to classical description, olfactory communication consists of four steps: (1) generation of chemical signals by a sender, (2) transmission to a receiver through adequate receptors, (3) identification and integration of chemical information, and (4) response behaviorally or physiologically to the signals (Eisenberg et al. 1972). Olfactory signals have typically long delay between emission and reception, but latter remain and longer durations (Eisenberg et al. 1972). More recently, neuronal mechanisms for odorant communication in mammals have been identified. Here, we review the previous works studying olfactory mechanisms.

Olfactory receptors (or odorant receptors) are expressed on the surface of sensory neurons, which are located in the upper part of nasal epithelium, in vertebrates and are

responsible for detection and recognition of various odors (see for review Rinaldi 2007). Expression of olfactory receptors is species-dependently variable. For example, mice have approximately 1,200 olfactory receptors, while humans have less than 400. Every olfactory sensory neuron expresses only one olfactory receptor. This rule is called “one neuron–one receptor rule” (Chess et al., 1994; Malnic et al., 1999; Serizawa et al., 2003). The olfactory sensory neurons receive odorant information, and transmit to olfactory bulb with changing chemical signals to electrical information.

1.2.3. Vocal Communication

Vocal communication may be most complex type of communications. Vocal communication can be categorized into various aspects. Here, I introduce complexity-based categorization. Vocal communication can take place on different level of complexity (Jugens 1992).

In the lowest level, vocal communication is elicited by reaction. This reaction means non-learned motor pattern. This type of vocal includes vocalization in infant period. Infant shrieking (shrill cry) is observed is observed immediately after birth. This shrieking is not required any experience of hearing, and shrieking occurs also in deaf infants (Eibl-Eibesfeldt 1973). Such reactive vocalization is thought to be organized by innate releasing mechanisms according to ethologists. In the next level, voluntary vocalization control can be raised. This enables to produce innate vocal response in appropriate timing and/or situations. Typical examples for this include bark and howling. Finally the most complex level of vocal communication is voluntary control over acoustic vocal structure. This includes capability to produce new pattern of vocal behavior by invention or imitation.

1.2.4. Tactile Communication

Touch is an important form of communication for many species of animal. One of our (human) tactile communications is shaking hands. We should know the importance of tactile

communication for smooth communication. This type of communication supports the courtship process and friendly relationship. Many species of monkeys and primates are known to groom each other, and this is important not only for removing parasites, but also for secure social bonds. Mated birds are occasionally observed preening one another. By tactile communication, bees, not mammalian, let know information of the quality, direction, and distance of the food as well as information where foods are (Von Frisch 1950). The style of communication is compared with language. In view of physical property, tactile communication has disadvantage in range of available to communicate. Many invertebrates use antennae or whisker as the first line of contact. The most common use of tactile communication occurs during sexual behavior. Tactile signals by males let females know a sexually receptive state, in rodents.

1.3. Social Learning and Social Transmission

1.3.1. Observational Learning

Many animals organize groups and learn in social situations. We can learn from others. In a psychological expression, such learning process is called “social learning” (or vicarious learning). Theoretical progress was initially given by some sensational reports from Albert Bandura. One of his researches examined the imitation effect on children’s aggressiveness. Children readily imitated aggressive behavior by an adult model. Non-aggressive behavior of adult model also influenced and suppressed children observers’ aggressive behavior (Bandura et al. 1961). He proposed “social learning theory” in 1977 via publication of a book (Bandura 1971). His main idea is that human behavior is learned by observing others (modeling). Therefore, a word “observational learning” is also used. This view encloses important difference from typical view of behaviorisms which requires actual experiences containing positive or negative outcome in individual level and responses to associated signals. The view of observational learning does not need direct experiences or outcome. Observational learning is also found in some species of animals including monkeys (Mineka et al. 1984; Cook et al. 1985), birds (Klopfer 1961; Johnston et al.1998; Mason et al. 1981), rats (Baum 1969), mice (Carlier 2006; Guzmán et al. 2009), octopuses (Fiorito et al. 1992), and so on, but those should be separately considered from the observation learning because cognitive ability and visual recognition are different by species.

1.3.2. Social Transmission

Social learning is mediated by not only visual signaling but also by other sensory systems (Figure 1.2.1.). For example, rats can learn what food is able to eat via olfactory communication (see for review Galef et al. 2008). This process is called social transmission of food preference. “Social transmission” is wider social learning process via observation, olfactory communication, and other types of social communication (Figure 1.2.2.).

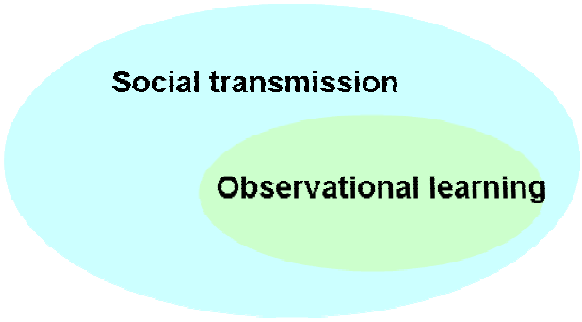

Fig. 1.2.1. Social transmission and observational learning

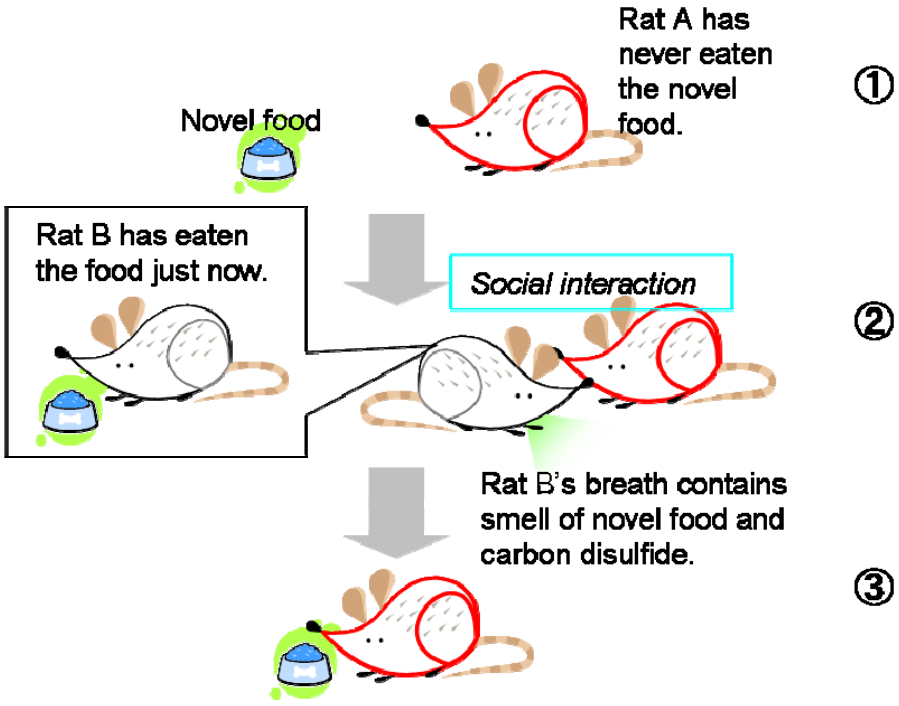

Fig. 1.2.2. Social transmission of food preference.

The phenomenon is consist of three processes. First, rats habit to refuse to eat a novel food. Here, rat A is naïve to the novel food. Another rat, rat B, has experience of eating the food, and rat B has eaten it just now. Social interaction is allowed between rat A and B. During interaction, rat A receive information from rat B. Olfactory cue (smells of novel food and rat B's breath) is received by rat A. After that, rat A will eat the novel food.

1.4. Principles of Learning

Learning is acquiring new knowledge, skills, or behaviors. Memory is ability to store, retain, and recall information. There are three important phases for learning and memory. Those are acquisition, consolidation, and recall. In brief explanation, acquisition phase corresponds to phase of learning. Consolidation and recall correspond to phase for memory. Field of learning and memory is quiet wide, and it should relate to social learning because social learning is also one of the learning. Here, we introduce principles of memory and learning.

1.4.1. Classification of Learning

Memories can be classified according to some criteria (e.g. function, content, duration, motivation, or nature) (see for review Squire 2004; Squire 2009). First, I would like indicate classification refers to time. By classification according to duration, memory can be divided into four; sensory memory, short-term memory, working memory, long-term memory. Sensory memory is memory which retains impressions of sensory information after the original stimulus has ceased. The lasting duration is dependent on sensory type, but typical duration is about 1-2 seconds. In short-term memory, memory is allowed to be recalled for a period of 10-20 seconds. Working memory allows storing information and supports executive and attentional functions in the period similar to short-term or more to a minute (see for review Baddeley 2003). These types of memory is limited in lasting duration, however, long-term memory allows unlimited lasting duration. Long-term memory sometimes lasts during whole life span. Importantly, long-term memory can be further classified by information type.

Long-term memory can be functionally categorized into declarative (explicit) memory and non-declarative (implicit) memory. Declarative memory can be sub-divided into semantic memory (memory for knowledge and facts) and episodic memory (memory for events). Non-declarative memory can be divided into procedural memory (memory for

motor or sensory abilities) and habits, which include habituation and sensitization. Implicit memory is more robust, and has tendency of lasting very long time (sometimes for whole life) and of tolerability of extinguishing. As another important classification for long-term memory, nature (associative memory vs non-associative memory) classification should be mentioned here. Associations between stimuli and responses or between two stimuli are formed by many behavioral tasks. There are two types of associative memories; “classical or respondent (Pavlovian) conditioning” and “instrumental or operant conditioning”. In the former one, contingencies between stimuli and responses (unconditioned response) are coupled, and the animals are in unavoidable conditions (Pavlov 1927). On the other hand, in later one, the animals are allowed to perform some behavioral responses, and associative experience between stimuli and a certain responses are received under such conditions (Skinner 1937; Skinner 1963). There two types of association memories; appetitive and aversive memories.

1.4.2. Avoidance Learning

Avoidance learning is learning to avoid aversive stimuli. In laboratory, there are two models for avoidance learning. One is active avoidance learning, and the other one is passive avoidance learning. In active avoidance learning, experimenters typically use cue signals. Animals are put in light and dark boxes, and cue signal is presented (punishment). Aversive stimuli (electrical shocks) are induced in animals until they stay the dark box. After several trials, animals come to move to the light box immediately after cue presentation (Fig.1.4.1.). This active avoidance is also called escape-avoidance learning. On the other hand, in passive avoidance learning, animals receive shock after entering dark box (punishment). Typically after one trial, animals will not enter dark box (Fig.1.4.2.). This passive avoidance learning is also called inhibitory avoidance learning.

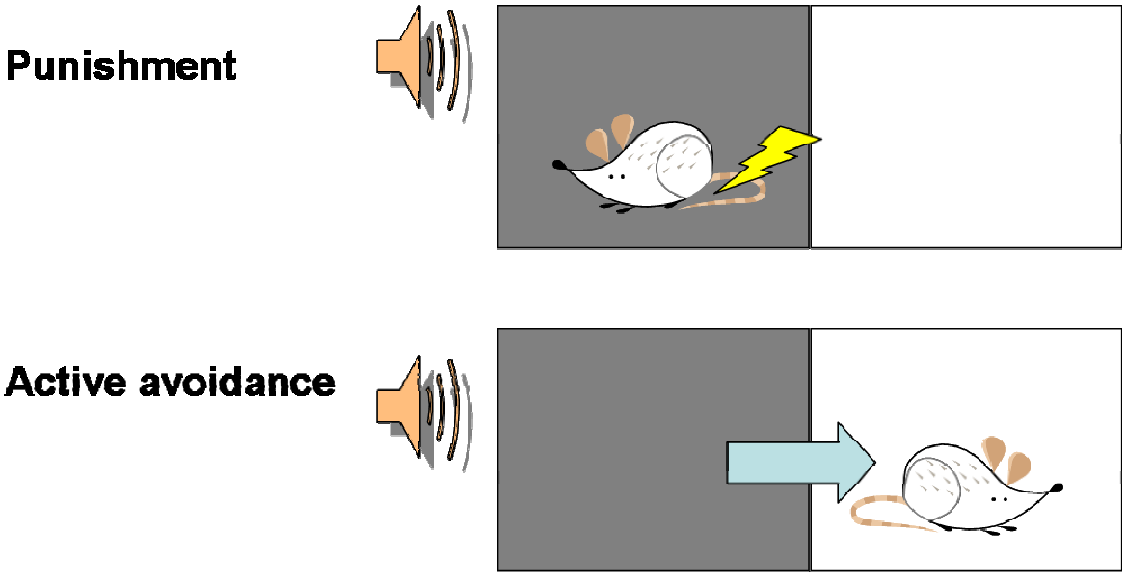

Fig.1.4.1. Active avoidance learning. As a punishment, animals receive aversive stimuli immediately after cue presentation. After several such trials, animals will move to different box in response to cue presentation.

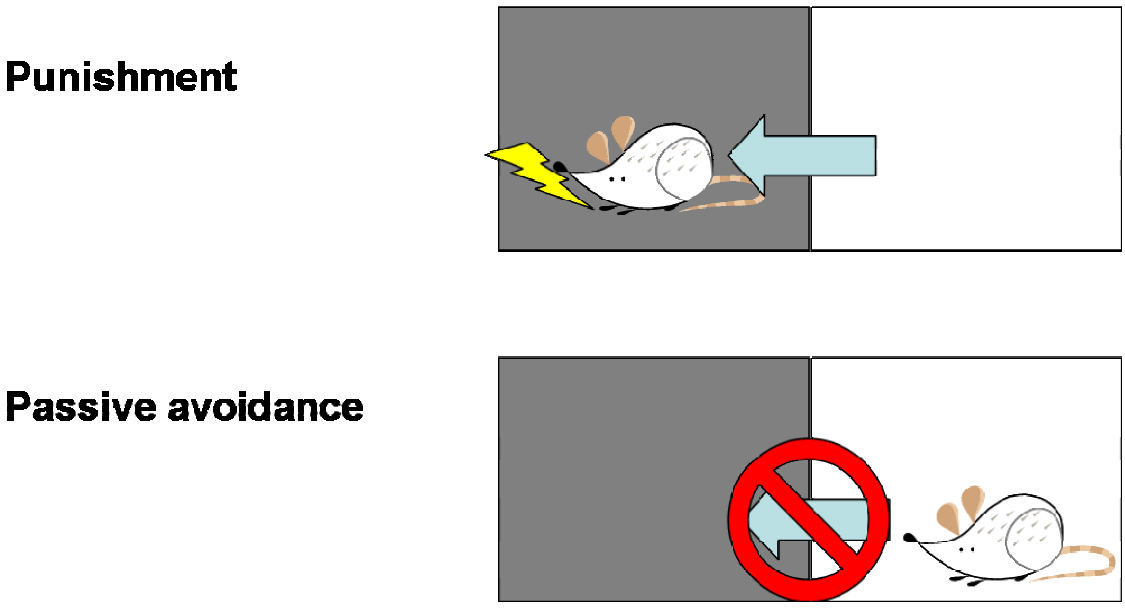

Fig.1.4.2. Passive avoidance learning. As a punishment, animals receive aversive stimuli after entering a dark box. After that, animals will not enter the dark box.

1.5. Aim of Study

Humans and other species of animal receive many types of information from other individuals. This is called “social transmission” as previously described (see Section 1.3.2. pp. 19) and is found in humans, primates, birds, and rodents. Avoidance learning is quite important learning for living, but there is little understanding of “social transmission of avoidance”. The present study aimed to understand behavioral and neuronal mechanisms for social transmission of avoidance in rats. We modified and used a paradigm of passive avoidance learning (see pp. 23), and studied the effect of social interaction with other individuals on avoidance behavior by systematic experiments which include experiment for (1) environmental factor and characteristics for individuals, (2) characteristics for social relationship, and (3) involvement of specifics brain regions (Fig. 1.5.1.).

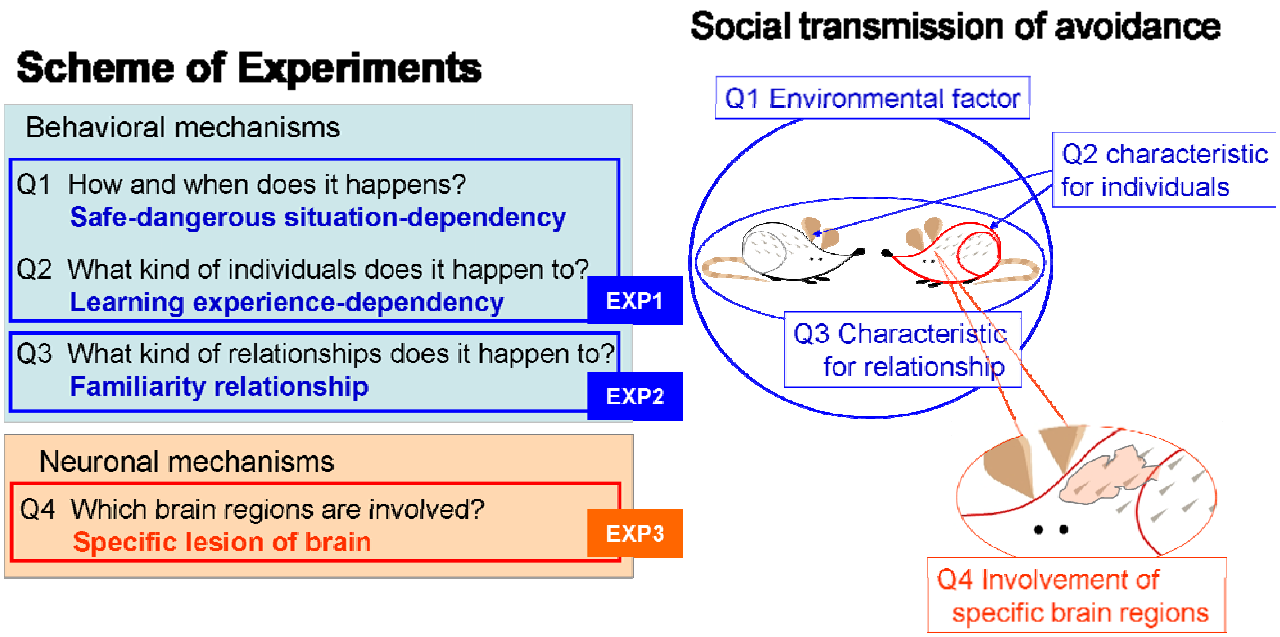

Fig. 1.5.1 Conceptual diagram for whole study.

1.6. Chapter Summaries

This thesis contains three chapters. The first chapter is this introduction, which attempts to provide the reader with historical and theoretical background and previous works in broad fields of social neuroscience. This thesis focused on behavioral and neurological mechanisms for social transmission of avoidance as I describe later, and the following chapters are experimental reports. Chapter 2 describes behavioral studies to investigate behavioral mechanisms for social transmission of avoidance. We demonstrate the importance of inner factors (previously acquired experiences of learning) and outer factors (situations of social partners or experimental environments) there. In chapter 3, we show the lesion experiment to investigate relevant brain area for social transmission of avoidance.

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Chapter 2

Behavioral Studies: Behavioral Characteristics of the Social Transmission

2.1. Effect of Previous Experience of Avoidance Learning

Abstract

Rats receive information from other conspecifics by observation or other types of social interaction. Such social interaction may contribute to the effective adaptation to a change of environment. Learning to avoid dangerous places or objects is rapidly occurs with even a single conditioning session, and the conditioned memory tends to be sustained over a long period. The avoidance is important for adaptation, but the details of the conditions under which the social transmission of avoidance is formed are unknown.

Here, we examined the effect of the previous experience of avoidance learning on social transmission of avoidance. We systematically investigated social influence on avoidance behavior using a passive avoidance test in a light/dark two-compartment apparatus. Rats were divided into two groups, one receiving foot shocks and another with no aversive experience in a dark compartment. Experienced and inexperienced rats were further divided into subjects and partners. In Experiment 1, each subject experienced (1) interaction with an experienced partner, (2) interaction with an inexperienced partner, or (3) no interaction. In Experiment 2, each subject experienced interaction with a partner that received a shock in front of the subject. The entering latency to a light compartment was measured and compared among the conditions.

The avoidance behavior of experienced rats was inhibited by interaction with inexperienced rats or experienced rats in a safely-changed situation. The avoidance of experienced rats was reinstated in a dangerously-changed situation by interaction with shocked rats, while the avoidance of inexperienced rats was not affected by any social circumstances. These results suggest that transmitted information among rats can be updated under a situational change and that the social enhancement and inhibition of avoidance behavior depends on previous experience in rats.

2.1.1. Background

Various social animals interact with conspecifics, and use information from other animals to adapt their environments. The transmission of information by interaction or observation is called social transmission. Social transmission is shaped with social clues which consist of visual, olfactory, acoustic or other types of information from conspecifics. Many studies have shown that social interaction or simple observation of other animals' behavior has significant effects on food choices (Zentall et al. 1972; Galef et al. 1985; Kitami et al. 1990), spatial information about feeding locations (Galef et al. 1983, Galef et al. 1997), acquisition of motor patterns (Hirata et al. 2000; Biro et al. 2003; Carlier et al. 2006), and avoidance (Hall and Suboski 1995; Brown 2003) in many species of vertebrate including primates, birds, fish, and rodents (for a review Galef and Laland 2005). Rats, one of the most common experimental animals, prefer the food same as what conspecific ingested recently (Galef et al. 1985; Galef and Whiskin 2003). This social transmission of food preference is thought to be formed by association between food odorants and a volatile component of a rat's breath (Galef et al. 1988).

One of the most important behaviors to survive is avoiding behavior to dangerous objects or places. Some previous studies reported that rats did not learn avoidances socially (Galef et al. 1983; Galef et al. 1990). For example, rats do not learn avoidance just by watching conspecifics receiving a shock (White et al. 1998) or by interaction with poisoned conspecifics (Galef et al. 1990). Other paper showed that rats learn to avoid a candle flame by exposure to another rats acquiring the same avoiding responses (Lore et al. 1971). These conflicting results probably come from the different experimental conditions.

One possible factor is subjects' experience. The various responses followed by social interaction could be affected by responder's experience. For example, social recognition requires semantic memories and knowledge obtained previously by experiences (Gallagher et al. 2003). The functional imaging studies using human subjects found that the temporal lobe, where memory retrieval and recall are involved, were activated during recognition of familiar voices (Nakamura et al. 2001), the recollection of familiar face and scene (Nakamura et al. 2000), and the retrieval of emotional episodic memory (Dolan et al. 2000). These data

suggest that social responses depend on memories that subject experienced. Perception of other's pain, and empathy for pain, are dependent upon two factors: top-down factors (i.e. features of observer's experience of pain and knowledge) and bottom-up factors (i.e. observation of person's pain expression and contextual pain cues) (for a review Goubert et al. 2005). A recent research has shown that rats, like humans, can apply previous learning to adapt new situations (Murphy et al. 2008). Top-down factor should be important for various perceptions and decision making even by rats. In the previous studies concerning social transmission of avoidance, the most researches used naïve rats as subject animals. From the view that not only social cues but also subjects' experience are important for the social recognition, one possible explanation for the reason why rats did not learn avoidance socially could be that the association between top-down factors (social clues from others) and bottom-up factors (avoiding experience of individuals) was not formed because naïve rats have no experiences of pain or another aversive stimulus. The present study focused on subjects' experience of avoidance learning and investigated uncertain dynamics; social influence on avoiding behavior with environmental change. We flamed following two hypotheses: i) experienced subjects' avoidance are influenced by inexperienced as well as experienced rats' behaviors, and ii) the experienced rats' sensitivity to social interactions is higher than that of inexperienced rats.

2.1.2. Materials & Methods

Subjects

The subjects were 58 male Wistar rats aged 8 weeks acquired from Kyudo co. They were freely given food and water, and housed in two per cage for one week before the start of the experiments. Housing conditions were thermostatically-controlled at 22-24 °C with a light/dark cycle (lights on: 08:00—20:00). The experiments were performed under the control of the Ethics Committee of Animal Care and Experimentation in accordance with the Guiding Principles for Animal Care Experimentation, Kyushu Institute of Technology, Japan, and with the Japanese Law for Animal Welfare and Care.

Apparatus

The experiments took place in a test chamber consisted of two compartments; one of which, the light compartment (D25 cm×W25 cm×H27 cm), and the other of which, the dark compartment (D30 cm×W30 cm×H30 cm) (Fig.2.1.1). The two compartments were divided by a sliding door. Electric shocks are delivered by a shock generator (SGS-002, Muromachi Kikai Co., Ltd., Tokyo, Japan). In Experiment 2, removable partition was used to prevent subject animals from transferring the compartment earlier than the partners.

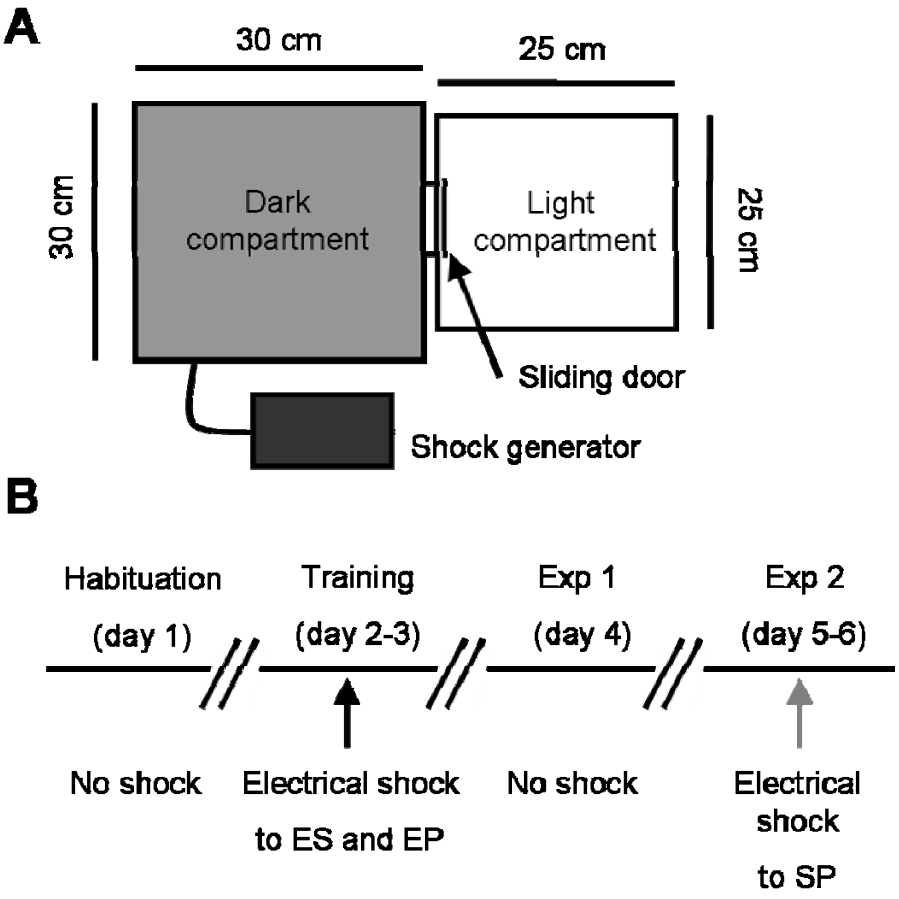

Fig. 2.1.1. The experimental design. (A) Experimental apparatus. (B) Time schedule of this study. The black arrow shows electric shock to the experienced subjects and partners (ES: experienced subjects; IS: inexperienced subjects; EP: experienced partners; IS: inexperienced partners). The gray arrow shows electric shock to the partners (SP: shocked partners).

Procedure

All treatments or behavioral tests were done on the light cycle (12:00-20:00) as the following sequences (whole schedule was shown in Figure 1B.).

1. Training

On the first day of this session (day 1), all animals were placed in the light compartment for 1 min individually and habituated to the experimental apparatus. After this interval, the sliding door was raised and the latency to enter the dark compartment was recorded. On the second day (day 2), single electrical shock (0.5 mA, 5 sec) was induced inescapably on 30 animals in the dark room after each animal entered the dark compartment, and they were used as the experienced subjects and partners. The other 28 animals received no electrical shocks were used as inexperienced subjects and partners. The experimental apparatus was cleaned with alcohol to remove odors before treating the next subject. On the third day (day 3), the latency of each animal to enter the dark compartment was measured. The schematic diagram of the training is shown in Fig. 1C.

2. Experiment 1

All subjects were divided into three groups; i) together with experienced partner (EP), ii) with inexperienced partner (IP), iii) without any partner (No). On the day next to training session (day 4), each subject was placed in the light compartment. They are paired with or without the partner rats for 1 min. After the interval, the sliding door was raised and then the latencies to enter the dark compartment were measured with the cut-off time 15 min. This experiment was performed without any electric shocks. The schematic diagram of the Experiment 1 is shown in Fig. 1D.

3. Experiment 2

The day next Experiment 1 (day 5), experienced and inexperienced subjects were put in the experimental apparatus individually and habituated to the dark compartment in 20 min. On the second day (day 6), 30 min before the test trial, each animal was placed in the light compartment and then the latencies to enter the dark compartment were measured with cut-off time 5 min. Thirty minutes after the pre-test trial, each subject was placed in the light

compartment with the partner for 1 min. All partners were the rats already used in Experiment 1, have given single foot shock, because of stabilizing partners' pain-reaction (habituation to the shock). After the interval, the sliding door was raised and then electrical shocks (0.5 mA) were induced to the partners. The partners always entered the dark compartment earlier than subject rats because of the partition. After the additional interval (30 sec) followed by returning of the other rat to the light compartment, the partition was removed. Then the latencies to enter the dark compartment were measured (cut-off time 15 min). Then we compared the latency of between the two conditions; with no partner conditions and with shocked partner conditions. The schematic diagram of the Experiment 2 is shown in Fig. 1E.

Data analysis

In Experiment 1, statistical significance of the difference among the groups of animal was assessed using Turkey-Kramer multiple comparison test. In Experiment 2, statistical significance of difference between in absent of partners and in present of partners was evaluated using the paired *t*-test. The criterion for the statistical significance was $p < 0.05$ (two-tailed).

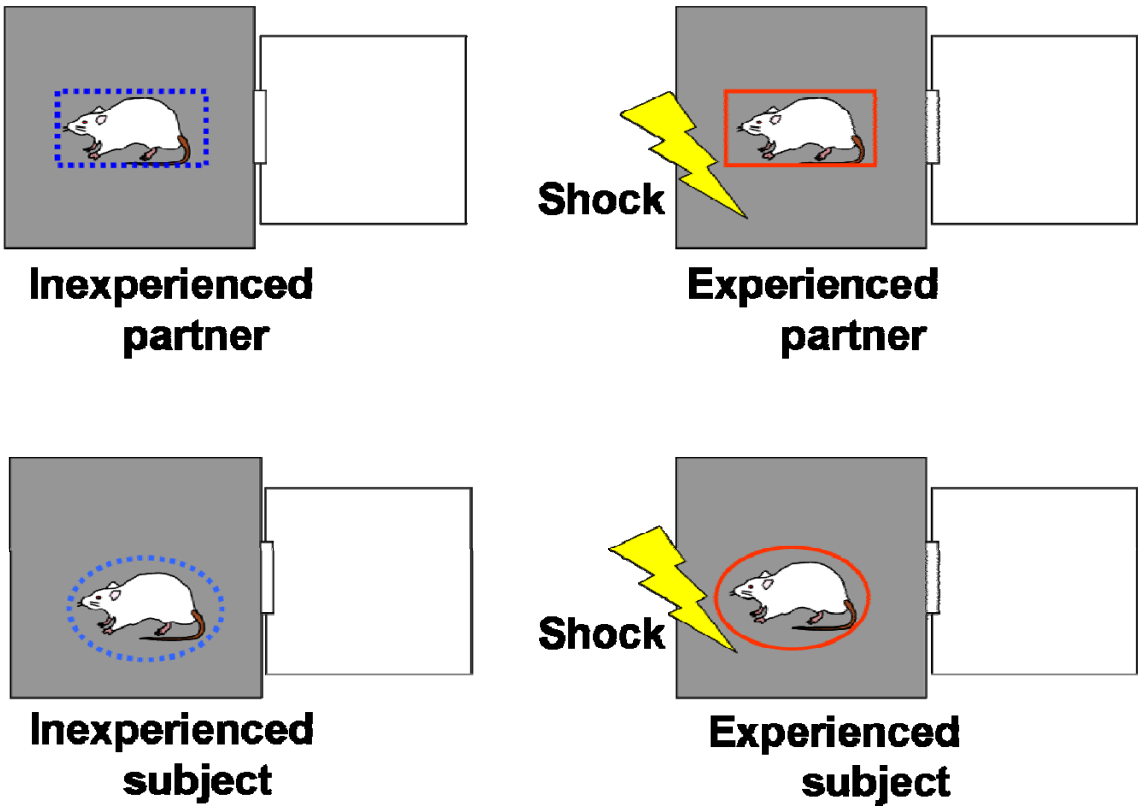

Fig.2.1.2 The schematic diagram of the training session. Left row indicates the treatment for the inexperienced subjects and inexperienced partners (IS: experienced subjects; IP: inexperienced partners); Right row indicates the treatment for the experienced subjects and partners (ES: experienced subjects; EP: experienced partners).

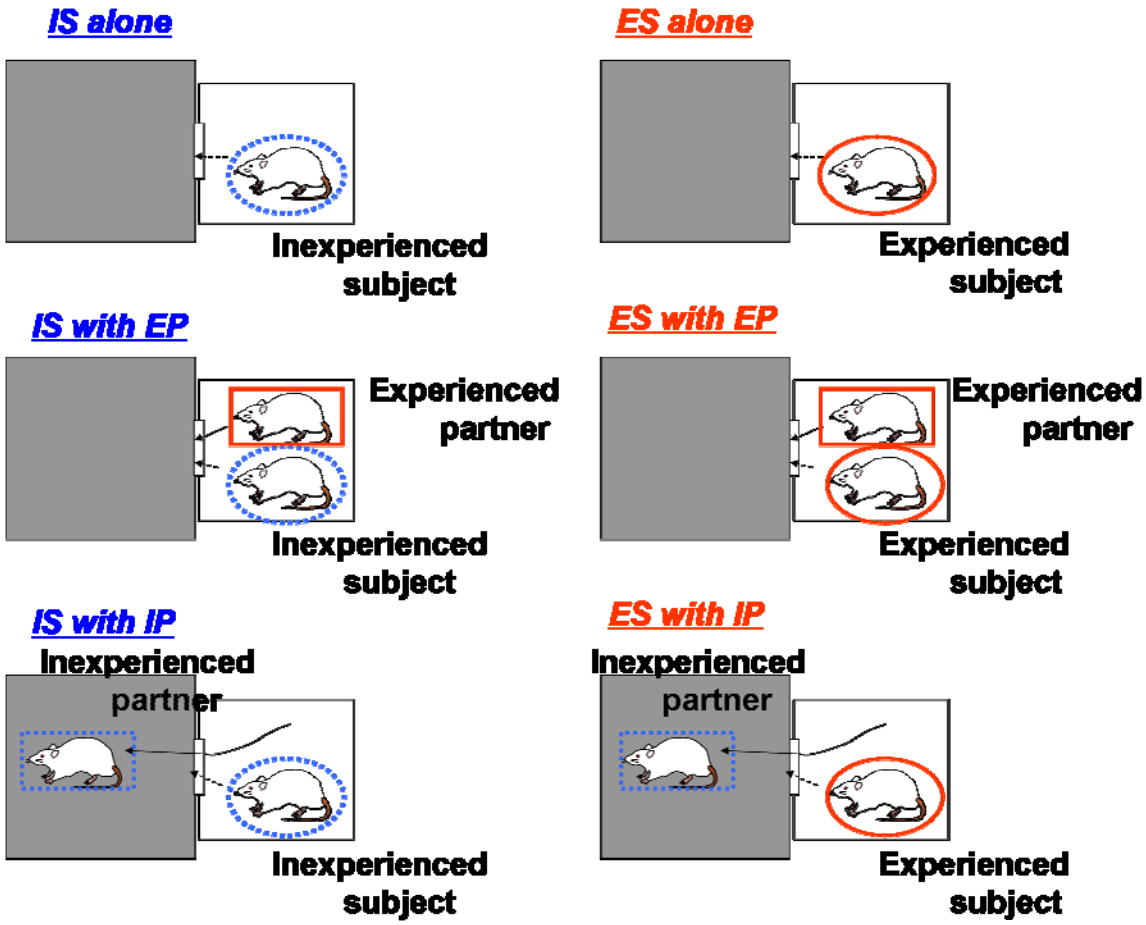

Fig.2.1.3. The schematic diagram of Experiment 1. The left row indicates the conditions for inexperienced subjects. Right row indicates the conditions for the experienced subjects. Non-interactive conditions are shown at the top line. Interactive conditions (with an experienced partner and with an inexperienced partner) are shown at lower part of the figure.

2.1.3. Results

Social interaction on avoiding behavior under safe situation

For preparation, we trained 30 rats (15 subjects and 15 partners) to avoid the dark room individually by electrical stimuli (0.5 mA, 5 sec), and the other 28 rats (14 subjects and 14 partners) did not learn. The trained rats and untrained rats were used as experienced rats and inexperienced rats, respectively. We examined the influences of social interaction on the avoiding behaviors under safe situation by using following 6 conditions; i) experienced subjects with inexperienced partner (ES with IP), ii) experienced subjects with experienced partners (ES with EP), iii) experienced subjects without any partners (ES alone), iv) inexperienced subjects with inexperienced partners (IS with IP), v) inexperienced subjects with experienced partners (IS with EP), vi) inexperienced subjects without any partners (IS with No). For the summary, all combinations are presented in Table 1. One day after the preparation (day 2), we measured the step-through latency of both subjects individually. All of experienced rats did not enter the dark compartment within 5 min (mean $\pm$ s.e.m. = 1102 $\pm$ 40 s), while inexperienced rats enter within 1 min (mean $\pm$ s.e.m. = 15 $\pm$ 2 sec). There was not significant difference among the three groups of experienced subjects ($P > 0.05$) as well as inexperienced subjects in avoiding behavior.

In the next day, we measured the latency with social interaction under the safe condition. We found that the latency of group of ES-IP was significantly shorter than both groups of ES with EP ($P < 0.001$, ES with IP vs. ES with EP) and ES-No ($P < 0.0001$, ES with IP vs. ES with No). Interestingly, the avoidance response of ES with EP was also shortened ($P < 0.01$, ES with EP vs. ES with No, Figure 2.1.4). However, latencies of all three groups of inexperienced subjects were not different from one another ($P > 0.8$, for all pairs, see Figure 2.1.4.). Similar results were found in the staying duration at the dark compartment of both subjects (Fig.2.1.6.).

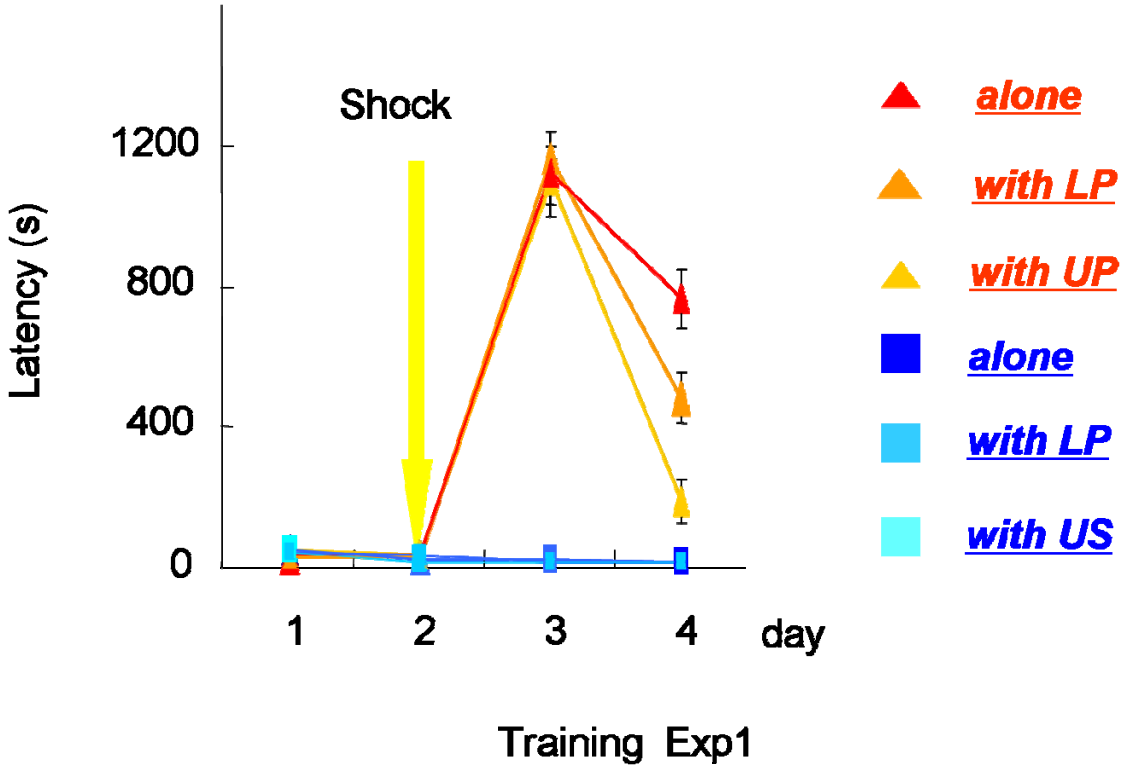

Figure.2.1.4. The latencies on time course. Through day 1 to day 4, the subjects took habituation (day1), receiving shock (day 2), measurement of basal avoidance level (day 3), and interaction with EP or IP or without any partners (day 4).

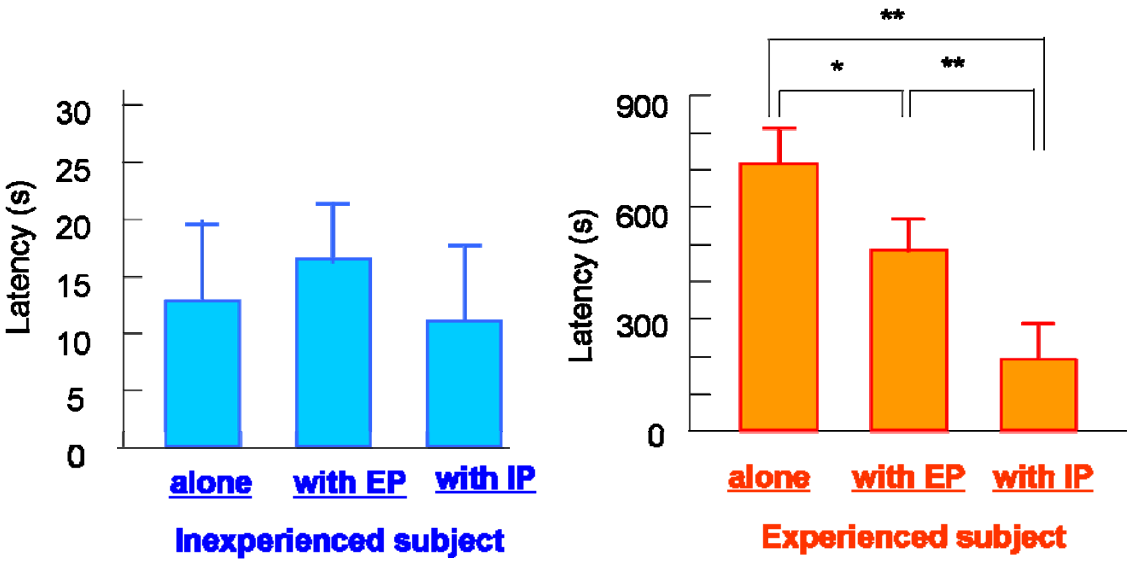

Fig.2.1.5. The effect of social interaction on avoiding behaviors under the safe situation. Step-through latency (mean ± s.e.m.) of the experienced subjects during the testing performed 24 h after shocking at the dark compartment of experimental apparatus. The step-through latencies of inexperienced subjects under the three conditions (IS alone, IS with EP, IS with IP) are shown at the left row. The latencies of experienced subjects under no interaction (ES alone), under interaction with experienced partner (ES-EP), and under the interaction with inexperienced partner (ES-IP) are shown at right side. (*: $P < 0.05$; **: $P < 0.01$)

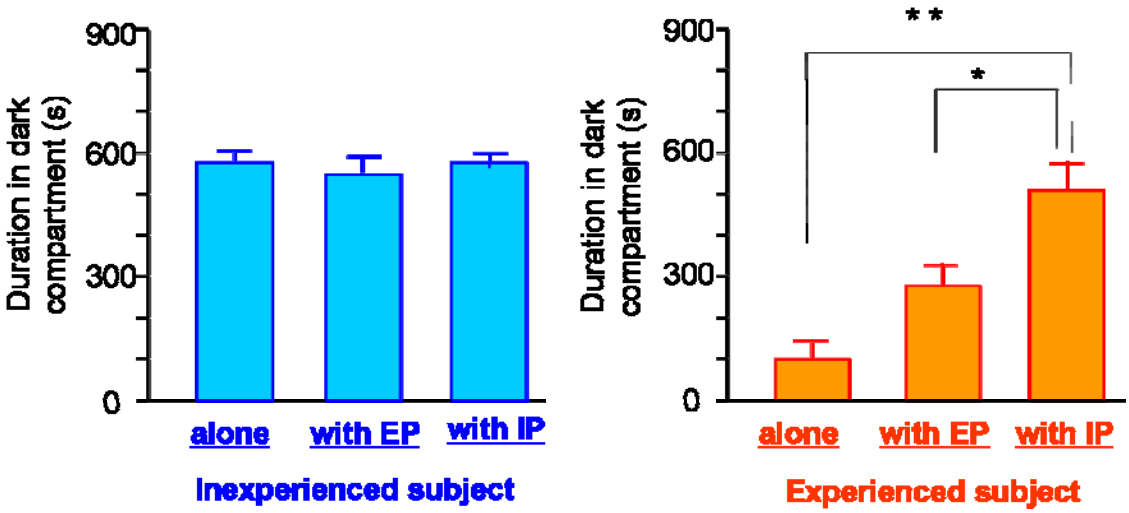

Fig.2.1.6. The duration of staying dark compartment. Mean ± s.e.m. are represented as bar. The duration of one IS with IP subject was defected due to the failure of measurement. (*: $P < 0.05$; **: $P < 0.01$)

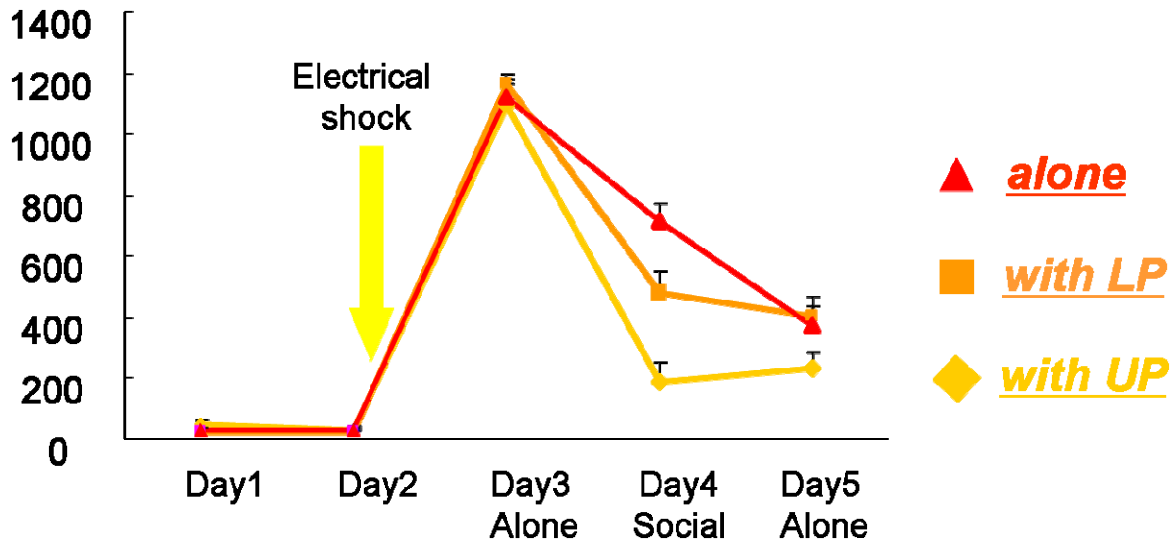

Fig.2.1.7. The latencies on time course. On day 5 the latency was measured under alone conditions. Alone group showed shortening change, but social groups (with LP and with UP) showed no change in avoidance behavior.

Table 1. The all conditions for the Experiment 1 and Experiment 2.

Condition	Interactive	Subject	Partner
Experiment 1			
ES alone	NO	Experienced	(-)
ES with EP	YES	Experienced	Experienced
ES with IP	YES	Experienced	Inexperienced
IS alone	NO	Inexperienced	(-)
IS with EP	YES	Inexperienced	Experienced
IS with IP	YES	Inexperienced	Inexperienced
Experiment 2			
ES-No	NO	Experienced	(-)
ES-SP	YES	Experienced	Shocked
IS-No	NO	Inexperienced	(-)
IS-SP	YES	Inexperienced	Shocked

Social interaction on avoiding behavior under dangerous situation

The partners had given a foot shock stimulus during retention time of the subjects, and then we compared the latency between asocial and social conditions (Fig. 2.1.8.). The all conditions for this were indicated in Table 1. This behavioral test was analyzed using identical animals because the avoiding behavior of the experienced subjects can vary individually. First, we measured the subjects' basal avoidance without social interaction (ES-No, IS-No). The mean latency of ES-No was 123.6 $\pm$ 19.4 (s), and that of the IS-No was 8.3 $\pm$ 1.6 (s). There was significant difference between two subjects ($P < 0.001$). After 30 min interval, the subjects were placed in experimental setting again, and interacted with shocked partners (ES-PP, IS-PP). Then, the latencies of the subjects were measured. The latency of the ES was significantly increased by the shocked partners (ES-No vs. ES-SP, $P<0.05$, Figure 2.1.9. right). Not all, but some of them showed clearly prolonged retention. On the other hand, the avoiding behavior was not enhanced in inexperienced subjects at all. Their latency tended to decrease rather than increase (IS-No vs. IS-SP, $P = 0.1$, Figure 2.1.9. left). These results indicate that the information from shocking partners has facilitatory effect on avoidance in the experienced subjects

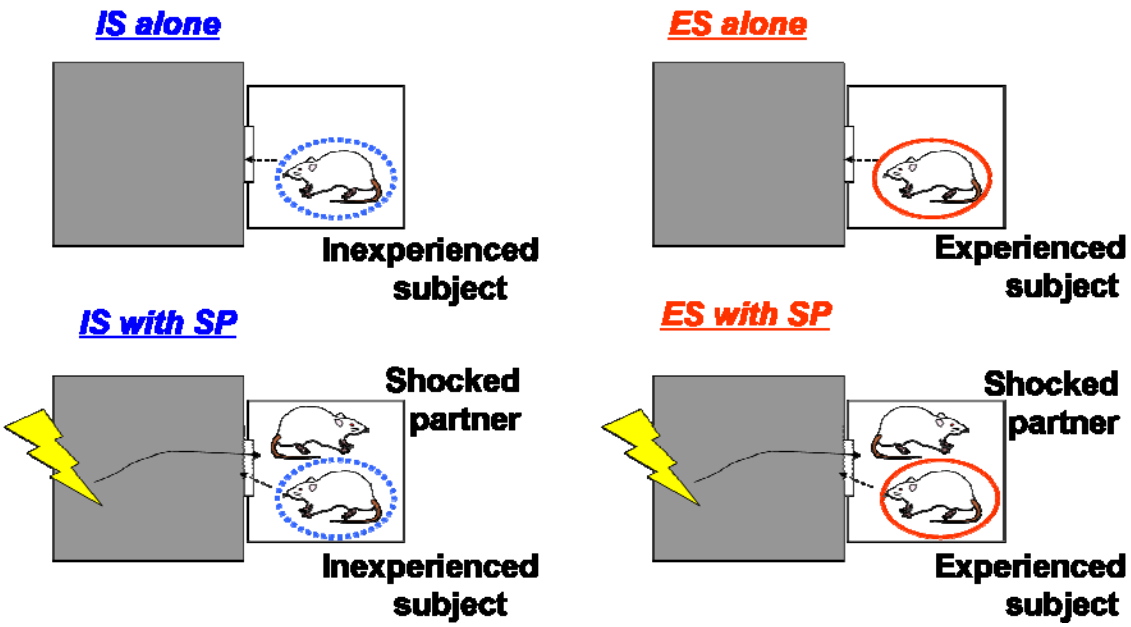

Fig.2.1.8. The schematic diagram of Experiment 2. Upper row shows non-interactive conditions (IS alone and ES alone) and the lower row shows interactive conditions (IS with SP and ES with SP).

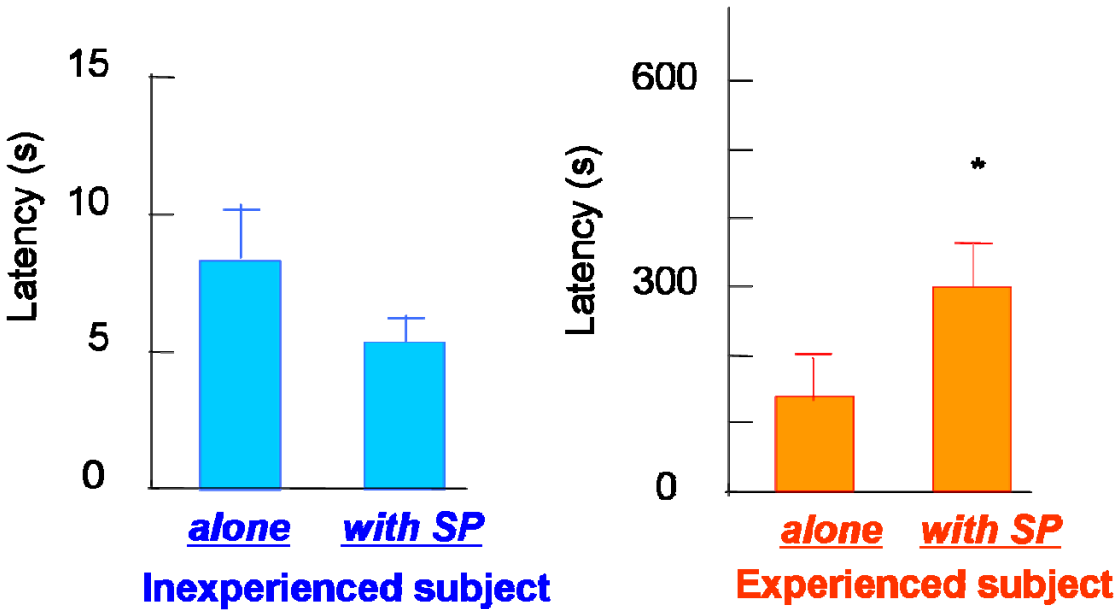

Fig.2.1.9. The effect of social interaction on avoidance behaviors of ES and IS under the dangerous situation. (Left) Latency of the experienced subjects under asocial condition (ES alone) and social condition (ES with SP). (Right) Latency of the inexperienced subjects under no interactive condition (IS alone) and interactive condition (IS with SP). The number of the experienced subjects (ES alone and ES with SP) and that of the inexperienced subjects (IS alone and IS with SP) were n = 15 and n = 12, respectively. (*: $p < 0.05$)

Effect of “experience of shock” on social facilitation of avoidance

Experienced animals showed facilitation of avoidance under social and dangerous situations. “Experience” here includes two dissociable experiences: experience of shock and experience of entering dark room. To asses the effect of experience of only shock, we conducted another psychological experiment. Animals divided into two groups. And one experiences electrical shock under a context different from the dark room. And the other one experiences only staying same context without electrical shock. Then both groups were tested as Experiment 2. We found that both groups did not show significant facilitation of avoidance after partner had shocked (Fig. 2.1.10.).

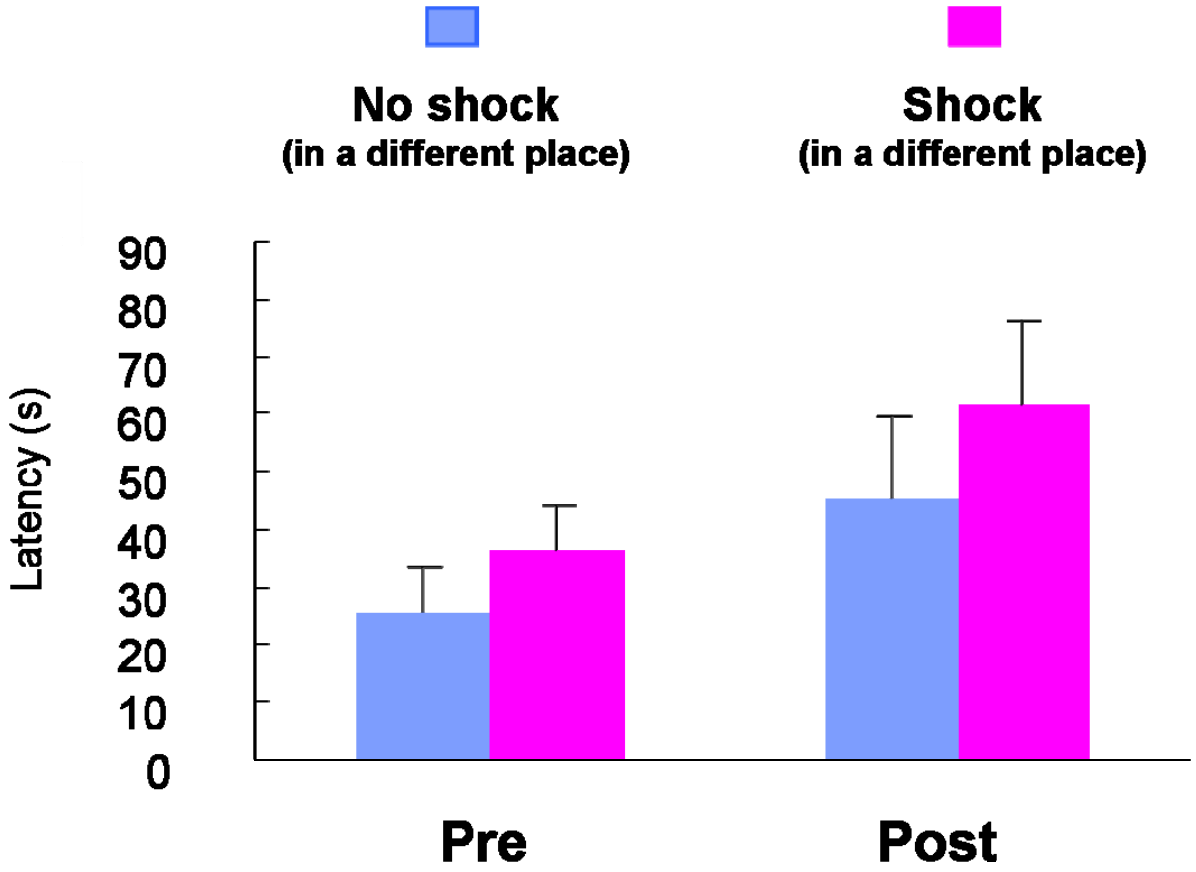

Fig.2.1.10. The effect of shock experience on social facilitation of avoidance. Latency of no-shock subjects (blue) and shock subjects (purple) are shown as mean ± SEM. There was no significant difference. The number of the subjects in No shock and that of in Shock were n = 15 and n = 16, respectively.

2.1.4 Discussion

In the current study, the behavioral influences of social interaction between two rats in changing environment were systematically evaluated by focusing on the previous experience of passive avoidance learning. The major results were followings: (1) learned avoiding behavior was inhibited by social interaction with neighboring partners, especially not-avoiding partners; (2) avoiding behavior of experienced rats was reinstated by shocked partner; (3) there were none of the inexperienced rats whose avoiding behavior was modified by any kinds of partners. Taken together, these results indicate that previous learning is a crucial factor for the social learning of avoidance in rats. Our findings suggest a view in which the prerequisites for the social learning of avoidance may include previous learning experience of subjects as well as alarming social cue from others.

Social interaction induces inhibitory influence on avoidance of experienced subject in safe conditions

The experienced subjects were inhibited by the partners in the no-shock conditions. These inhibitory influences of social interaction were also found in learned aversion to a flavored food (Galef 1986) and conditioned fearful response (Kiyokawa et al. 2004; Kiyokawa et al. 2007). New finding of the present study is that inhibitory influences depend on partner's experience. The strength of inhibitory influence was much higher by inexperienced partners than by experienced partners. This suggests that the previous learning of partners has a specific role for the social modulation of avoidance. How do social partners affect avoiding behavior of other individuals? Some studies have shown that individual vigilance was depressed by increasing group size (Elgar 1989; Lima and Dill 1990) or by shortening neighbor distance (Elgar et al. 1984; Roberts 1988) in various animals. The depressed vigilance may prompt inhibitory influence on avoidance. These effects can explain inhibitory influence of experienced partners. The group effect cannot explain why influence of inexperienced partners is higher than that of experienced partners. Inexperienced partners

inhibited the avoidance more strongly than experienced partners, even though the two rats were placed in the very limited space in the ES-EP conditions. Therefore, there should be other mechanisms. Rats have been thought to have some high-order cognitive abilities such as imitation through observation to acting others (Heyes et al. 1992), and causal reasoning (Blaisdell et al. 2006). One possibility is that the rats might imitate the behavior of inexperienced partners introducing dark compartment without awareness. Another one is that the rats might expect extinction of dangerous stimuli by inference from partners' behavior.

Social interaction with shocked partners can induce facilitatory influence on avoidance

As already mentioned, the previous studies suggested that social transmission of avoidance do not occur in naïve rats (Galef et al. 1983; Galef et al. 1990; White et al. 1998). The present results that the avoidance behavior of inexperienced subjects was not facilitated by social interaction in neither no-shock conditions nor shock conditions are consistent with the previous studies. However, we observed that social interaction facilitated avoidance in avoidance-experienced rats. A previous research also showed that conditioned fear was recovered by presentation of shocked partners in Pavlovian conditioning (Riess 1972). Our results provide the possibility of social learning of avoidance in operant learning paradigm, not only Pavlovian conditioning but also operant one. We demonstrated also that experience of only shock, non-contextual aversive stimuli, does not work for the reinstate of avoidance behavior. This suggests that experience of contextual aversive stimuli is essential for social facilitation of avoidance. The present systematic experiments empirically showed the unexamined differences between avoidance-related adaptation of experienced rats and inexperienced ones under social environments.

Social cues for the social transmission about avoidance in rats

Animals transmit various types of social cues, and those signals tell important information to other companions. The present results clearly demonstrate that social cues from a partner determine contents of social transmission. Social cues emitted by partner rats can be categorized into two types with according to situations on the partners and stimulus applied to the partners. One is accompanied by punishment or negative stimulus such as electrical shock to individual animals. This type of social cues can be announcement of aversive or danger for others. Actually, for example, fish emit alarm substances when they are attached by enemy. Those substances are social cues that trigger avoidance in others (Von Frisch 1938). Another one is accompanied by reward or positive stimulus such as food to individuals. That can be announcement of favorite or safety for others. Social transmission of food preference in rats (Galef 1985) is an example.

What signals are important for the adaptation to changing environment? The present study investigated social transmission of information with environmental change; from danger to safety and vice versa, and may help to answer the question. The results suggests alarming vocalization emitted from electrically-shocked partners (sound), excretion including urinary and feces (smell and pheromone), and struggling motion (vision) act as signals for an announcement of danger. For an announcement of safety, none of shock-induced reaction of partners may be important signal. In social animals, avoiding or facilitating a behavior by many types of social cue effectively controls their adaptation to changing environment.

How does individual experience affect on social learning?

Previous individual experiences have an important role for social learning. What is the importance of the learning experience in the processes of the social learning? There seem to be two possibilities, at least.

First, individual experiences work to enhance the acquisition of information from other animals during observation. Some studies indicate aversive experience enhance the

sensitivity of acquisition of information (Fletcher and Wilson 2002, Wilson 2003, Li et al. 2008). Getting information from others is the first step of social learning. There is no doubt about importance of the quality of getting information in social learning. How can this explain the present results? By following this hypothesis, experienced subjects were affected by other partners because of enhancement of sensitivity, but inexperienced subjects were not because sensitivity was not enough level. This interpretation can explain present results partially, but it is difficult to explain all by only this interpretation because of following reason. In this experiment none of inexperienced subjects was affected by partners although inexperienced subjects received similar social cues as experienced subjects did. Actually, the previous study has shown that inexperienced rats get information from other conspecifics showing fear response (Knapska et al. 2006). This is inconsistent with the first hypothesis. Next hypothesis can explain that result.

Second, when getting social cues, individual experiences are recalled and works to associate individual experience with information from other conspecific to plan next appropriate action. That is another promising hypothesis. If avoidance-learning is recalled under the influenced of partner's cues, avoiding behavior will be quickly reacquired even after avoiding responses were extinct. Although there is no direct evidence that individual memory is recalled via another conspecific in rats, memory can be recalled by various associative stimuli. The physiological study which has shown that motion-selective neurons exhibit unprecedented selectivity for the shape after shape- motion association (Schlack & Albright 2007) suggests that learned experiences also can be recalled by associative stimuli which may include social cues at least in visual processing. The neural mechanism where social cues are associated with individual experiences should be elucidated in future. These two possible functions may support some stages of social learning.

Our results provide evidence that individual experience is one of the important and indispensable factors for social learning. The social learning of avoidance has been little advanced may be because behavioral experiments focusing on individual experience are not so popular. Additional progress of the behavioral studies considering individual experience may facilitate understanding neural mechanism for social learning through cooperation with neurological studies that have been revealing the neural mechanisms of various types of

learning.

2.1.5. Conclusion

In conclusion, we have shown that undefined efficacy of social interaction, focusing on experience of rats. Through the whole experiments, the experienced subjects were influenced by both experienced and inexperienced partners with or without shock stimuli in their environments. That suggests that rats can adapt their behaviors with utilizing both by interaction with variety types of partners and by individual experiences on multiple social situations.

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2.2 Effect of Partner Difference (Familiarity)

Abstract

Rats receive information modulating their avoidance behavior from other conspecifics. Social animals make groups, and the relationship among the members of a group is formed through housing together. However, the involvement of familiarity on social transmission of avoidance is not well known. This study examined the effect of familiarity on social transmission of avoidance in rats. We used Long-Evans rats and allowed them to interact with a familiar partner housing at same cage for 4-5 weeks (cagemate) or with an unfamiliar partner housing at different cage (non-cagemate). The experiment was conducted by inhibitory avoidance (passive avoidance) paradigm using step-through shuttle box consisting of light and dark chambers. As result, interacting with familiar partner tended to induce less effect on social inhibition of avoidance. There were no significant effects of familiarity on social facilitation of avoidance. These results suggest that partner difference can affect social inhibition of avoidance even on small way.

2.2.1 Introduction

Social animals interact with other conspecifics and transfer information for effective adaptation to their environments. Rats transmit information modulating their avoidance behavior. This is called social transmission of avoidance in our studies. In social transmission of avoidance, the animals are able to be divided into two types: “transmitter” and “receiver”. The transmitter is the animal emits information to other animals, while the receiver is the one receive information from the transmitter.

Social relationship is one of the most important factor to organize many aspects of social behavior, such as social contact (social investigating behavior) and the aggressive behavior (to form the social hierarchy). A behavioral test for social memory or social recognition has utilized behavioral difference among familiar conspecifics and unfamiliar conspecifics; investigation time to animal each other is longer in unfamiliar relation (Thor and Holloway 1982). In social transmission of food preference, the relationships between the transmitter (or demonstrator) and the receiver (or observer) have effects on the degree of food preference. Awazu and his colleagues showed that the relationship between two rats, a demonstrator and an observer, has stronger effect in unfamiliar pairs than in familiar pairs (Awazu et al. 1998). They also showed that subordinate rats strongly transferred food preferences than dominate rats (Awazu et al. 1998). Someone can speculate that familiar or dominant animals affect more strongly than unfamiliar or subordinate animals. That is not fact in social transmission of food preferences by rats. That is, however, fact in some other cases. Interestingly, other species of rodents, gerbils (Meriones unguculatus) do not transfer the food preference to the unfamiliar and no kin ones to the receivers (Valsecchi et al. 1996). Familiarity is one of the factors well-known as modulating social transmission.

In terms of social transmission (or social learning) of avoidance, there are some reports that shows kinship and familiarity modulate the social transmission of avoidance. The studies by Kavaliers and colleagues using deer mice learning to avoid micropredators (biting fies) by self-burying showed that social learning of avoidance responses were higher in kinship and familiar pairs than in non-kin or un-familiar pairs (Kavaliers et a. 2005). In addition to deer mice, a variety of rodents including rats have been shown to discriminate

between kin and non-kin and familiar and non-familiar conspecifics (Grau 1982; Holmes 1986; Heth et al. 1988; Paz et al. 1999; Hurst et al. 2001; Valsecchi et al. 2002). Rats, whose avoidance is influenced socially, however, have been not known whether their social modulation of avoidance is affected by familiarity or not.

As an important view point, the avoidance response is not perfect as an adaptive behavior. In nature, animals need to make a decision to obtain maximized outcome. Animals will pay some costs when they display avoidance responses under a situation. For example, animals coincidentally in hunger, thirsty, and threaten by predators are forced to choose the best behavioral option. Inevasible behavioral trade-offs between the benefits of avoidance behavior and the costs of it regarding optimization of feeding and reproduction, and survival (Abrams 1986; Lima et al. 1990; Sih 1990; Sih 1992; Abrams 1994; Lima 1998; Jonnson et al. 2000). Actually, rats and other rodents show “minimized” avoidance response in response to the threat (i.e. predator’s coming), because some avoidance responses (refuges use) has costs for a loss of time (for mating, feeding, or foraging) and physiological constraints such as hypoxia (Sih 1992; Abrams 1994; Jonnson et al. 2000). It should be important to observe the process of regulation avoidance behavior, which means regulation in both inhibitory and facilitatory directions.

In the present study, we investigated the effect of the familiarity on social transmission of avoidance in both inhibitory and facilitatory way using modified passive avoidance paradigm.

2.2.2 Materials & Methods

Subjects and housing

The subjects were 42 male Long Evans rats acquired Kyudo Co., Ltd. (Kumamoto, Japan). They were able to access to food and water, and housed two per cage for 4 or 5 weeks. Housing conditions were thermostatically controlled at 22–24℃ with an inversed dark/light cycle (lights on: 20:00—08:00). The experiments were performed under the control of the Ethics Committee of Animal Care and Experimentation in accordance with the Guiding Principles for Animal Care Experimentation, Kyushu Institute of Technology, Japan, and with the Japanese Law for Animal Welfare and Care.

Apparatus

Same apparatus as the experiment for effect of previous experience of avoidance learning (section 2.1) was used.

Experimental Protocol

All treatments or behavioral tests were conducted during the light cycle (19:00–8:00). All subjects were housed with pairing for at least 4 weeks in order to construct their familiarity. After that period, at age 9 weeks, we measured the passive avoidance learning of each animal over 3 days. (On the 1st day, animals were habituated the apparatus for 3 minutes. Animals received electrical shock when the animals enter the dark room on the 2nd day. We measured the latency to enter the dark room on the 3rd day.) All animals were divided into two groups on half-and-half by equating the avoidance level between the groups: familiar group and unfamiliar group. Subjects in familiar group were allowed to interact with familiar partners (the housing mate), whereas that in unfamiliar group were able to interact with unfamiliar partner (non-housing mate). On the fourth day, we measured the avoidance inhibition under social conditions (familiar or unfamiliar conditions). First, we put each subject into light room with familiar or unfamiliar partners at the starting the test. The animals were able to interact for 1 min, and then we measured the latency after opening the partition. The cut-off time was 20 min. After the measurements, we measured the latency

again under individual condition in order to compare the avoidance level between social and individual conditions. Day 5, we measured the avoidance reinstatement by shocking partner. As first session of day 5, we measured the latency twice under individual conditions with time lag (1 h). This procedure was for inducing extinction of avoidance (in day5-1) and for measuring the avoidance level on pre-interaction (in day5-2). Third session on day5, we put the subject and partner into the light room and allowed to interact each other for 1 min. We allowed the partner alone to enter the dark room, and then induced foot shock (0.5 mA, 3 s, 1-3 times). After interval of 30 s, we removed the partner, which had returned to the light room. The latency of the subject was measured. We conducted crossover experiment by reversing subjects and partners to each others. The shocked partners were treated as subjects, and the subjects were treated as partners after day 6. During day 6-8, the procedure was same as day 3-5 except for the replacement of subjects and partners.

Statistical Analysis

Data analyses were performed by using Excel Tokei (SSRI statistical software). Before analysis, the Kolmogorov-Smirnow test was performed for normality. Separate ANOVAs were subsequently performed to determine the effect of familiarity (difference between group of the cagemates or non-cagemates). To determine the difference of social avoidance facilitation between cagemates or non-cagemates, we used a relative value (post latency /pre latency) as facilitation ratio and changed value (post latency ― pre latency). Difference between the facilitation ratio and facilitation change were determined by using Student's t-test. We used Spearman rank correlation coefficient matrix to presume the factor may affect the social avoidance facilitation. The criterion for significance was $P < 0.05$.

2.2.3 Results

Effect of familiarity on social inhibition avoidance

Subjects were pair housed for at least 4 weeks. That was probably enough duration. According to previous study, the effect of familiarity of rats was found in social transmission of food preference during 10 days (Awazu et al. 1998). We allowed interaction with housing partners (Familiar group) and with non-housing partners (Unfamiliar group). Results are shown in Fig. Both groups showed almost same level of avoidance learning (ANOVA: main effect of familiarity: passive avoidance learning: F = 0.013, P = 0.90). Under the social conditions, the avoidance of familiar group was longer, but it did not reach the significant level (ANOVA: main effect of familiarity: social avoidance inhibition: F = 3.58, P = 0.06). Then we again measured the latency of the subjects under individual conditions by removing the partners. Both groups showed almost same level of avoidance recovery (ANOVA: main effect of familiarity: avoidance recovery by partner remove: F < 0.001, P = 0.99). Comparison between replacement of subjects and partner showed significant effect on passive avoidance learning (ANOVA: main effect of replacement: F = 4.86, P = 0.03) and social avoidance inhibition (ANOVA: main effect of replacement: F = 8.30, P = 0.006). This difference probably due to the frequency difference of induced foot-shock. In our study, familiarity of the partner affected very little on social avoidance inhibition.

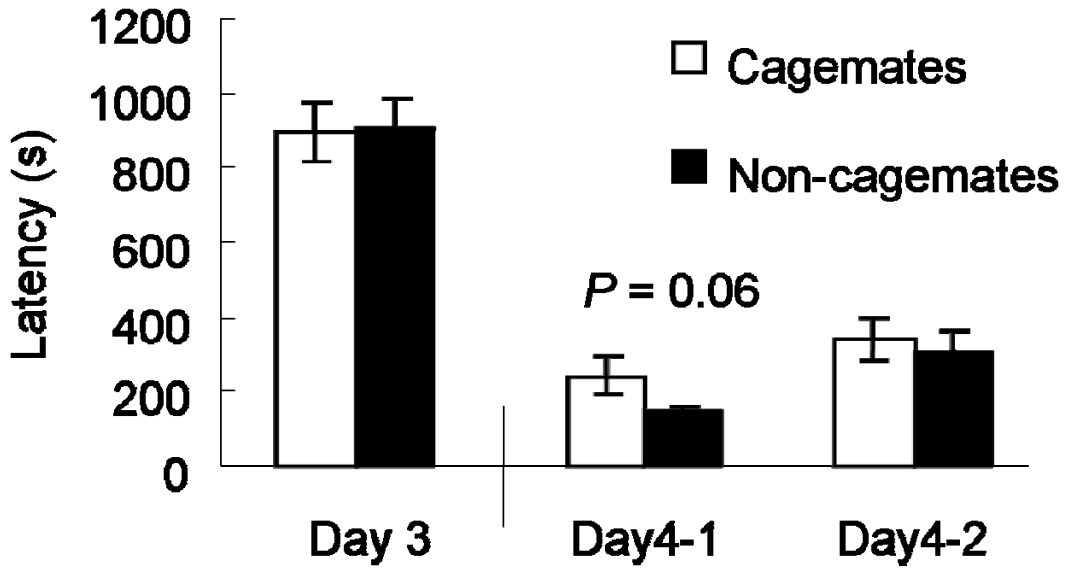

Fig.2.2.1. Effect of familiarity on social inhibition of avoidance.

Data are derived from whole animals the present study used.

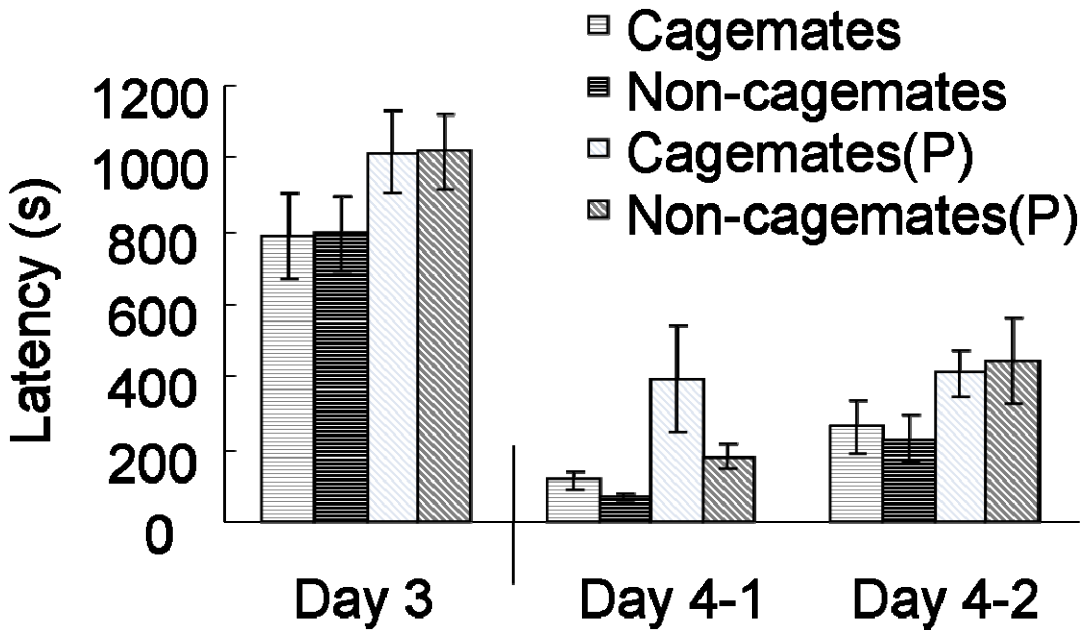

Fig.2.2.2. Effect of familiarity on social inhibition of avoidance.

Data are separately represented as cagemates, non-cagementes, cagemates (partner), and non-cagemates (partner).

Effect of familiarity on social avoidance facilitation

On day 5, the avoidance level was measured three times. First, we examined the initial avoidance for the day and keep the subjects in the experimental apparatus for 20-30 min to induce the extinction process. One hour after the first measurement, we measured the latency again as the avoidance level on pre-condition. The avoidance score was almost same level between the Cagemate group and Non-cagemate group (P = 0.81, Student t-test). In third trial, the subjects were allowed to interact with the partners (cagemates or non-cagemates) which were randomly selected and had given the shocks (0.5 mA, 3-6 s). After removing the partners, the avoidance level was measured. As results, the avoidance tended to greater in cagemates than in non-cagemates (P = 0.09, Mann-Whitney U test). Avoidance of cagemates was significantly facilitated (P = 0.009, Wilcoxon test), but not in non-cagemates (P = 0.42, Wilcoxon test) Data are shown in Fig.2.2.3. Further analysis, calculating the post/pre facilitation ratio of individual data, showed similar effect (P = 0.09, Mann-Whitney U test, Fig.2.2.4.).

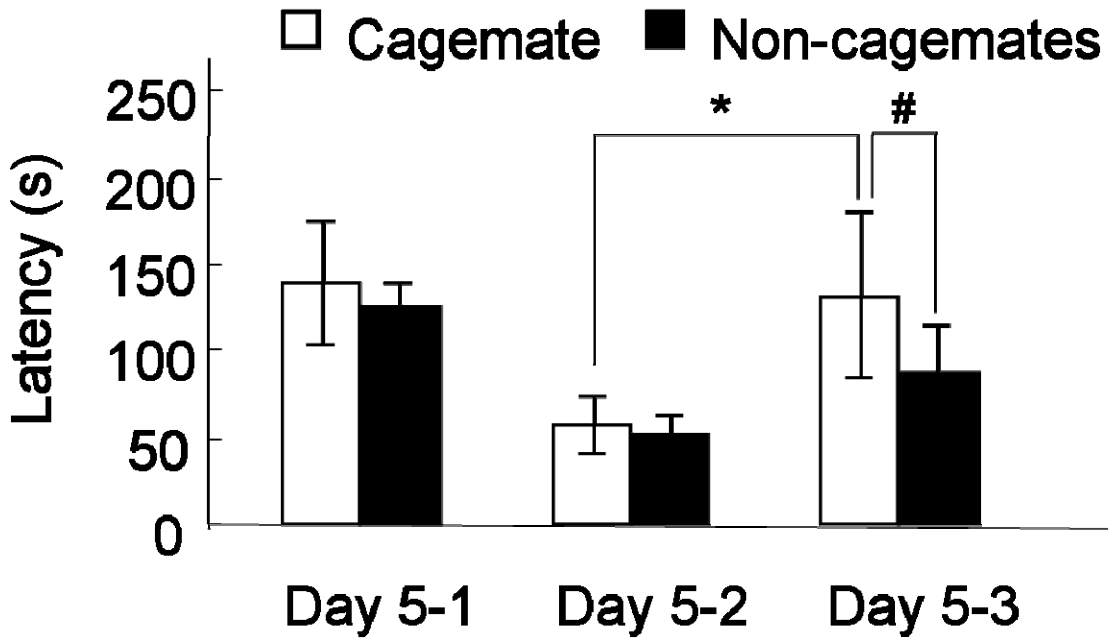

Fig.2.2.3. Effect of familiarity on social facilitation of avoidance.

There are significant differences between latency of cagemate Day 5-2 and Day 5-3 (*; Wilcoxon test). Facilitation tended to be higher in cagemate than in non-cagemate (#; Mann-Whitney U test).

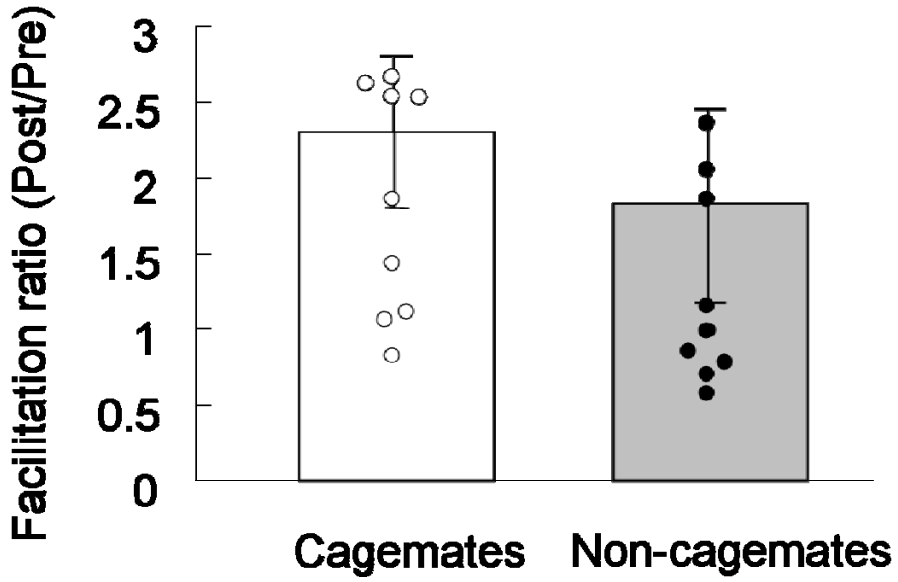

Fig.2.2.4. Facilitation ratio of cagamates and non-cagemates. Cagemates tended to show greater facilitation (*P* = 0.09, Mann-Whitney U test).

Facilitation level correlated with the individual avoidance level before the interaction

We further examined the correlation between the facilitation ratio or facilitation change (post latency — pre latency) and the avoidance level on day 3 and day 4 in order to presume the effective factor(s) on previous conditions. For analysis under all subjects, we found significant correlation between facilitation ratio (%) and facilitation change (⊿) ($R = 0.93$, $P < 0.01$) and between the facilitation ratio and avoidance level on day 5-1 ($R = 0.56$, $P < 0.05$). There are no significant correlation between facilitation ratio or change and individual previous avoidance level in the cagemate group. In the non-cagemate group, on the other hand, we found significant negative correlation on between avoidance level on day 3 and the facilitation ratio ($R = -0.69$, $P < 0.05$) or change ($R = 0.77$, $P < 0.01$) and significant positive correlation between facilitation change and avoidance level on day 5-1 ($R = 0.64$, $P < 0.05$).

Table 1 The matrix of Spearman rank-correlation coefficient

Factor	%Facilitation	⊿Facilitation	Day 3	Day 4-1	Day 4-2	Day 5-1
For all subjects (n = 21)						
%Facilitation	1.0000	0.9373**	-0.2695	0.1943	0.0091	0.3532
⊿Facilitation	0.9373**	1.0000	-0.2328	0.2565	0.2481	0.5664*
For cagemates (n = 10)						
%Facilitation	1.0000	0.8545**	0.3865	0.1636	0.0909	0.1394
⊿Facilitation	0.8545**	1.0000	0.4724	0.1758	0.5515	0.5394
For non-cagemates (n = 10)						
%Facilitation	1.0000	0.9636**	-0.6979*	0.3091	-0.1727	0.6182
⊿Facilitation	0.9636**	1.0000	-0.7723**	0.3545	-0.1455	0.6455*

* P < 0.05; ** P < 0.01

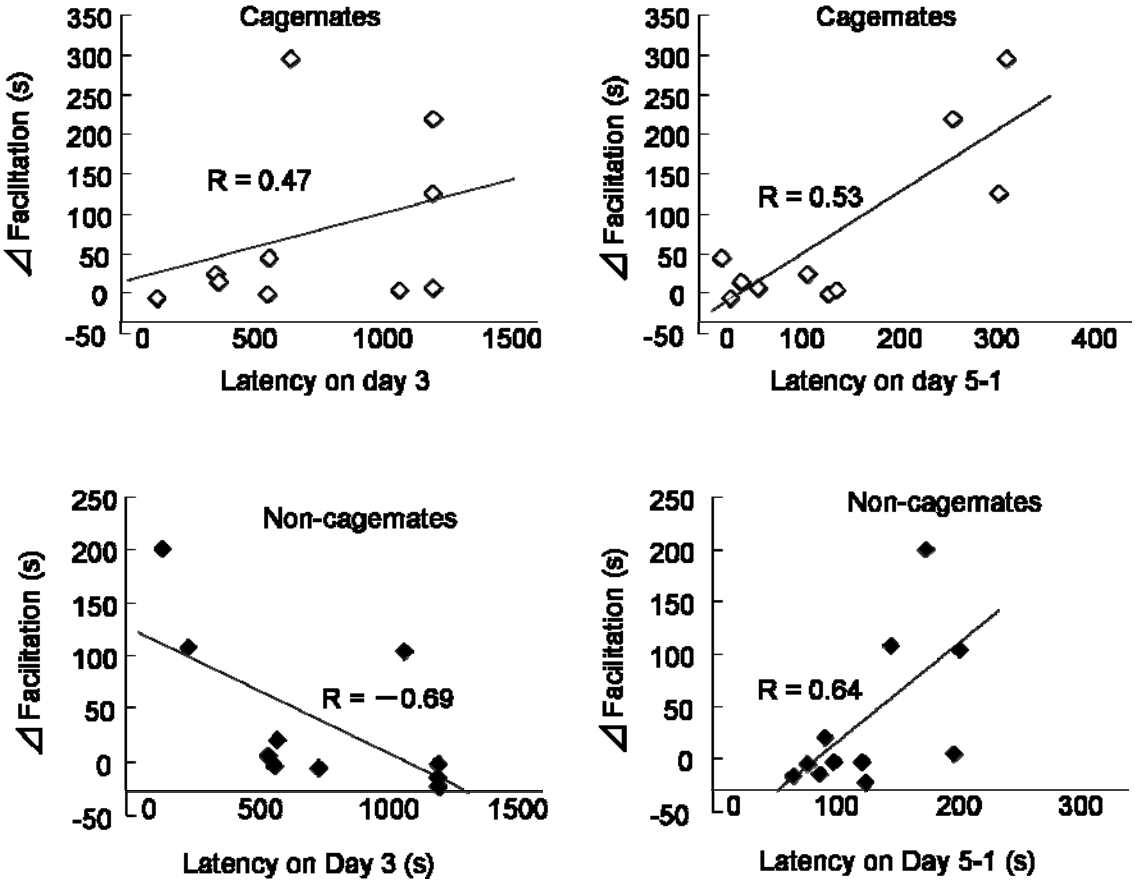

Fig.2.2.5. Correlation between avoidance-facilitation and latency on days prior to the interaction. There is inversed the correlation with latency on Day 3 (acquisition) to facilitation between cagemate and non-cagemate groups, but similar positive correlation (Day5 (adjacent avoidance) and facilitation) was found.

2.2.4 Discussion

In this study, we investigated the effect of familiarity on social transmission of avoidance. The whole present results showed that the effect of familiarity was small on social inhibition or facilitation of avoidance. Analyzing detail of the experimental results, however, we found small but important differences in partner familiarity on social transmission of avoidance.

Familiar partner has less effect on social inhibition of avoidance than unfamiliar one. The difference was not statistically significant, but almost reached the significance. There are some similar reports that showed the effect of familiar partners was less than unfamiliar partners. For example, the food preference was preferentially transferred from unfamiliar partner in rats (Awazu et al. 1998). Other research showed that the duration of social interaction was longer in those rats paired with a novel partner than those paired with a familiar partner (Barefoot 1975; Monroe 1977). Partner novelty is the one of the important motivation for social interaction and attractiveness for rats (Thor et al. 1988). Importantly, long time social interaction inhibits the activity of hypothalamic-pituitary-adrenal (HPA) axis, which leads high corticosterone levels in response to a stressful situation (Armario et al.1983). We do not measured the duration of social interaction during the present experiment, but the novelty of the partner stayed in the dark room might have facilitating effect on the social interaction.

Social facilitation of avoidance was not significantly differed among the rats paired with familiars and those paired with unfamiliar partners. Following the results and previous studies (Awazu et al. 1998), this result seems to be contradictive, and this may come from the different mechanisms of the two different types of social transmission. In our speculation, the difference between the results (for social inhibition of avoidance and that for social facilitation of avoidance) is based on the different fashion of the transmission. For example, social inhibition of avoidance can come from similar mechanisms of social transmission of food preference. One of the mechanisms is based on the high investing behavior to unfamiliar animals, producing a long time of social interaction (large transmission of information). The subjects were allowed relatively long time to interact with the partners in social inhibition paradigm, while the condition of social facilitation did allow

very limited term for social interaction. Therefore the difference of social interaction might be kept low in the social facilitation of avoidance. In social facilitation of avoidance, 'empathic reaction to familiar partner' is one of the possible mechanisms. A research showed pain-induced reaction is more strongly facilitated by familiar partner than by unfamiliar partner (Langford et al. 2006), suggesting that sensitivity of painful response is lower in familiar animals.

The correlations between the avoidance facilitation and the avoidance latency on previous trials were significant in some couples. Positive correlations on day 5-1 indicate the social facilitation of avoidance tends to depend on the avoidance level on the short time before the social interaction. Rats which marked higher level of avoidance on day 5-1 can show higher social facilitation of avoidance with according to the results. This correlation is stable and almost same level among the both familiarity groups. On the other hands, the avoidance level on day 3 (training period) showed negative correlation to the facilitation change in familiar group, totally different characteristic to unfamiliar group. That suggest the first avoidance learning level relates the level of the social facilitation of avoidance, but the relation is not stable. The present results are partially consistent and partially inconsistent with the previous study showing that the social facilitation of avoidance is dependent with the previous avoidance learning (Masuda et al. 2009). The negative correlation of familiar group implies that avoidance learning process can affect social facilitation of avoidance with two directions.

What is the functional significance of unfamiliar partner's stronger effect? Galef (1993) hypothesized social transmission of food preference has a role to reduce a cost for expanding feeding repertoires. Feeding foods eaten by unfamiliar conspecifics can facilitate the effective expansion of feeding repertories with low costs. Avoiding dangerous place is quite important function to save their lives. Expanding available place is also important for searching food or mates. Places unfamiliar conspecifics locate may have higher potential to hold variety of foods or mates than that familiar ones locate.

2.2.5 Conclusion

In this study, we investigated the effect of familiarity on social transmission of avoidance. Social interaction with familiar partners did not transfer social signals more effectively than that with unfamiliar partners. Instead, inhibition effect of unfamiliar partner tended to be stronger. This tendency may be adaptive for acquiring variety foods and mates.

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Chapter 3

Lesion studies: Identification of Important Brain Areas for Social Transmission of Avoidance

3.1 Medial prefrontal cortex lesion

Abstract

Animals receive information through interaction with the conspesifics and adapt to their environment effectively. This transmission of information is called social transmission. Rodent medial prefrontal cortex (mPFC) is functionally homologous to the dorsolateral prefrontal cortex (DLPFC) in primates, which is thought to support executive function and social recognition, and may play a role for the social functions in rodents, but functional roles of rodent mPFC in social transmission have been not clear. Previous study showed that social interaction induces inhibitory or facilitatory influences on avoidance response (step-through inhibitory avoidance) under safe or dangerous situations, respectively. Using this paradigm, we investigated the effect of bilateral mPFC lesions on social transmission of avoidance in rats. The avoidance behavior was measured as latency to enter a dark compartment. Under interactive safe condition, animals with NMDA based lesion in mPFC displayed normal social inhibition of avoidance, but impairment in spontaneous recovery of avoidance response which was observed in the sham-operated rats as usual. Under dangerous situations the social facilitation of avoidance was found in animals with mPFC damage, and the facilitation ratio of mPFC lesions was significantly higher than that of shams. The present study suggest that mPFC in rodents have a role in social transmission of avoidance, especially for controlling the balance between memory acquired from individual and social experiences.

3.1.1. Introduction

Social transmission, transmission of information modulating other's behavior, has been investigated in food preference (Galef et al. 1985; Galef et al. 1988), motor learning and skill (Carroll el al. 1982; Carroll et al. 1985; Frey et a. 2006; Voelkl 2007; Price et al. 2009), fear responses (Knapska et al. 2006; Schyns et al. 2009), and avoidance (Mineka et al. 1988; Hall et al. 1995; Brown 2003; Masuda et al. 2009). Neurological studies have investigated and revealed the brain regions relevant to such social transmission. For example, social transmission of food preferences, the involvements of hippocampus (Bunsey et al. 1995; Alvarez et al. 2001; Clark et al. 2002; Countryman et al. 2005; Boix et al. 2007; Countryman et al. 2007; Smith et al. 2007), subiculum (Clark et al. 2002), cholinergic transmission in basal forebrain (Vale-Martinex et al. 2001; Recceri et al. 2004; Bielsky et al. 2005; Boix-Trelis et al. 2006) and prefrontal cortex (Winocur et al. 1999; Ross et al. 2005; Ross et al. 2006). Observational learning of motor action has been investigated in human using fMRI (Decety et al. 1997; Frey et al. 2006) and in some species of animals (Leggio et al. 2000). In social transmission of avoidance, however, almost nothing has been known about the neuronal mechanisms.

Neuropsychological studies indicate that the medial prefrontal cortex (mPFC) of rats is the homolog of the primate DLPFC (Kolb 1974; Kolb 1990; Preuss 1995; Uylings et al., 2003; Vertes, 2006). Rodents' mPFC is a key region for multiple cognitive functions. Previous neurological studies suggest that mPFC is involved in executive functions (for review, see Dalley et al. 2004), attentional selectivity (Muir et al. 1996), working memory (Eichenbaum et al., 1983; Granon et al., 1994), strategy switching (Ragozzino et al., 1999; Birrell et al. 2000; Rich et al. 2007), discrimination of temporal delay (Catania 1970; Roberts 1981; Dietrich et al. 1998), and temporal organization of behavior (Kesner 2000). In addition, mPFC involves extinction learning of fear conditioning (Quirk et al. 2000). There should be modulating process of avoidance in social transmission of avoidance. It is possible that social transmission of avoidance is rooted in the neuronal process of mPFC. Here, we hypothesized that mPFC involves the social transmission of avoidance and examined the effect of exitotoxic lesion of mPFC on social transmission of avoidance.

3.1.2. Materials & Methods

Animals

Forty male Wistar rats (Kyudo, Kumamoto, Japan) weighing 210–230 gm aged 7 weeks were used in the present study. The animals were housed two per cage with food and water available ad libitum. Housing conditions were thermostatically controlled at 22–24°C with and maintained on a 12 hr dark/light schedule (lights on at 20:00-8:00). The experiments were performed under the control of the Ethics Committee of Animal Care and Experimentation in accordance with the Guiding Principles for Animal Care Experimentation, Kyushu Institute of Technology, Japan, and with the Japanese Law for Animal Welfare and Care.

Surgery

The rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and mounted on a stereotaxic device. An incision was made to expose the skull, and small holes were drilled in the skull above the injection sites. They then received either NMDA lesions (n = 20) or sham operation (n=20). A dose of 15 mg NMDA (Sigma, USA) was dissolved in 1 ml of phosphate-buffered saline (0.1 M, pH = 7.4). NMDA solution was freshly prepared on the day of surgery. We infused in four sites of the mPFC: (AP: + 3.7; ML: ± 0.7 mm; DV: − 3.0) and (AP: + 2.7 mm; ML: ± 0.7 mm; DV: − 3.5 mm). The volume was 0.3 μl per site. The sham operated animals received the same surgical procedure except for infusion an equivalent volume of phosphate buffer. A recovery period of at least one week was allowed.

Histology

After the completion of behavioral testing, the rats were deeply anesthetized with intraperitoneal urethane and perfused transcardially with a fixative containing 10% formaldehyde. For histochemical verification, coronal sections (40 μm) were prepared with a freezing microtome and mounted on the slide glass coated with silane. They were then stained using cresyl violet. We examined under microscope to determine the extent and location of the NMDA-mediated lesions.

Apparatus

The test chambers same as the previous study was used.

Behavioral tests

Tests for social transmission of avoidance

All behavioral tests were recorded with video camera (Olympus, μ1030 SW) and stored as movie files. The behavioral test same as the previous study was conducted. The experiments were organized of successive 5 days: day 1-3: avoidance learning (training) session; day4: social avoidance-inhibition session followed by individual probe test; day 5: social facilitation of avoidance session including two trials for preparation. After habituation, all subjects received electrical shock in the dark compartment when they had intruded into there. On day 3, we measured the subject's latency to enter the dark compartment as an index of avoidance behavior. We removed the subjects which latency was less than 2 min (n = 2: lesion; n = 3: sham). Two min after entering dark compartment, the subjects were removed from the apparatus. All experimental subjects were learned subjects (experienced passive avoidance learning). On day 4, the subjects were allowed to interact with naïve partners (safe social conditions). The avoidance behavior of the subjects were examined under safe social conditions (lesion: n = 11; sham: n = 10) or under individual conditions (lesion: n = 7; sham: n = 7) for control test to examine the effect of lesion on extinction learning. On day 5, the subjects were allowed to interact with shocked partners (dangerous social conditions). The latency to enter the dark compartment was measured under individual conditions and then measure again under dangerous social conditions (lesion: n = 12; sham: n = 9). Then we compared the latency between individual and dangerous social conditions. All behavioral tests were occurred between 12:00 and 18:00.

Open field test

Animals were place in the open-field apparatus of square field (80 × 56 × 40 cm), in which an object (12 × 9 × 7 cm) was placed at the center. They were allowed to move freely for 10 min. We measured 1) total distance moved; (2) frequency and duration of rearing (standing on hindlegs); (3) time spent in center area; (4) the frequency and duration of grooming. The

total distance moved was evaluated as an index of animals' basic activity, rearing behavior and the time spent in center area were evaluated as an index of exploratory behavior, respectively. The frequency and duration of grooming was evaluated as an index of responsibility to the novel environment.

Elevated plus maze

The apparatus was made of translucent brown acrylic material and consisted of 2 open arms (50 × 10 cm) and 2 closed arms (50 × 10 cm). The wall was 39-cm high, and the apparatus was elevated to 50 cm above the floor. The arms extended from a center square platform (10 × 10 cm) and were arranged so that the arms of same type were located at opposite site to each other. Each rat was placed on the center square platform and was allowed to move freely for 5 min. We recorded the time spent in open arms, number of entries into the open and closed arms. We also calculated the number of ratio of the time spent in open arms (staying duration in open arms/ staying duration in closed arms) and ratio of open arm entries (open arm entries/closed arm entries). The ratio of time spent in open arms and the ratio of open arm entries were evaluated as an index of anxiety-like behavior.

Statistical analysis

The results were express as mean and standard errors of the mean (S.E.M.) except for the facilitation ratio, which was expressed as mean and S.E.M. but also as individual law data. All data were analyzed by SPSS software (ver. 16.0). We conducted the Kolmogorov-Smirnow test for normality. In comparing the difference between the avoidance level of mPFC-lesioned animals and sham-operated animals, Student's t-test was used. The facilitation in each group was statistically examined by paired *t*-test. The difference of avoidance facilitation ratio of lesioned animals and sham-operated animals was examined using Mann–Whitney's *U* test due to lack of normality. Statistical differences were considered significant was $P < 0.05$.

3.1.3. Results

Histology

Fig.3.1.1. shows the area of minimal and maximal extent of mPFC lesion for subjects, and Fig.3.1.2.shows examples of mPFC lesion and sham-operated brain sections.

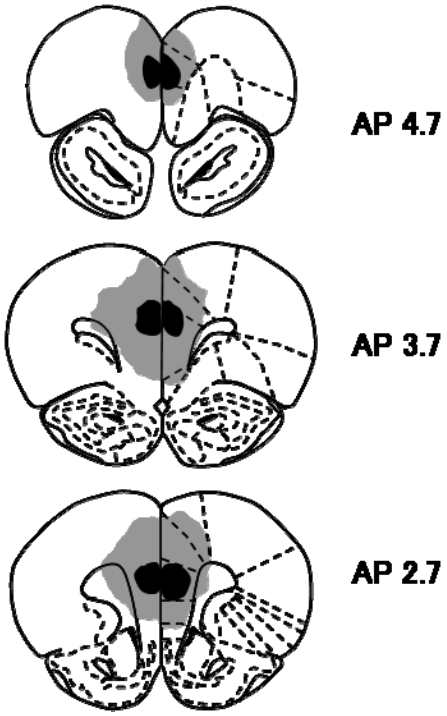

Fig.3.1.1. NMDA lesion of medial prefrontal cortex. Maximum (black) and minimal (gray) extent of medial prefrontal lesions are displayed using the brain atlas (Paxinos and Watson, 1998).

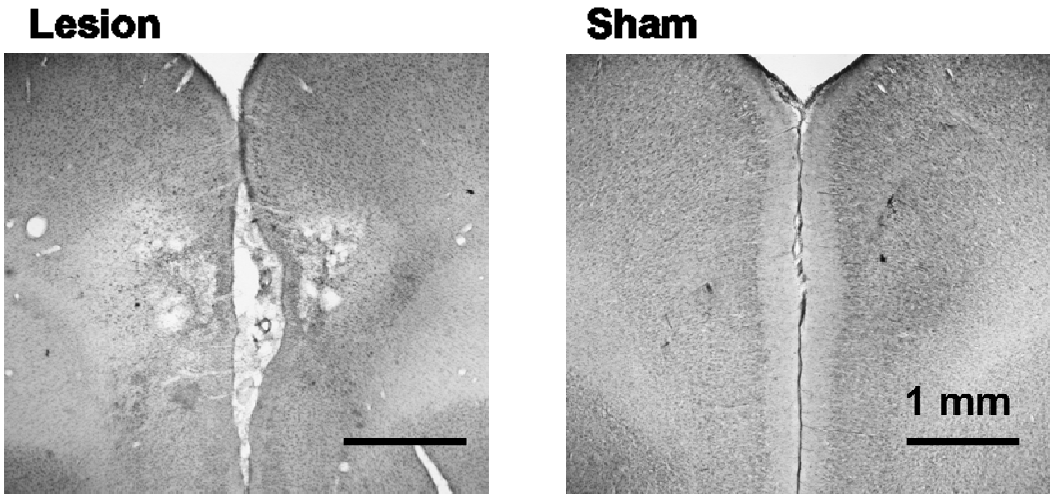

Fig.3.1.2. Examples of lesioned brain sections.

Left shows a brain section with medial prefrontal damage (from a lesioned animal). Right demonstrates a brain section with no damage (from a sham-operated animal).

Effect of mPFC lesion on social inhibition of avoidance

Rats with mPFC lesion learned the avoidance responses at the similar level as sham-operated rats (Fig.3.1.3). The next day, the subjects were allowed to interact with the naïve partners, which would suppress the avoidance responses of the animals with avoidance learning. The experimental overview is shown in Figure 3.1.4. Then we found that the avoidance responses of animal with mPFC damage inhibited by naïve partner similarly to the sham-operated animals (Fig.3.1.5.).

One hour after the first trial (for interacting with naive partners), on second trial, we measured the avoidance responses of both subjects on single-subject conditions to compared the avoidance responses between social and asocial conditions. We previously observed that the avoidance response was recovered in response to social to asocial conditional change. In the present experiment, we observed the recovery of avoidance responses in sham-operated animals as usual. In mPFC lesioned animals, however, the recovery was not found (Fig. 3.1.5.).

One concern to explain the attenuation of the avoidance-recovery is the facilitatory effect of lesion mPFC on extinction of avoidance learning. If mPFC lesion facilitates the extinction process, the avoidance responses itself should be attenuated strongly. Actually, extinction of fear conditioning, one of the emotional (Pavlovian) learning same as avoidance learning, is disrupted by mPFC lesion (especially infra-limbic region of mPFC) (Quirk et al. 2000). In addition to the lesion study, neurons in mPFC response to the cue signal for extinction of fear conditioning (Milad et al. 2002). Therefore, to investigate the effect of mPFC lesion on extinction of passive avoidance learning, we conducted two sequential asocial-asocial trials. We did not found the significant effect on extinction of passive avoidance learning as shown in Fig. 3.1.5.

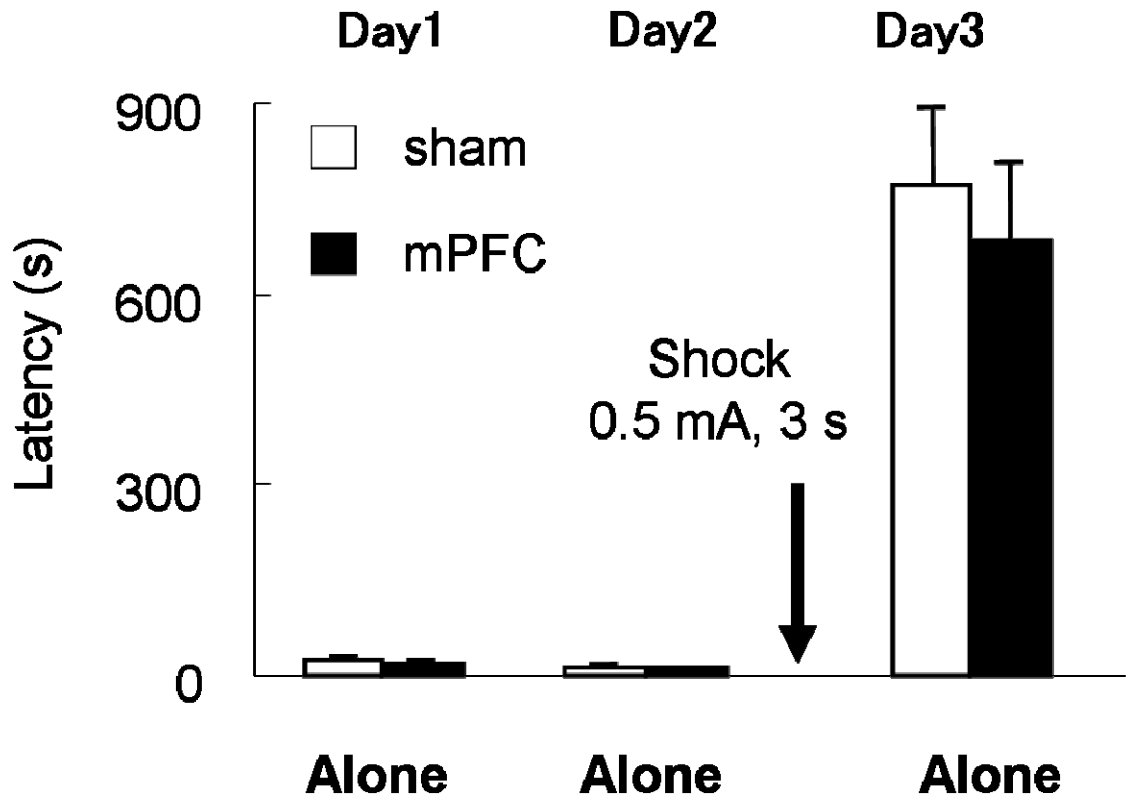

Fig.3.1.3. Latencies, as an index of the avoidance level, of the lesioned and sham-operated animals. On day 2 the all subjects received an electrical shock at the dark compartment, and 24 hours later they showed long retention time for entering. There was no significant difference between two groups in latency on day 3 and other two days.

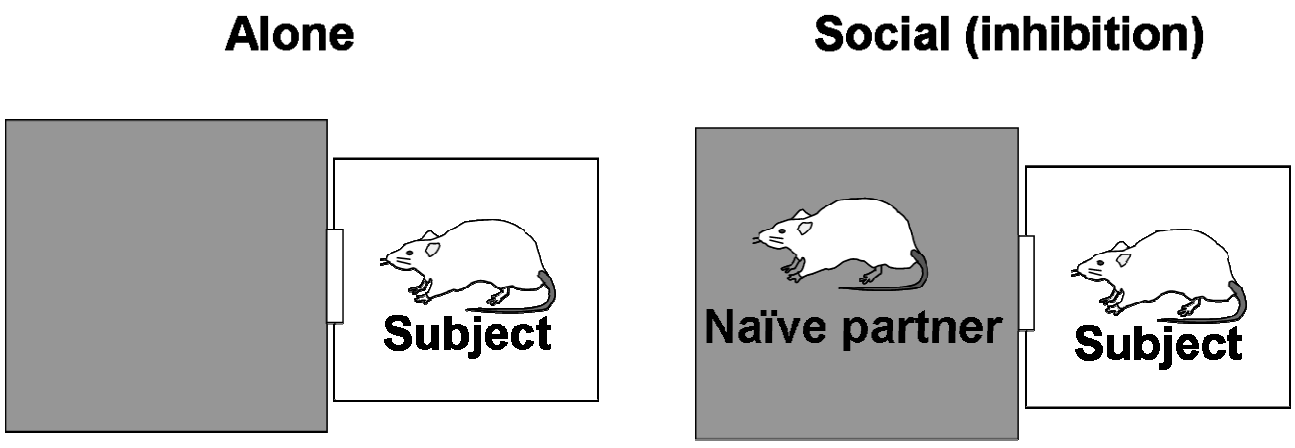

Fig.3.1.4. Experimental overview of the test for social inhibition of avoidance (day 4). In alone conditions of this test, the subjects were placed alone in the light compartment at the start of the test (left). In social conditions of this test, the subjects were placed with naïve partners in the dark compartment at the start of the test (right). The avoidance behavior of the subjects which learned passive avoidance will be inhibited by naïve partners.

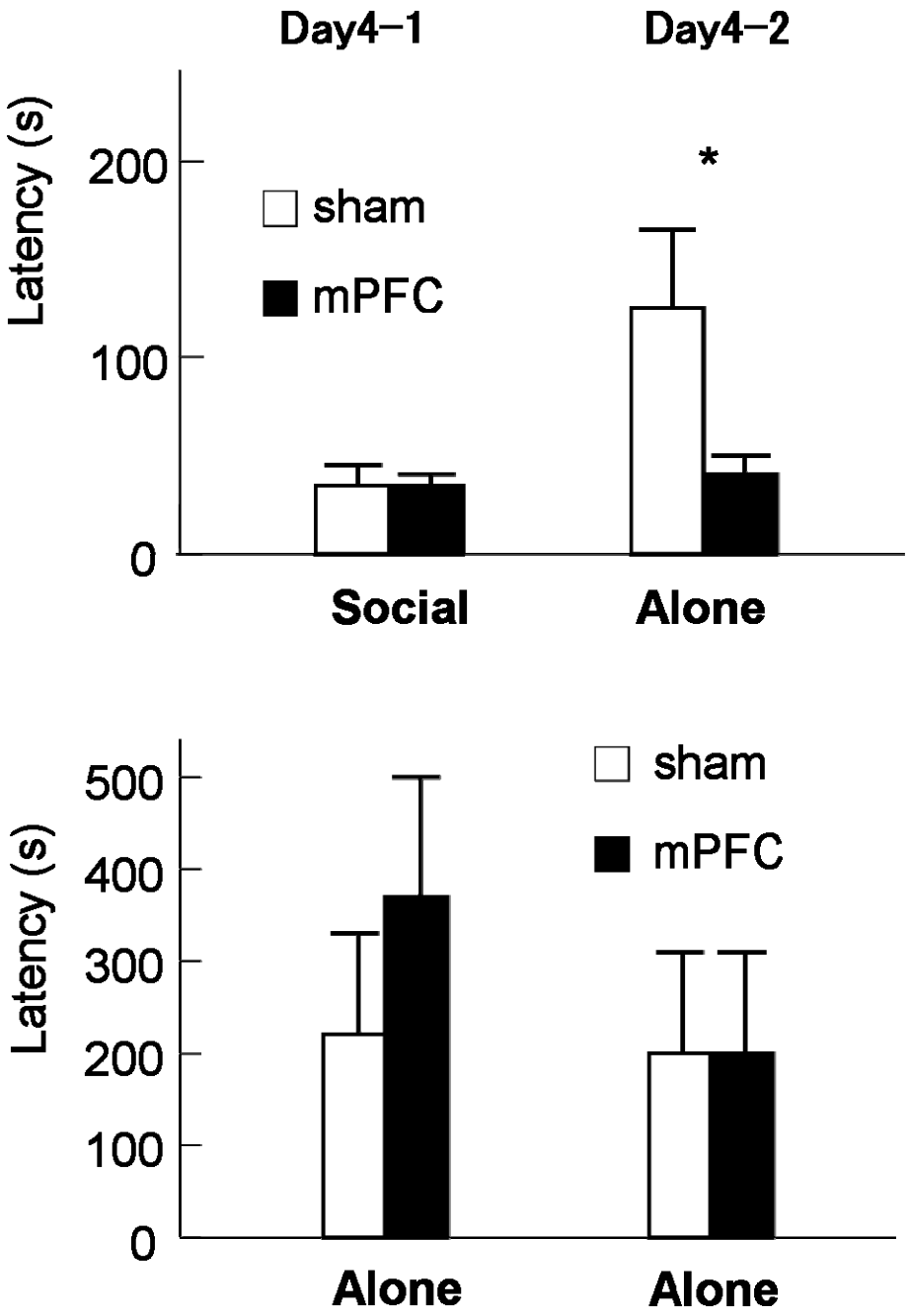

Fig.3.1.5. Effect of mPFC lesion on social inhibition of avoidance. Top graph shows the latency on the alone (day4-1) and social conditions (day4-2). The avoidance level was not different between two groups at first trial, but animals with mPFC lesion showed shorten latency at the second trial. Lower graph shows the latency on successive two alone conditions (day4-1, day4-2). There are not different between two groups.

Effect of mPFC lesion on social facilitation of avoidance

Interacting with shocked partners can induce facilitation of avoidance responses (Masuda et al. 2009). On day 5, we conducted three consecutive measurements consisting of two asocial trials and one social trial (Fig. 3.1.6.). Compared between latter asocial trial and last social trial, the change of latency of the both subjects was measured and used as an index of social facilitation of avoidance. After first asocial trial, on day 5-2, the latency was not significantly different. And, on day 5-3, we did not found significant difference between mPFC lesion and sham-operated subjects (Fig. 3.1.7.). We further analyzed the facilitation ratio determined by the relative retention time (social/asocial) in individual subjects of mPFC lesion and sham-operated animals. In such facilitation ratio, there were significant difference between mPFC lesion and sham. The facilitation ratio was higher in mPFC than in sham-operated animals (Fig. 3.1.8.). Even on relatively short-scale, the avoidance responses were facilitated by mPFC lesion.

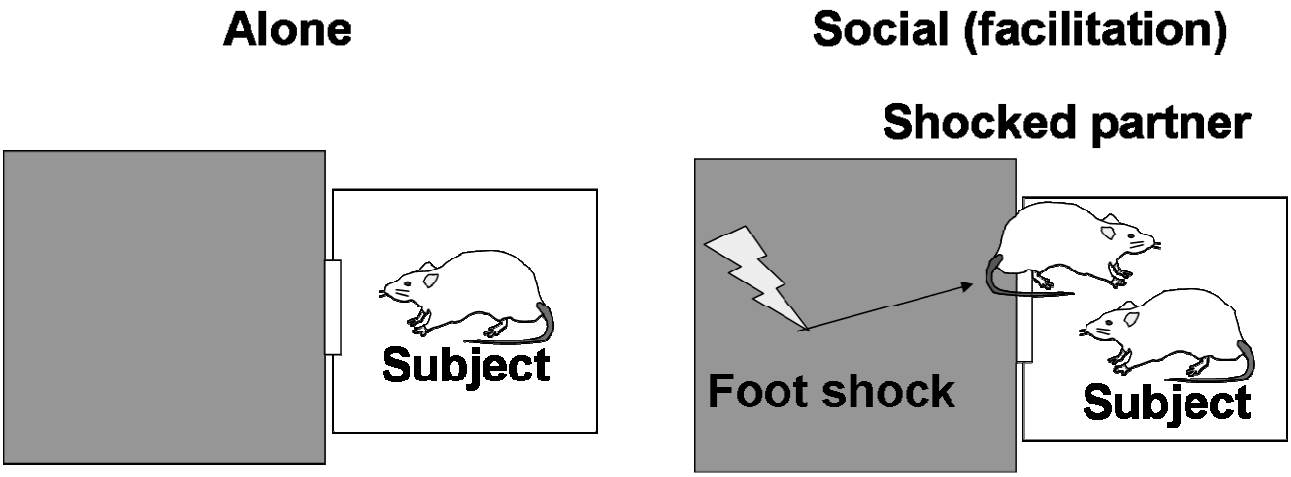

Fig.3.1.6. Experimental overview of the test for social facilitation of avoidance (day 5). In alone conditions of this test, the subjects were placed alone in the light compartment at the start of the test (left). In social conditions of this test, the subjects were placed with shocked partners, which received foot shock (0.5 mA, 3 s) by entering dark room, in the light compartment at the start of the test (right). The avoidance behavior of the subjects which learned passive avoidance will be enhanced by shocked partners.

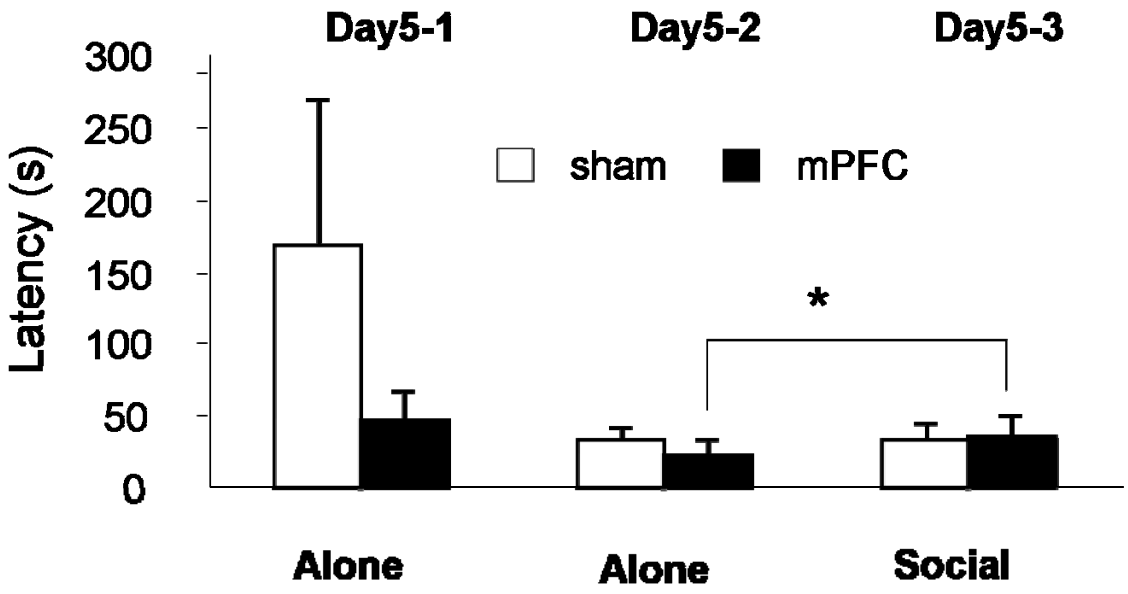

Fig.3.1.7. Effect of mPFC lesion on social facilitation of avoidance. The graph shows the latency on the alone (day5-1, day5-2) and social conditions (day5-3). After first trial under alone condition, the avoidance level was equally observed (day5-2). In the trial for social facilitation of avoidance (day5-3), the avoidance level was significantly enhanced only in mPFC lesion group (*; $p<0.05$).

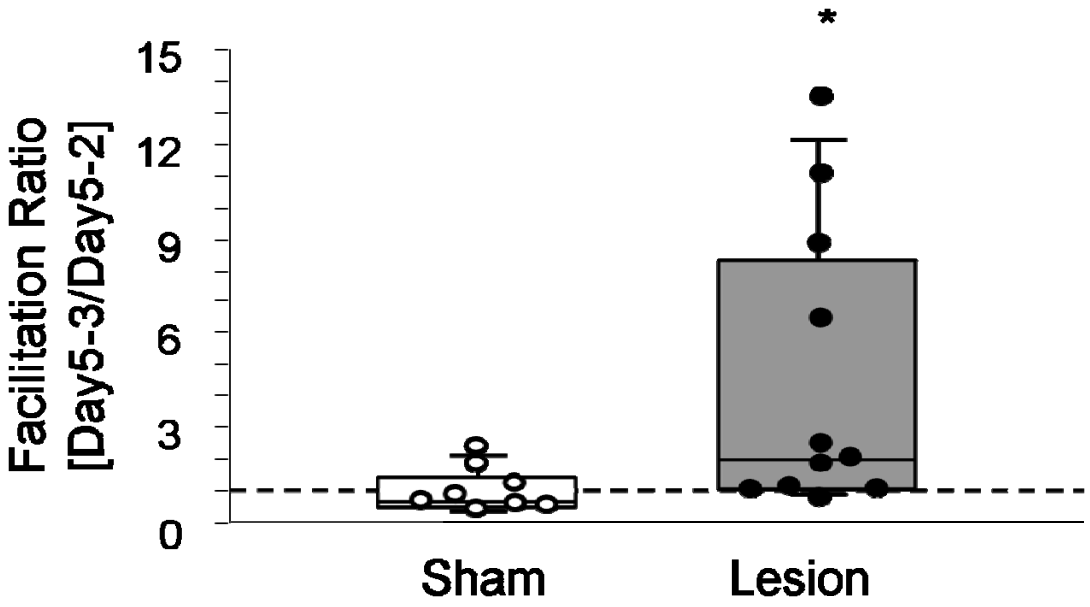

Fig.3.1.8. The facilitation ratio of sham-operated and mPFC lesion groups. Animals with mPFC lesion showed higher changing rate of avoidance responses in facilitatory direction. (*; $p<0.05$)

Effect of mPFC lesion on activity and anxiety

To examine the effect of NMDA-induced lesion of mPFC on basic behaviors other than social transmission or passive avoidance, we conducted Open-field test and Elevated-plus maze test. We did not find the significantly difference between mPFC lesion and sham-operated groups in measured behavioral parameters including total distance moved, time and frequency of rearing behavior and grooming behavior, and spend time and frequency of introduction of center area (Table 3.1.1.). As the results of Elevated-plus maze test, mPFC lesion rats showed not significant but tendency to introduce the open-arms (p = 0.6). In addition, the duration time of grooming behavior in the apparatus for Elevated-plus maze test was significantly longer in mPFC lesion than in sham-operated groups (p<0.05; Table 3.1.2.). These results suggest that lesion of mPFC may affect anxiety-like behavior in the present study.

Table 3.1.1. Means and SEM of the Open-field test.

	Lesion		Sham		
	Mean	SEM	Mean	SEM	*P* value
Distance moved (cm)	2880	288	2459	225	0.27
Glooming #	2.28	0.83	2.85	0.63	0.59
Glooming time (s)	14.4	1.91	22.1	5.02	0.21
Rearing #	47.7	6.33	42.2	3.25	0.46
Rearing time (s)	89.9	12.6	99.9	13.5	0.60
Center #	10.85	2.18	7.71	2.85	0.39
Center time	32.8	12.8	15.0	6.3	0.23
Center latency (s)	48.1	11.7	80.5	37.8	0.42

Table 3.1.2. Means and SEM of the Elevated-plus maze test.

	Lesion		Sham		
	Mean	SEM	Mean	SEM	*P* value
%Open entry #	6.13	1.72	12.34	2.50	0.064
Open time	3.68	1.71	6.91	2.61	0.25
Glooming #	1.14	0.52	1.71	0.40	0.40
Glooming time	2.47	4.24	13.40	1.01	0.027*
Rearing #	20.43	2.51	17.14	1.72	0.30
Rearing time	33.42	6.56	35.81	3.24	0.74

(*; $p<0.05$)

3.1.4. Discussion

First, we briefly describe the present results. We investigated the involvement of mPFC on social inhibition and facilitation of avoidance under pharmacological brain lesion by NMDA infusion to mPFC. Our behavioral experiment demonstrated following results. (1) Animals with mPFC lesion showed normal level of social inhibition of avoidance, but (2) they did not show avoidance-recovery when social partners were disappeared. (3) In social facilitation of avoidance, the changing rate of latency was higher in mPFC lesion group than in sham-operated animals.

In our study, lesioned rats were modified by social partners more easily in both social inhibition and facilitation of avoidance. How can we interpret such modifications? According to the previous mPFC lesion studies, lesions of mPFC in rats disrupt reversal learning (Li et al. 1998; Salazar et al. 2004) and rule learning (Joel et al. 1997). These suggest that mPFC has functional roles for behavioral flexibility (De Bruin et al. 1994; De Bruin et al. 1997; Ragozzino et al.1999; Brown et al. 2002). If behavioral flexibility is disrupted by mPFC lesion, behavioral modification is not able to be more sensitively occurred. In our minds, those ideas can not explain the results of the present study. Let us consider more detail mechanisms for mPFC function. By considering for the social inhibition and facilitation to two parallel mechanisms, it is possible to explain the present results.

There are several sub-regions of mPFC. Infra-limbic (IL) region, one of the sub-regions, is thought to have a specific function for learning. Quirk and his colleague revealed that lesion of IL region results in stronger recovery of extinguished fear conditioning than control (Quirk et al. 2000). In a view of “recovery of fear learning“, the present result for social facilitation has similarity to the previous works of IL lesion. Because our extent of lesion included infra-limbic region, social facilitation of avoidance was potentiated by the effect of lesion of this sub-region. However, this interpretation requires more additional remarks. The extinction process of passive avoidance learning was also investigated in the present study. And, the result was lesion of mPFC did not affect the extinction of passive avoidance learning (Fig.3.1.5.). To answer this contradiction, we should describe the procedural difference between two types fear learning: fear conditioning and passive avoidance learning. In fear

conditioning, subjects receive shock with pairing of “cue signal” (typically use light or tone) several second prior to the shock. In passive avoidance learning, subjects receive shock with entering to a place (i.e. dark place). To study extinction process of fear conditioning, subjects exposure to the cue signals, while subjects do not have such clear signals in passive avoidance learning. In social facilitation of avoidance, social cue is exposed to subjects. In social contact, behavior of physical contact to a partner, lesion of mPFC also facilitates the number of the contacts (Shah et al. 2003). In addition, mPFC lesions impair “prepulse inhibition”, a test for examining sensory filter that acts to prevent unnecessary information (i.e. noise) being sent into cognitive process (Lacroix et al. 2000). This prepulse inhibition is also impaired in schizophrenia patients (Braff et al. 1978; Anscombe 1987; Braff et al. 1990). Assuming that “cue signals” are required for the facilitation of recovery of extinguished fear learning, mPFC lesion may also potentiate the social cue –induced facilitation of avoidance due to abnormality of sensory filter.

The other phenomenon of the present experiment is that mPFC lesioned rats showed sustained attenuation of avoidance responses. This was not observed in sham-operated rats. Is it also understood that the disruption of sensory filter affected the sustained attenuation? The change of condition on day 4-2, alone condition after social condition, is a kind of cues. This explanation is quiet complex and ambiguous. One of the simple and intelligible hypotheses is that recollection of memory was impaired by mPFC lesion. Recent study showed recollection of memory of rats with mPFC damage was impaired (Farovik et al. 2008). The pattern of performance was consistent with the human studies. Impairment on standard item recognition (Stuss et al., 1994) and severe deficits in recollection (Janowsky et al., 1989; Gershberg et al., 1995; Alexander et al., 2003) were found in patients with DLPFC damage. Interestingly, the deficit was limited in accuracy of the recognition performance. Lesioned animals showed familiar responses to the old items used the task (non-match-to-sample task) same as control, but they showed abnormal responses to the new items. Similar result was reported in attentional selectivity (Muir et al. 1996). In such task, memory should be paired with certain object-to-reward relation. In also social inhibition of avoidance, memory should be recollected by pairing with the social conditions in control rats. Disruption of recollection of “socially-paired memory” may be the reason of sustained attenuation of

mPFC lesion group. Actually some researches report that rats with mPFC damage are impaired to select between multiple alternative strategies (Birrell et al. 2000; Ragozzino et al., 2003; Rich et al. 2007). These also suggest that mPFC has a function of appropriate recollection and using strategy of memory.

As one probable interpretation of the present results, the effect of mPFC lesions result in facilitating social transmission of avoidance in two ways. Because of the complex functions of mPFC even in rats, mPFC filters social information and balances the information from individual experience (inner) and social experience (outer) for their decision making in normal animals with intact mPFC. This is probably new perspective for the functions of mPFC. The present research focused on the functions of mPFC in the social situation, and the social transmission may be organized by multiple functions which are installed in multiple brain regions. This is first example of the study that empirically suggests “combination” of the separated “pure brain functions” produce social functions that is “high cognitive performance”.

3.1.5. References

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Chapter 4

Conclusion

4.1. Summary of the Study

In this thesis, behavioral mechanisms and neurological mechanisms for social transmission of avoidance were examined. In this chapter, we summarize findings at first, and then describe future works to understand mechanisms for social transmission of information in animals.

To understand behavioral mechanisms for social transmission of avoidance, we examined effects of partner, effects of situational change under social interaction, effects of previous experience, and effects of relationship among paired animals on avoidance behavior. We found:

- Learned avoidance behavior is easy to be inhibited by partner under safe situation. (Social inhibition of avoidance)
- Unlearned partner who will enter dark room freely exerts greater inhibition than learned partner which will not enter there. (Dependence of partner)
- Inhibited avoidance behavior is partially recovered when partner is removed. (Transient inhibition)
- Avoidance behavior is reinstated by shocked partner. (Social facilitation of avoidance)
- Facilitation is induced only in learned rats, which previously experienced punishment in the dark room, not in unlearned rats. (Dependency of experience)
- Facilitation is not observed in punishment-experienced rats, which experienced punishment in different place from dark room of interaction place. (Dependency of contextual experience)
- Familiar relationship can introduce greater effect on social facilitation of avoidance. (Familiarity difference)

To understand neurological mechanisms for social transmission of avoidance, we examined

effects of medial prefrontal cortex (mPFC) lesion on social inhibition and facilitation of avoidance. We found following things.

- Medial prefrontal cortex lesion does not disrupt social inhibition of avoidance.
- Medial prefrontal cortex lesion produce sustained social inhibition of avoidance. (Sustained inhibition)
- Medial prefrontal cortex lesion can facilitate social facilitation of avoidance. (Facilitation of social facilitation of avoidance)
- Medial prefrontal cortex lesion can facilitate social inhibition and facilitation of avoidance. (Negative control by mPFC)

4.2. Further Works

4.2.1 Identification of Sensory Systems for Social Modification of Avoidance

We found some important factors which modify social transmission of avoidance as described. The factors include environmental situations, previous experience of individuals, and social relationships. These factors naturally changeable in wild animals, and were useful for expecting and estimating dynamics of animal's behavior. However, we still do not understand 'how' social transmission of avoidance is occurred. Next issue is sensory processing for social transmission of avoidance. Although sensory systems which may involve in social interaction are relatively complicated, some previous studies found that some systems critically generate specific effects (olfactory system: social buffering and social transmission of food preference; vision system: social modulation of pain sensitivity). Involvement of such sensory systems is needed to be examined in the future.

4.2.2. Identification of Primary Brain Areas for Social Transmission of Avoidance

Lesion of the medial prefrontal cortex did not produce any deficits of social transmission of avoidance. Although it is unknown that there are primary brain regions for social transmission of avoidance, there are some candidates: hippocampus, other areas of the prefrontal cortex, and higher sensory areas. It is probably necessary for understanding neuronal mechanisms to investigate the effects of lesion of those regions.

4.2.3. Monitoring Neuronal Activity during Social Interaction which can Induces Social Transmission of Avoidance

If the primary region is identified, we will have question about detailed mechanisms. How do the neurons in there work during social transmission? To answer this, wee need to find and monitor the neurons which may link to the social transmission. We hope to start this challenging study in the near future.

Publication List

Peer Reviewed Research Publications

Masuda, A., Aou, S.: Social transmission of avoidance behavior under situational change in learned and unlearned rats. PLoS ONE Vol. 4, Issue 8, August 2009, e6794. pp. 1-7.

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Masuda, A., Yamakawa, T., Zimin, L.: “Micromanipulation system based on local vibration”, Proceeding of SICE Annual Conference 2008, 2A04-4, pp. 1747-1750, Tokyo, July, 2008. (Oral)

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Masuda, A., Aou, S., Natsume K.: “Weekly development of synaptic actions during high K^+-induced epileptiform activity in rat hippocampal slices.” The 31st Annual Meeting of Japan Neuroscience Society, P1-s04, Tokyo, July, 2008.(Poster)

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Non-Reviewed Conference Presentations

Masuda, A., Aou, S.: “Inhibitory control by the medial prefrontal cortex on social learning in rats.” East-Asia Inter-University Workshop on Brain Engineering 2010 (EAW’10), PS-, Daegu, March, 2010. (Poster)

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