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The same subnuclei of the amygdala are activated when fear contagion occurs between humans, and between humans and rats

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I am afraid of rodents and I never thought that my doctorate thesis would be on them. That I would conduct research on them. Research on fear. On the fact that rats are afraid of humans. This is probably the weirdest thing that has ever happened to me.

This work is an expression of the fact that the last seven years have been important to me. I learned a lot, I was in amazing places, I met smart, inspiring people. I found out about myself that I am even more stubborn than I thought. After the birth of my child, during the pandemic, this work saved me, and I felt extremely grateful for it.

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Contents

Abbreviations

ANOVA …… analysis of variance
ACC …….. anterior cingulate cortex
BA …… basal amygdala
BDNF ……. brain-derived neurotrophic factor
BL ……. basolateral amygdala
BOLD ……... blood-oxygenation level dependent
BtBC ……. brain-to-brain coupling
CeA ……... central amygdala
CeAl …….. central amygdala, lateral division
CeAm …… central amygdala, medial division
CM …… centromedial amygdala
CR ……. conditioned response
CS ……. conditioned stimulus
CS+ ……... conditioned stimulus, reinforced
CS- …… conditioned stimulus, not reinforced
CTRL …… control group
DTI ……. diffusion tensor imaging
EPI …… echo-planar imaging
EMG ……. electromyography
EXP …….. experimental group
FDR …….. false discovery rate
FFT ……... fast Fourier transform
fMRI ……. functional magnetic resonance imaging
FPS ……. fear-potentiated startle
FWE …….. familywise error
GLM ……. general linear model
IFG ……. inferior frontal gyrus
IPL …… inferior parietal lobule
IQR ……... interquartile range
ITF …… inducible transcription factor
La …….. lateral amygdala
LFP ……... local field potential

M …….. mean

ME ……..... median

MeA …….. medial amygdala

MEG ……. magnetoencephalography

MR …… magnetic resonance

MRI …….. magnetic resonance imaging

PAM ……. Perception-Action Model

ROI ……... region of interest

SCR …….. skin conductance response

SD ……. standard deviation

SEM …….. standard error of the mean

sMRI ……. structural magnetic resonance imaging

US ……. unconditioned stimulus

USV …….. ultrasonic vocalization

vmPFC …….. ventromedial prefrontal cortex

Abstract

Fear contagion is an automatic process of aligning one animal's emotional state with another's emotional distress. It has been described in different social species, including rats and humans. Reading the emotional states of others has recently been suggested to play an essential role in detecting danger. If so, one could expect fear contagion to be a cross-species phenomenon. However, this hypothesis has yet to be tested. Both rat and human studies implicated the amygdala, a brain structure crucial for processing emotions, in fear contagion.

Further, the rat studies showed that two main parts of the amygdala, which differ morphologically and functionally - the basolateral and centromedial nuclei - are involved in emotional transfer. Such a detailed analysis of the amygdala activity has yet to be performed for human-human emotional transfer. In this doctoral thesis, I aimed to test whether the cross-species (human-rat) fear transfer occurs and whether it involves the basolateral and centromedial parts of the amygdala (study 1). Their involvement was also verified during the human-human fear contagion (study 2).

In study 1, the habituated rats were handled by familiar humans who underwent the fear conditioning task (or an emotionally neutral task in the control condition). Following the interaction, the rats' amygdala activations were analyzed using the expression of c-Fos, a marker of neuronal activation. I observed that the rat amygdala was activated to a greater extent in the experimental rats compared to the control rats. That was true for both the basolateral and centromedial divisions. The behavioral differences between the experimental and control rats further confirmed the successful transfer of fear from human to rat.

Study 2 was performed using functional magnetic resonance imaging (fMRI). Participants (so-called observers) were placed in the fMRI scanner and watched their friends (so-called demonstrators) undergoing the classical fear conditioning paradigm. In this task, a neutral stimulus was repeatedly paired with aversive electrical stimulation applied to the forearm. I analyzed the observers' brain responses to the electric shocks administered to their friends and found enhanced activations in the amygdala. Also, here, both the basolateral and centromedial divisions were activated.

The thesis provides the first neural evidence for interspecies fear contagion. The findings indicate that both main divisions of the amygdala respond when human fear is transmitted to another human and a rat. This suggests a common brain circuit involved in perceiving fear socially in humans and rats. I argue that it could have evolved to enable sharing of the emotional cues essential for survival across species.

Streszczenie

Zarażanie strachem jest automatycznym procesem dopasowywania stanu emocjonalnego jednego zwierzęcia do dyskomfortu emocjonalnego drugiego. Zostało opisane u różnych gatunków społecznych, w tym u szczurów i ludzi. Wyniki badań prowadzonych w ostatnich latach sugerują, że odczytywanie stanów emocjonalnych innych osobników odgrywa zasadniczą rolę w wykrywaniu niebezpieczeństwa. Można więc przypuszczać, że zarażenie strachem jest zjawiskiem międzygatunkowym. Ta hipoteza nie została jednak dotychczas przetestowana. Zarówno badania na szczurach, jak i na ludziach wykazały, że ciało migdałowate, struktura mózgu kluczowa dla przetwarzania emocji, jest zaangażowane w proces zarażania strachem. Co więcej, badania na szczurach wykazały, że dwie główne części ciała migdałowatego, które różnią się morfologicznie i funkcjonalnie - jądra podstawno-boczne i środkowo-przyśrodkowe - biorą udział w społecznym przekazywaniu emocji. Szczegółowa analiza aktywności ciała migdałowatego nie została dotychczas przeprowadzona dla międzyludzkiego transferu emocjonalnego. Badania przeprowadzone w ramach niniejszej rozprawy doktorskiej miały na celu określenie, czy jest możliwy międzygatunkowy transfer strachu (człowiek-szczur) oraz czy obejmuje on podstawno-boczną i środkowo-przyśrodkową część ciała migdałowatego (eksperyment 1). Zaangażowanie tych struktur zostało też zweryfikowane w procesie międzyludzkiego zarażania strachem (eksperyment 2).

W eksperymencie 1 zhabituowane szczury wchodziły w interakcję ze znajomymi sobie osobami, które wcześniej zostały poddane warunkowaniu strachu (lub wykonały zadanie neutralne emocjonalnie w warunku kontrolnym). Po interakcji aktywacje ciała migdałowatego szczurów analizowano za pomocą ekspresji białka c-Fos, które jest markerem aktywacji neuronów. Zaobserwowano, że ciało migdałowate szczurów aktywowało się w większym stopniu u szczurów z grupy eksperymentalnej w porównaniu do szczurów z grupy kontrolnej, i dotyczyło to zarówno jądra podstawno-bocznego, jak i środkowo-przyśrodkowego. Ludzko-szczurzy transfer strachu został dodatkowo poparty różnicami behawioralnymi, które zaobserwowano między szczurami z obu grup.

Eksperyment 2 przeprowadzono przy użyciu funkcjonalnego rezonansu magnetycznego (fMRI). Uczestnicy przebywający w skanerze fMRI (tzw. obserwatorzy) widzieli swoich przyjaciół (tzw. demonstratorów) wykonujących zadanie oparte na klasycznym warunkowaniu strachu. W tym zadaniu neutralny bodziec był wielokrotnie łączony z awersyjną stymulacją elektryczną przedramienia. Analiza aktywacji mózgowych obserwatorów w odpowiedzi na nieprzyjemne szoki elektryczne aplikowane ich przyjaciołom wykazała zwiększoną aktywację

ciała migdałowatego. Również w tym eksperymencie zaobserwowano zaangażowanie zarówno jądra podstawno-bocznego, jak i środkowo-przyśrodkowego.

Niniejsza praca doktorska prezentuje pierwsze mózgowe dane wskazujące na międzygatunkowe zarażenie strachem. Przedstawione wyniki wskazują, że obie główne części ciała migdałowatego aktywują się, gdy ludzki strach jest przekazywany zarówno innemu człowiekowi, jak też szczurowi. Sugeruje to wspólny obwód mózgowy zaangażowany w społeczne postrzeganie strachu u ludzi i szczurów. Argumentuję, że mógł on wyewoluować, aby umożliwić dzielenie się emocjonalnymi wskazówkami, które dla różnych gatunków są niezbędne do przetrwania.

1. Introduction

1.1. What is emotional contagion?

The term ‘emotional contagion’ has been introduced by Hatfield et al. (1993), who defined it as ‘the tendency to automatically mimic and synchronize expressions, vocalizations, postures, and movements with those of another person’s and, consequently, to converge emotionally’. Various species are able to share emotions of their conspecifics. The examples are pigs showing behavioral changes following observation of demonstrators who underwent either positive or negative treatment (Reimert et al., 2017), songbirds mates showing cortisol covariation during stressful situations (Perez et al., 2015), or ravens showing negative cognitive bias after witnessing a conspecific in a negative emotional state (Adriaense et al., 2019). Also rodents are able to share fear through social interactions (Knapska et al., 2006; Panksepp & Lahvis, 2011; Panksepp & Panksepp, 2013), which will be discussed in detail further in the thesis.

Hatfield et al. (1993) describe emotional contagion as involving processes such as emotional mimicry (imitation) and facial feedback (emotional experience arising from the mimicked emotional expression; Darwin, 1872; Dimberg & Söderkvist, 2011). Within this theoretical framework, emotional contagion should not be mistaken for mimicry. The observer’s reaction goes beyond a simple imitation of the demonstrator’s behavior: it is flexibly adjusted to the observer’s own situation (Keysers et al., 2022). An example are rodent observers running away or hiding when encountered with a demonstrator showing freezing - a defensive behavior defined as absence of movement except for respiration (Curzon et al., 2011). One of the human studies has recently demonstrated that the observers’ facial activity explains the relationship between observed and felt emotions (Olszanowski et al., 2020), which indicates that facial mimicry may be a necessary, yet not sufficient process involved in emotional contagion (but see (Hess & Blairy, 2001; van der Schalk et al., 2011).

The emotions that have been investigated in terms of emotional contagion are most often referred to as ‘play’ (Osvath & Sima, 2014; Palagi et al., 2015; Schwing et al., 2017) and ‘distress’ (Edgar et al., 2011; Oliveira et al., 2017; Perez et al., 2015) or simply categorized as positive and negative. Research on the latter category is more common, and has been mostly conducted using rodent models. In humans, several fMRI studies showed that the amygdala, the anterior insula and the frontal operculum are the areas that activate in humans observing

facial expressions of disgust (Wicker et al., 2003), happiness (Hennenlotter et al., 2005) and pain (Botvinick et al., 2005).

What is the function of emotional contagion? First, it enables signaling emotional states, which makes the social interactions much more predictable, and second, it constitutes a basis for the social learning of emotions. The latter is extremely important from the evolutionary point of view because vicarious learning of distress enables avoiding harm. It is crucial to emphasize that emotional contagion is adaptive, and social animals are eager to read the emotional signals of others. As I will describe in next chapters, animals actively approach their distressed conspecifics in order to learn about their state, because this augments their chances of survival. Such an explanation is in accordance with the view that has recently been proposed by Keysers et al. (2022): they argue that one of the reasons why emotional contagion has evolved and become so widespread across species, is receiving information important for survival, while at the same time avoiding experiencing aversive stimuli directly. This is a novel perspective, standing in opposition to the classical approach emphasizing the importance of emotional contagion for the motivation of mammalian mothers to care for their offspring (de Waal & Preston, 2017). In this classical view the strength of emotional contagion is related to the level of familiarity between animals. However, besides the inconsistent results of research on the effect of familiarity on the effectiveness of emotional contagion (Hernandez-Lallement et al., 2022), this classical perspective does not explain why emotional contagion is so common among animals that do not nurture their offspring (Burbano Lombana et al., 2021; Ruiz-Monachesi & Labra, 2020).

According to the Russian doll model of empathy (de Waal & Preston, 2017), one of the most influential empathy theories, emotional contagion is a building block of empathy and its primary form (de Waal, 2012). It results from the basic mechanism of the Perception-Action Model (PAM), which consists of a spontaneous matching between the target's and the observer's neural responses. The neurobiological evidence for the PAM involves mirror neurons - the shared brain representations for perception and action. The cells responding similarly to the performed and observed actions were first described in macaques and they were found to reside in the subdivisions of the rostral inferior parietal lobule (de Waal & Preston, 2017; di Pellegrino et al., 1992). In humans, mirror neurons used to be long identified merely within the ventral premotor cortex (inferior frontal gyrus, IFG) and inferior parietal lobule (IPL; Chong et al., 2008; Kilner et al., 2009), but the groundbreaking single-cell recordings study (Mukamel et al., 2010) revealed additional brain areas showing mirror properties: the supplementary motor area, the hippocampus, the parahippocampal gyrus and the entorhinal

cortex. Similar activations were previously reported in studies using functional magnetic resonance imaging (fMRI; Gazzola & Keysers, 2009; Keysers & Gazzola, 2009). It has been proposed that not only motor, but also emotional resonance occurs through the shared brain representations mechanism (Carr et al., 2003; Keysers & Gazzola, 2006). Jabbi and Keysers (2008) suggested that during observation and imitation of emotions, the core hubs of the mirror neuron system (IFG and IPL) activate the insula, which further activates other structures of the limbic system, i.e., the amygdala.

A theory that is alternative to the Russian doll model of empathy - the combination model (Yamamoto, 2017) - assumes that emotional contagion is the manifestation of matching with others, one of the three main factors co-creating empathy (the other two factors are understanding of others and prosociality). According to this view, each of the three main components is independent from the others but the combinations of different factors are possible. Such understanding, unlike the Russian doll model, does not imply any link between emotional contagion and motor mimicry. Thus, studies using this theoretical framework do not assume mimicry to be evidence for emotional contagion (although they may independently co-occur). This example clearly shows that the theoretical assumptions that researchers make do have a strong influence on the measures that need to be employed to infer emotional contagion (Adriaense et al., 2020). However, regardless of the theoretical perspective, the presence of emotional experience should be reported in both the demonstrator and the observer, to claim that emotional contagion took place. Using the multi-component model of emotion (Anderson & Adolphs, 2014) one can investigate the behavioral, physiological and cognitive manifestations of emotions to prove their occurrence. In humans, subjective feelings can additionally be assessed. The more measures employed, the better probability that a particular emotion was actually measured.

1.2. Emotional contagion as a basis for social learning of emotions

The experimental paradigm that has been widely used to study how the emotions are acquired, is the classical conditioning (Pavlov, 1928). It assumes that initially neutral stimulus (conditioned stimulus, CS), when repeatedly paired with a biologically significant event (unconditioned stimulus, US), acquires affective properties, and a conditioned response (CR) to the CS is developed (LeDoux, 2000). The Pavlovian conditioning constitutes the basis for the protocols used in research on social learning of emotions. In social species vicarious learning occurs very often, and is particularly beneficial in the case of the aversive emotions.

For example, social learning of fear enables avoiding danger and costly first-hand experiences. Research using the observational fear learning paradigm (Jeon et al., 2010; Knapska et al., 2010; Mineka et al., 1984) have shown that animals who observe the fear expressed by a conspecific in response to an aversive stimulus (e.g., an electric shock, US) that co-occurs with a certain neutral stimulus (e.g., a tone, CS), eventually learn to react aversively (CR) when a tone (in the absence of electric stimulation) is encountered (Panksepp, 2004). In this case, learning occurs although the observer has never experienced the physical, aversive stimulation themself - simple observation of the conspecific's aversive reactions is enough to acquire the conditioned response. The demonstrator's behavior constitutes the cue indicating the emotional value that is associated with the presentation of CS, and thus plays a role of the US. Such learning is indirect and exclusively social but has been shown to be as effective as direct acquisition of emotions (Lindström et al., 2018; Olsson et al., 2007), but see (Dou et al., 2023).

Taking into account that emotional contagion occurs when the emotions of one animal are shared with another one, it seems obvious that this process is involved in the social learning of emotions. Prochazkova and Kret (2017) argue that a mouse observing a cagemate receiving electric shocks associated with a tone, and eventually acquiring a fear-conditioned reaction to this tone, is an example of emotional contagion. However, studies focused on the process of the social learning of emotions often ignore emotional contagion and do not control for its occurrence. For example, the protocol for studying the observational fear conditioning in humans divides the whole process into two parts: the observational learning phase (when the association is being learnt) and the direct-expression phase (when the acquired conditioned response is tested (Haaker, Golkar, et al., 2017). Research using this protocol has mainly focused on the effectiveness of the social fear learning and its moderators, employing different experimental manipulations (Golkar et al., 2015; Haaker, Yi, et al., 2017; Selbing & Olsson, 2019). None of the previous studies has indicated emotional contagion as a basic process that potentially underlies the observational fear learning. Some of the manipulations have involved the experimental change in the level of the observer's empathy (Olsson et al., 2016) and affect sharing (Müllner-Huber et al., 2022) but the emotional contagion has not been directly linked to the social learning of emotions so far.

Some of the researchers have argued that the well-established term 'fear conditioning' is actually misleading and should be replaced with 'defense conditioning' or 'threat conditioning' (LeDoux, 2014). According to this view, threat detection and defense response mechanisms should not be identified with fear mechanisms. Specifically, the nonconscious threat responses should be differentiated from the conscious fear responses. While I agree with

this perspective, a plethora of studies mentioned in this thesis has referred to the notion of fear when describing basic defensive reactions to threats, most often induced by means of the Pavlovian conditioning procedure. Thus, in this work the term 'fear' will be used to describe the observed defensive reactions, not the subjective emotional state (Keysers et al., 2022).

1.3. Fear contagion in rodents

The rodent paradigms tailored for studying fear contagion assume the interaction of two animals which are usually called the demonstrator and the observer. The emotional state of the former is manipulated by means of the fear-inducing procedure, then the interaction takes place, and subsequently the state of the latter is measured to assess whether the contagion occurred. In contemporary rodent research two main fear contagion paradigms have been established: the imminent fear model and the remote fear model (Keysers et al., 2022; Knapska et al., 2006; Kondrakiewicz et al., 2019).

In the imminent fear model, both animals share the cage divided by a perforated transparent partition, so that rats can watch, hear and smell each other. The observer watches their mate being fear-conditioned: aversive footshocks are delivered to the demonstrator every time the sound (conditioned stimulus, reinforced; CS+) appears. When the observer hears the silence, which is indicative of the demonstrator's freezing, their auditory thalamus and ventral auditory cortex projections to the lateral (La) amygdala are activated. In turn, the La activates the basal (BA) amygdala and its projections to the central amygdala (CeA), where the information is integrated and an adaptive behavior is guided: freezing or hiding, depending on whether an escape route is available (Andraka et al., 2021). The level of freezing of the observer has been shown to correlate with the level of freezing that the demonstrator displays (Andraka et al., 2021; Atsak et al., 2011; Han et al., 2020). So-called vicarious freezing of the observer is considered an evidence for fear contagion. Additionally, the 22-kHz ultrasonic vocalizations (USV; calls of this frequency are the 'alarm calls') recorded in both demonstrators and observers are indicative of fear experienced by both subjects (Andraka et al., 2021).

In the remote fear model the demonstrator receives aversive footshocks prior to the interaction and subsequently interacts with the observer in another cage. The fear that the demonstrator shares with the observer is remote, because the observer has no clue about its origin. Still, they can see, hear and smell their mates, and studies using this paradigm have reported that the observers react with increased risk assessment behaviors, such as rearing (Andraka et al., 2021; Kondrakiewicz et al., 2019). This indicates the observers' motivation to

learn about the potential threat. Additionally, the expression of c-Fos, a marker of neuronal activation, has been reported to be enhanced in the central, medial, lateral, basal and basomedial nuclei of the amygdala. No differences between the demonstrators and observers have been found except for the central nucleus, in which the observers show even higher activation compared to the demonstrators (Knapska et al., 2006). Rats studied using this paradigm show short, high-frequency USVs (50-70-kHz) indicative for peaceful social interactions (Andraka et al., 2021; Knutson et al., 2002).

The choice of the behavioral response to the demonstrator's fear is controlled by the CeA. Two separate populations of neurons have recently been found in this region, one of them guiding the freezing or hiding behavior when facing imminent danger (a demonstrator receiving shocks) and the other orchestrating the exploratory behaviors when encountering remote danger (a previously shocked demonstrator; Andraka et al., 2021). The causal role of the CeA in responding to the other's fear, together with the reports showing the CeA activations during first-hand experience of fear, suggest that a mirroring mechanism involving the amygdala may underlie fear contagion in rats (Carrillo et al., 2019; Paradiso et al., 2021).

The level of fear contagion has been shown to be similar in both male and female rats (Han et al., 2020). During an interaction with a fear-conditioned demonstrator, both male and female rats have been found to show a similar pattern of behavior - most importantly, the typical reaction consisting of the engagement in social exploratory behaviors has been reported (Mikosz et al., 2015). At the same time, the estrus cycle phase has been indicated as a factor modulating susceptibility to fear contagion: an interaction with a fear-conditioned mate has enhanced active avoidance learning in males and diestral females, but not in estral females (Mikosz et al., 2015). These results suggest that sex-related differences in susceptibility to fear contagion are subtle, but should be taken into account. Regarding the neural data, the activation of the observer's amygdala following an interaction with a fear-conditioned demonstrator has so far been shown only in male rats (Andraka et al., 2021; Knapska et al., 2006).

The studies on the neural mechanisms underlying observational fear learning revealed also an important role of the ACC. Inactivation of the affective pain system involving the ACC as well as parafascicular and mediodorsal thalamic nuclei in mice has been shown to impair observational fear learning, measured in terms of an extent of the freezing behavior (Jeon et al., 2010). The $Ca_v1.2$ type Ca^{2+} channels in the ACC have been found to be responsible for this inhibiting effect. The parafascicular and mediodorsal thalamic nuclei represent the emotional dimension of pain, as opposed to the ventral posterolateral and posteromedial thalamic nuclei, which are parts of the sensory pain system, and were not involved. This result concurs with the

assumption that observers experienced emotional, not sensory, pain during the observational fear learning. Furthermore, this study provided evidence for a differential role of the ACC and the amygdala. While inactivation of ACC impaired only acquisition of observational fear, inactivation of the lateral amygdala caused a disruption of both acquisition and expression of learnt fear. These findings have been further supported by Allsop et al. (2018), who has shown that the aversive value of the observed cue is encoded in the projection from the ACC to the basolateral amygdala. Additionally, a selective inhibition of this projection resulted in an impaired acquisition of observational fear, but had no impact on the expression of observationally learnt fear.

Another study, carried out in rats, confirmed an important role of the ACC in pain contagion. In a study by Carrillo et al. (2019), a complex experimental manipulation enabled observing neuronal activity related to the experience of pain, witnessing another rat receiving aversive stimulation, and displaying a conditioned response to the fear-conditioned stimulus. Multi- and single-unit recordings revealed that the majority of neurons in the explored area responded to the pain-, and not fear-related conditions. Additionally, a subpopulation of these pain-sensitive neurons has been found to respond similarly to both experienced and vicarious pain, and has thus been identified as pain-specific mirror neurons. Conversely, a minority of neurons has responded to the fear-conditioned sound. These results suggest that the ACC responds to direct and vicarious pain, and is less involved in the fear-conditioning response. Similarly, the ACC' involvement in pain has been earlier reported in human studies (Lamm et al., 2011).

1.4. Fear contagion in humans

The paradigm that has been used most often to study emotional contagion in humans involves displaying emotional stimuli while measuring activity of the facial muscles, and subsequently asking about the felt emotions. The facial electromyography (EMG) allows for measuring the activity of muscles involved in emotional reactions, e.g., *zygomaticus major* pulls up lip corners, which is indicative of smiling, *depressor anguli oris* works in the opposite way lowering lip corners, *corrugator supercilii* is responsible for lowering the eyebrows, which is often the case during anger expression, and *levator labii superioris* lifts the upper lip. Observing the specific combinations of muscles' activity allows for inferring about particular emotions being expressed (Hess et al., 2017; Olszanowski et al., 2020); most often these are happiness, sadness, anger and disgust.

One of the few human studies on fear contagion employed expressive movements of the whole body, not only the facial muscles, and looked at the brain activations using fMRI (de Gelder et al., 2004). Observation of fearful body expressions enhanced activations in brain regions specifically linked to the emotional processing, e.g., amygdala, orbitofrontal cortex, posterior cingulate, anterior insula. Interestingly, these areas were not activated when expressions of happiness were observed. Fearful body expressions also activated the areas related to action representation (inferior parietal lobule, supplementary motor area, inferior frontal gyrus) and motor response (motor cortex, putamen, caudate). The authors suggested that the integrated activity of these areas might reflect the fear contagion process and the following preparation of action. The described pattern of activations in response to fearful vs. neutral body expressions was not found in the autism spectrum disorder patients as compared to the neurotypical individuals (Hadjikhani et al., 2009).

The series of studies using the observational fear conditioning protocol (Haaker, Golkar, et al., 2017) have shown that observation of another person receiving electric shocks results in an enhanced skin conductance response (SCR; Kaźmierowska et al., 2022; Olsson et al., 2007; Szczepanik et al., 2020), which is an index of the autonomic nervous system activity. Such a physiological reaction in response to the demonstrator's emotional expression may indicate the emotional contagion process. Additionally, several studies have found augmented brain activations in the fear-relevant circuit during the observational learning phase: bilateral amygdala, anterior insula and anterior cingulate cortex have been identified as involved in the social acquisition of fear (Lindström et al., 2018; Olsson et al., 2007). As their activation was recorded in response to the observation of the demonstrator's fear, it might be suggested that they reflected the fear contagion process. In contrast, defensive reactivity measured by the fear-potentiated startle (FPS) has not been shown to elevate during acquisition of the social fear (Selbing & Olsson, 2019; Szczepanik et al., 2020). However, this measurement was recorded following the loud sound during the CS presentation, and not in direct response to the demonstrator's aversive reaction. Thus, FPS might not be specific enough to indicate the fear contagion process.

In a recent study by Müllner-Huber et al. (2022) the affect sharing process was indicated as a mechanism of the vicarious fear learning. Affect sharing was defined as 'a core aspect of empathy that describes the ability to partially re-experience how another person is feeling' (Müllner-Huber et al., 2022; Singer & Lamm, 2009). Similarly to emotional contagion, it does not require any cognitive components such as perspective taking or judgment about the emotional state of another person. However, unlike emotional contagion, it occurs even in the

absence of emotional stimuli (e.g., even when symbols or colors indicative of another individual's emotional state are presented; Singer, 2006). In the mentioned study, hypnotic suggestions were used to manipulate the level of affect sharing. In the 'high' condition participants received a suggestion 'to be open and sensitive for the feelings of others and to feel what the demonstrator feels', while in the 'low' condition the suggestion was 'to be closed against and distanced from the feelings of others, and not to feel what the demonstrator feels' (Müllner-Huber et al., 2022). Besides the fact that the high affect sharing resulted in higher effectiveness of the observational fear learning as compared to the low affect sharing, differences were also observed during the fear acquisition phase. During high vs. low affect sharing, participants showed increased skin conductance response to the social US (the demonstrator's aversive reaction), and higher self-reported unpleasantness of the shocks administered to the demonstrator and also the unpleasantness related to watching the demonstrator themselves. Together, these results constitute evidence for the affect sharing and prove its causal role in the vicarious fear learning process.

Another of the recently published studies has shown the brain-to-brain coupling (BtBC) between the demonstrators and observers during the observational fear learning (Pan et al., 2022). Using magnetoencephalography (MEG), it has been found that a low-frequency brain oscillatory activity is downregulated during the observational fear learning. What is more, an enhanced coupling of the centro-frontal channels in demonstrators and observers has been indicated as a mechanism underlying observational fear learning in humans. In particular, BtBC in a fronto-limbic circuit (including the insula, ventromedial and dorsolateral prefrontal cortex) has been found to predict the magnitude of SCR conditioned responses in the test phase. Additionally, a coupling of pupil dilation patterns has been found between demonstrators and observers in response to the upcoming electric shocks during the observational fear learning phase. As the coupling of pupil dilation patterns has been considered an index of shared attention and emotions (Kang & Wheatley, 2017), shared attention and emotions have been suggested as potentially underlying BtBC. Thus, shared fear leads to the synchronization of the demonstrator's and observer's brain activity, which has an impact on the effectiveness of the observational fear learning.

A similar, and probably the most common paradigm that employs observation of the aversive responses of another person, is the empathy-for-pain paradigm (Singer et al., 2004). In this paradigm, an observer lies in the fMRI scanner and either experiences painful stimulation or witnesses another person undergoing aversive stimulation. Such a design enables a comparison between responses to the self-experienced and observational pain (Klimecki-Lenz

& Singer, 2013). Different studies have shown that overlapping brain areas are involved in both nociceptive and empathic pain, e.g., the anterior insula and parts of the cingulate cortex (Corradi-Dell'Acqua et al., 2011; Lamm et al., 2011; Singer et al., 2004; Zaki et al., 2016). On the other hand, the vicarious pain signature has recently been proposed (Zhou et al., 2020), indicating a multivariate pattern of brain activations which is specific for the pain acquired through the social means. Apart from the empathy for pain, also pain contagion has recently been demonstrated, and suggested to underlie the pain learning process (Buglewicz-Przewoźnik et al., 2022).

While the paradigms (and even the brain areas activated) are similar, it should be emphasized that fear and pain are not identical concepts. According to the perceptual-defensive-recuperative model of fear and pain, they activate different motivational systems and serve different functions. Fear defends an animal against natural dangers, and pain promotes an animal's recovery from injury (Bolles & Fanselow, 1980). Moreover, in the observational fear conditioning paradigm it is actually crucial that the unconditioned stimulus is 'uncomfortable, but not painful', the electric shocks are short, and the demonstrators are instructed to react 'in a natural yet noticeable manner' (Kaźmierowska et al., 2022).

1.5. Interspecies emotional contagion

Emotional contagion occurs across animals of different species, which can be called emotional eavesdropping. Heterospecifics (the opposition of conspecifics) are the majority of most natural communities, and they may actually be better sources of information than conspecifics (Magrath et al., 2015). For example, they can share information about food resources, at the same time not competing for them (as conspecifics could do; Seppänen et al., 2007). Importantly, the demonstrators do not have to be closely related to the observers; it is sufficient that they share the ecological parameter of interest with the observers (e.g., food resources, predation risk, breeding success).

Previous studies have shown that animals are able to recognize the emotional expressions of other species. The emotional eavesdropping often occurs in interactions between humans and other animals, especially domesticated species. Such an adaptation might be considered advantageous, as recognizing humans' emotions is beneficial for animals sharing their living space with humans. For example, dogs have been found to show both physiological and behavioral response when exposed to human infant cries. Increased levels of cortisol were found in both dogs and human adults listening to the human infants' sounds. Additionally, dogs'

behavior indicated alertness and submissiveness (Yong & Ruffman, 2014). It has also been shown that dogs are able to differentiate between negative and positive emotions in humans (Albuquerque et al., 2016; Müller et al., 2015) and are sensitive to chemical signals related to human emotional states (D'Aniello et al., 2018). Dogs have also been shown to be more attentive to humans' emotional vocalizations compared to the non-emotional ones, and to show negative emotional contagion regardless of whether the sounds that they heard were derived from humans or dogs (Huber et al., 2017). Last, but not least, interaction with a stressed human was shown to result in a decreased memory performance in dogs (Sümegi et al., 2014), not only indicating that emotional contagion may happen on the interspecies level, but also that it may be measured as a change in the cognitive task performance.

Also in horses, the ability to process emotional expressions of humans is considered a result of the domestication process (Outram et al., 2009). Horses have been shown to be sensitive to human emotional cues: they adjusted their behavior accordingly to the observed disgust (Baba et al., 2019), and their heart rate increased after exposure to the human angry face (Smith et al., 2016). Goats, a species domesticated for the purpose of food production, have also been found to be sensitive to human facial expressions, and to prefer happy faces compared to the angry ones (Nawroth et al., 2018).

The mere presence of humans during experimental procedures in animal research has been shown to impact the animals' behavior and physiology. A study involving a human-mouse interaction has previously indicated the impact of the experimenter's sex on the baseline physiological responses measured in mice (Sorge et al., 2014). Male and female mice exposed to male and not female experimenters turned out to show a robust stress response and related pain inhibition. The nature of the human-mouse communication was olfactory, as the effect was reproduced using male- and female-worn T-shirts involving axillary secretions. The human pheromones responsible for this effect were additionally identified. A similar study has recently shown that male and female rats display anxiety-related behaviors during an interaction with a male and not female experimenter, and they are intensified in female rats. This effect was related to changes in the levels of corticosterone and oxytocin, and was shown to be further elevated during a stressful experimental manipulation (Faraji et al., 2021). These studies indicate that mice and rats read the cues that are sent unintentionally by humans. These cues are mostly olfactory, and they change the behavioral and physiological reactions of rodents.

1.6. The amygdala and its role in fear processing

The amygdala is a brain structure located in the medial temporal lobe. It is a complex of heterogeneous nuclei that differ morphologically and functionally. Its two main parts are the cortico-medial region involving cortical, medial and central nuclei, and the basolateral region comprising lateral, basal and accessory basal nuclei (Sah et al., 2003). The cortico-medial region is morphologically similar to the striatum, associated with the olfactory processing system and considered evolutionarily primitive, while the basolateral region is evolutionarily newer and its cell composition resembles those observed in the neocortex (LeDoux, 2007). The LeDoux (2000) model of fear activation has proposed that there are two ways of processing fearful stimuli, both of them involving the amygdala. The 'high road' is the classic pathway including the lateral geniculate bodies of the thalamus, the primary visual cortex, the inferior parietal lobule and finally the amygdala. Rodent lesion studies enabled LeDoux to also identify the 'low road', which is the path that activates the amygdala via the thalamus, rapidly, without the cortex involvement (Morris et al., 1998, 1999; Vuilleumier et al., 2003). This latter strategy is undertaken when automatic, immediate reaction to a threat is required.

The amygdala has traditionally been linked to fear processing, being the central structure in the circuitry involved in fear conditioning (LeDoux, 2007; Phelps & LeDoux, 2005; Wilensky et al., 2006). Lesion studies have shown that patients with unilateral and bilateral amygdala damages lack the autonomic conditioned response to the fear-conditioned stimuli (Bechara et al., 1995; LaBar et al., 1995). Unilateral lesion of the amygdala has been demonstrated to have a similar effect in rats, that is to significantly reduce fear response (LaBar & LeDoux, 1996). Also the human neuroimaging studies have massively linked the amygdala with the classical fear conditioning process (Cheng et al., 2003; Knight et al., 2004, 2005; Krabbe et al., 2018; LaBar et al., 1998; Morris et al., 1998; Öhman, 2009; Whalen et al., 1998), but see (Fullana et al., 2016). Furthermore, the social transmission of fear has also been shown to involve the amygdala of the observers watching fear-conditioned others. This has been shown both in rodents (Andraka et al., 2021; Knapska et al., 2006; Twining et al., 2017) and humans (Kaźmierowska et al., 2022; Lindström et al., 2018; Olsson et al., 2007).

The classic lesion works of LeDoux have shown that the lateral nucleus of the amygdala is the sensory interface necessary for fear learning (LeDoux et al., 1990), and that different projections sent by the central nucleus of the amygdala mediate the conditioned fear response (LeDoux et al., 1988). Further rodent studies have consistently shown the crucial role of the basolateral and central amygdala in the Pavlovian fear learning (Ribeiro et al., 2011; Terburg

et al., 2018; Vazdarjanova et al., 2001). Different functional units of the amygdala have also been identified in the recent diffusion tensor imaging (DTI) human study. It has reported that the visual information enters the basolateral amygdala regardless of its emotional value, and may be subsequently passed to the centromedial amygdala, which responds uniquely to the stimuli that signal aversive outcomes (Balderston et al., 2015). This suggests that while the mere activation of the basolateral amygdala nucleus may not be indicative of aversive processing, the activation of the central amygdala is crucial for the occurrence of a fear response.

1.7. Observational fear learning in rodents as a model of empathy

According to the Russian doll model, emotional contagion is a primary form of empathy and relies on the perception-action mechanism, which is shared by all the higher-level empathic processes (de Waal & Preston, 2017). This implies that a spontaneous matching between the target's and the observer's neural responses is a common mechanism underlying both emotional contagion and empathy.

Kim et al. (2019) argue that the process in which the demonstrator's fear is recognized and shared, is a form of affective empathy, and is dependent on social perception. The Kim et al.'s claim suggests that the relation between affective empathy and emotional contagion is close. However, to date, it has not been determined whether rodents are capable of self-awareness (which is a prerequisite for empathy). It is thus unclear whether observational fear learning in rodents can be indicative of affective empathy (Keum & Shin, 2019).

The results of the research run in the last two decades have suggested that the vicarious fear learning circuit in rodents resembles the circuitry underlying empathy for distress in humans (Debiec & Olsson, 2017; Keum & Shin, 2019). Specifically, the involvement of the amygdala and ACC has been indicated in both rodent studies examining observational fear learning (Allsop et al., 2018; Andraka et al., 2021; Jeon et al., 2010; Knapska et al., 2006), and human works describing social learning of fear (Kaźmierowska et al., 2022; Lindström et al., 2018; Olsson & Phelps, 2007), and empathy for pain (Lamm et al., 2011; Singer et al., 2004). Also the oxytocin signaling mechanism has been described to work in a similar manner in rodents and humans: oxytocin has been found to enhance vicarious freezing in mice (Pisansky et al., 2017), and increase empathy for pain in humans (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013). This convergent neural and neurochemical evidence concurs with the view that

empathy is an evolutionary conserved social skill, and observational fear constitutes its fundamental part (Panksepp & Panksepp, 2013).

Given the opportunities offered by animal studies, it has recently become possible to describe the brain circuits underlying social fear learning in detail. The rodent results have indicated that the pattern of brain activations closely resembles what we have known from the human neuroimaging studies. A cross-species understanding of empathy enables us to look at the empathy-related phenomena such as emotional contagion in terms of basic processes that are conserved across species. From this perspective it becomes possible to learn not only about the neural correlates but also the actual mechanisms underlying empathy-related behaviors.

1.8. Overview of the used methods

c-Fos immunohistochemistry

c-fos is an immediate early gene expressed in the cell's nucleus. It was first found in the rat's fibroblasts (Curran & Teich, 1982), and soon after has it been identified in neurons (Dragunow & Robertson, 1987; Hunt et al., 1987; Morgan et al., 1987). It is a proto-oncogene, which means that once mutated, it can become tumor-inducing. It has thus been reported to be overexpressed in different types of cancer, but its presence has also been demonstrated under normal circumstances. c-Fos belongs to the family of inducible transcription factors (ITFs), which are able to influence the expression of the late response genes upon binding to the DNA-sequence (Kaczmarek et al., 2002). In the 1980s ITFs have been shown to participate in the cellular response to environmental changes (Curran & Franza, 1988; Morgan & Curran, 1986). Furthermore, the *c-fos coded* RNA and protein have been observed to rapidly increase following depolarization (Greenberg et al., 1986). Increase in the c-Fos level has often been referred to as an indirect marker of neuronal activation (Day et al., 2008; Gallo et al., 2018; Luyck et al., 2020), a marker of synaptic stimulation (Sagar et al., 1988) or an index of neuronal plasticity (Nikolaev et al., 1992).

The level of the c-Fos expression can be identified using immunohistochemical techniques. c-Fos based mapping of the brain activations provides a single-cell resolution and allows for a simultaneous tracing of the entire brain's activity (Jaworski et al., 2018). The baseline level of the c-Fos protein in the cell's nucleus is low and it increases following the stimulation, with the highest level of expression observed around 1.5 hours after the stimulation. Assuming that the studied animals are habituated to the experimental environment, and the study is well-designed, one may expect that the difference in the c-Fos expression level

between the experimental and control condition is a consequence of the used behavioral manipulation.

In general, c-Fos expression has been shown to reflect environmental novelty (VanElzakker et al., 2008; Zhu et al., 1995), and to be a necessary component of learning (de Hoz et al., 2018). Due to its involvement in the long-term plasticity in neurons (Miyashita et al., 2018), the level of the c-Fos expression has often been used to assess the plastic changes in the brain during various learning and memory paradigms (Doron & Rosenblum, 2010; Hadamitzky et al., 2015). Importantly, it has been studied in the amygdala, showing different activation patterns in different amygdala nuclei, and reflecting their functional specialization (Knapska et al., 2007). It has been proposed that in the basolateral amygdala, c-Fos expression reflects forming of the stimulus-value association; in the central amygdala it relates to attention and vigilance; and in the medial amygdala it increases in response to novel olfactory stimuli (Knapska et al., 2007). Notably, a great number of studies have reported c-Fos expression as an index of fear acquisition (Ivashkina et al., 2021; Martinez et al., 2013; Rajbhandari et al., 2016) and extinction (Gorkiewicz et al., 2022; Knapska & Maren, 2009; Schipper et al., 2019). Also studies using pharmacological interventions have reported changes in the level of c-Fos in the brain areas involved in fear processing (Radwanska et al., 2010; Singewald et al., 2003).

Functional magnetic resonance imaging

Magnetic resonance imaging is a non-invasive method of imaging the brain's structure (structural magnetic resonance imaging, sMRI) and function (functional magnetic resonance imaging, fMRI). fMRI enables recording the metabolic changes which accompany the neuronal activity. Specifically, these are changes in the blood oxygenation level, which result from the oxygen consumption in the excited neurons. Because of the fact that the hemoglobin has different magnetic properties depending on whether it is bound to the oxygen or not, changes in its oxygenation level influence the strength of the signal recorded in the magnetic field. This phenomenon is known as the BOLD (blood-oxygenation level dependent) signal (Ogawa et al., 1992). Due to the fact that fMRI is an index of the cells' metabolism, it is an indirect measure of the neuronal activity - it enables learning about different areas of the brain being activated by certain tasks, but it does not allow for inferring about the causal relationship between the stimulus and the neural response. Also, it is not possible to learn whether the activated neurons are excitatory or inhibitory - what we know is that they fired after some stimulus was presented. Still, the fMRI method was the first to enable observation of different areas of the human brain

becoming activated during execution of cognitive tasks, with a high precision and completely non-invasively.

The finding that was of particular significance for understanding the BOLD's nature, was the study by Logothetis et al. (2001) describing a simultaneous recording of BOLD and the neural activity from inside the visual cortex in monkeys. It has been shown that although BOLD is related to the number of activated neurons, it mostly reflects the local field potentials (LFPs), which are slowly changing signals recorded from large neuronal populations. Unlike the dynamic signals derived from single neurons, reflecting their action potentials, LFPs are the measure of the total activity of a local neural network. Thus, they reflect both the neuronal spiking and the sum of positive and negative postsynaptic potentials at many dendritic junctions. The conclusion of this experiment was therefore that the BOLD signal reflects the intracortical input processes, strong postsynaptic metabolic activity on dendrites, and local processing of neuronal information, rather than the output signal.

In order to examine the BOLD changes in response to the experimental manipulation, each voxel's time series is analyzed. Such a voxel-by-voxel approach is referred to as a mass univariate data analysis. Most often it involves the general linear model (GLM), which assumes that a linear combination of responses to stimuli, confounding variables and noise may be used to model the BOLD signal (Poldrack et al., 2011). Time courses of different experimental conditions are convolved with a hemodynamic response function (describing a typical BOLD response) to produce a prediction of how the BOLD signal should behave in response to different stimuli. The predicted time series is compared to the actual BOLD signal, and a parameter expressing the model's goodness is estimated for each voxel. These parameters are subsequently used for contrasting the activations obtained in different conditions (comparisons of different conditions are called 'contrasts'). Due to the fact that the brain image consists of hundreds of thousands of voxels which are spatially related to each other, applying a correction for multiple comparisons is a necessary step. For the analysis of small brain areas the 'small volume correction' approach is often recommended. It involves performing a multiple test correction in a subset of voxels, often limited to the mask of a certain region of interest (Poldrack, 2007).

1.9. Research goals and questions

The last two decades turned out to be groundbreaking in terms of the progress that has been made in research on the empathy-related phenomena, including emotional contagion, in

both rodents and humans. Despite a growing body of research suggesting similarities between brain circuitries involved in social transmission of fear in both species, an attempt to directly test how one of these species reacts to the fear of the other has still been lacking.

Thus, the main goal of my research was to investigate the brain mechanism underlying the interspecies fear contagion between humans and rats. As reviewed above, none of the interspecies studies has so far investigated emotional contagion phenomenon on the brain level. Also, it has not been examined before whether the contact with a fear-conditioned human results in any behavioral changes in a rat. Therefore, I aimed at characterizing the brain and behavioral effects occurring during the interaction of a fear-conditioned human with a rat, and comparing the observed neural response with the neural correlates of fear contagion in humans.

The specific research questions that I have posed are:

1. **Are rats sensitive to the human's fear?**

I assumed that a successful fear contagion between humans and rats would be indexed by the behavioral changes observed in rats, i.e., increased risk assessment behaviors and decreased number and/or frequency of ultrasonic vocalizations. Furthermore, I hypothesized that the rats' amygdala would be activated during the interaction with a fear-conditioned human. This assumption was made based on the fact that the amygdala has been found to respond to fear in a similar manner in both rats and humans.

2. **Which amygdalar nuclei are activated in rats during the human-rat fear contagion?**

I hypothesized that basolateral, central, and medial nuclei would be activated during an interaction with a fear-conditioned human. Such a prediction was based on the reports indicating the crucial role of these amygdala divisions in processing fear, and the previous study that revealed their activation in the remote fear contagion paradigm (Knapska et al., 2006).

The second goal of my research was examination of the amygdala involvement in the observational fear acquisition in humans. This has previously been done (Kaźmierowska et al., 2022; Lindström et al., 2018; Olsson et al., 2007), but never have the amygdala activations been studied in detail in this context. I aimed at investigating the activations of the basolateral and centromedial divisions of the amygdala during the observational fear learning phase of the observational fear conditioning protocol (Haaker, Golkar, et al., 2017; Szczepanik et al., 2020). Based on the previous research (de Gelder et al., 2004), I hypothesized that the activation of

the amygdala subnuclei would be accompanied by the activations in the brain areas relevant for the imitation process, which would reflect fear contagion. The results of this study have already been described elsewhere (Kaźmierowska et al., 2022), but here a subgroup of participants was analyzed (I chose the participants who were familiar to each other, which enabled a better comparison with the previous rat studies), and the analysis was focused on the activations of the amygdala divisions.

The research question here was:

3. **Do both the basolateral and centromedial amygdala activate during observational fear acquisition in humans?**

As rodent studies have shown that both the basolateral and centromedial subnuclei of the amygdala are activated by fear contagion, I hypothesized that also in humans the observation of the demonstrator receiving electric stimulation would activate both parts of the amygdala in the observers.

The results obtained in both experiments were planned to be compared to each other, as well as to the previous rat studies investigating the within-species fear contagion. Observing commonalities between results derived from various paradigms would constitute important evidence for the similar neural mechanism orchestrating fear contagion in humans and rats. For the first time, it would involve data from the paradigm involving emotional transfer between both of these species. Taking into account that according to the Russian doll model of empathy, the perception-action mechanism involved in emotional contagion is common for all the other empathy-related behaviors, the interspecies data presented in this thesis may constitute a valuable point in the discussion about the origins of empathy.

2. Methods

2.1. Experiment 1: human-rat fear contagion

Human caregivers and rat subjects

Nine human caregivers were involved in the experiment. They were male scientists, on average having 11.9 years of experience in working with rodents, and describing their proficiency in handling procedures as high (see Tab. 1 for details). All the caregivers had valid permissions to work with animals. The caregivers were informed that the electrical stimulation was a part of the experiment, and thus they were interviewed in terms of any health issues that could disallow their participation (e.g., heart diseases or metal elements inside the forearm). They received a financial remuneration of 350 PLN (~ 85 EUR) for their participation in the study.

Thirty-six male Wistar rats (180-200 g at the beginning of the experiment) were supplied by the Center of Experimental Medicine in Bialystok, Poland. The subjects were randomly paired and housed in home cages (56 × 37 × 20 cm) under a 12/12 light-dark cycle. The food and water were provided *ad libitum*.

The experiment was carried out in accordance with the Polish Act on Animal Welfare, after obtaining specific permission from the First Warsaw Ethical Committee on Animal Research. The protocol describing the human participants' involvement was approved by the Ethics Committee of the Faculty of Psychology at the University of Warsaw (decision from 28 November 2017). The procedure complied with the Ethical Principles of Psychologists and Code of Conduct published by the Polish and the American Psychological Associations.

Materials

In the questionnaire assessing the human caregivers' expertise in working with rodents, they were asked how long they have worked with animals, which species they have worked with, what kind of animal procedures they have used to perform and how frequently (0-5 Likert scale, from *never* to *very often*), how they rate their proficiency in handling procedures (1-5 Likert scale, from *very low* to *very high*), what their emotional attitude towards studied animals is, etc. The first set of questions referred to the species they have mainly worked with, and if it was not rats, additional questions referred to the rats.

Procedure

Each cage housed two rats that were randomly assigned to one human caregiver and one condition (experimental vs. control). The symbols enabling their identification were placed on the cages. Each caregiver had four rats assigned (two rats in the 'experimental' cage and two in the 'control' cage). The tail of one of the rats in each cage was marked, so that the rats could be differentiated and the order of handling controlled. Before the beginning of the experiment, rats were pre-handled by one of the experimenters to make them used to the contact with humans.

At the very beginning of the experiment all caregivers filled in the safety screening form and signed the informed consent. The first five days of the experiment were devoted to the handling procedure (Fig. 1A), which aimed at the rats' habituation. Each caregiver came to the laboratory individually, every day at the same time. The cage with the dedicated rats was placed on the experimental table and opened by the experimenter. The human placed his hands on the open cage for 40 s, after that took one of the rats into his arms and handled it for two more minutes. Then the rat was placed back into the cage and another one was taken into the arms for two minutes. Afterwards, the rats from the other dedicated cage were handled in the same manner. The order of the rats handled within a cage changed every day. Caregivers were not given any other specific instructions on how handling should be performed.

Days 6 and 7 were the control and experimental days, respectively. Such a design aimed at avoiding the transfer of strong negative emotions induced in the caregivers in the experimental task to the control condition. On day 6 (Fig. 1B) caregivers were informed that they would do a short computer task, in which squares of two colors (blue and yellow) would be presented. One of the colors was said to be repeatedly paired with mild vibrations that the caregivers would feel on the forearm thanks to the small device attached to this place. The vibrations were explained as not painful and similar to the ones emitted by a cell phone. The task was analogous on day 7 (Fig. 1C) but instead of mild vibrations, uncomfortable electrictic stimulation was applied to the caregivers' forearms. The stimulation consisted of five unipolar pulses of 1 ms duration applied in 200 ms intervals. Biopac STM100C and STMISOC stimulator modules, driven by a National Instruments USB-6001 analog output card was used to produce the pulses. Two Biopac EL509 electrodes (Ag/AgCl laminated, carbon composition contact, 11 mm diameter) placed 3.5 cm apart (measured between centers) filled with Spectra 360 salt free electrode gel were used. The appropriate level of stimulation was chosen for each caregiver individually. The experimenter increased it stepwise, and the caregivers rated the intensity using a scale from 1 (*imperceptible*) to 8 (*painful*). The target level was 6 (*very*

unpleasant but not painful). On both days the caregivers were informed that at the end of the day they would do the same computer task once again. The aim of such repetition was to maintain the induced emotional state in caregivers throughout the whole control/experimental day. On both days two galvanic skin response (GSR) electrodes were attached to the caregivers' fingers besides the vibration or stimulation device.

On days 6 and 7, caregivers performed the computer task: 12 squares (conditioned stimuli, CS) were presented on the screen one by one, each lasting for 9 s. The caregiver watched 6 CS+ (conditioned stimuli, reinforced; squares of one color) and 6 CS- (conditioned stimuli, not reinforced; squares of the other color) displayed on the screen in pseudo-random order, with a given CS repeated at most twice in a row. The assignment of color to CS+ and CS- was counterbalanced across caregivers. Four out of six CS+ (first, second, fourth and sixth) were reinforced with the unconditioned stimulus (US; mild electric vibrations on day 6 and uncomfortable electric shock on day 7), which appeared 8 s after the CS+ onset. CS- were never associated with the US. Between the CS presentations, a fixation cross appeared on the screen with a jittered duration (10-15 s). Stimulus presentation was controlled using Presentation v19.0 software (Neurobehavioral Systems, Berkeley, CA, USA). The caregivers were asked to simply watch the squares.

The computer task lasted around 5 minutes and immediately afterwards the electrodes were detached and caregivers were asked to put on the lab coat and gloves, and enter the animal room. They took the appropriate cage, placed it on the dedicated place on the table and opened it. Then the handling followed exactly in the same manner as during the handling phase. The experimenter watched the time and informed the caregivers when to move on from the "hands on the cage" (40 seconds) to the "rats in the arms" (2 minutes) phase. When the interaction was over, the cage was closed and placed back on the shelf. On day 6 caregivers had recording electrodes attached once again and they underwent the computer task once more (because I wanted them to believe that on the next day the same thing would happen). However, when the interaction phase was finished on day 7, there was no need to repeat the task. Caregivers were debriefed and received a remuneration for their participation.

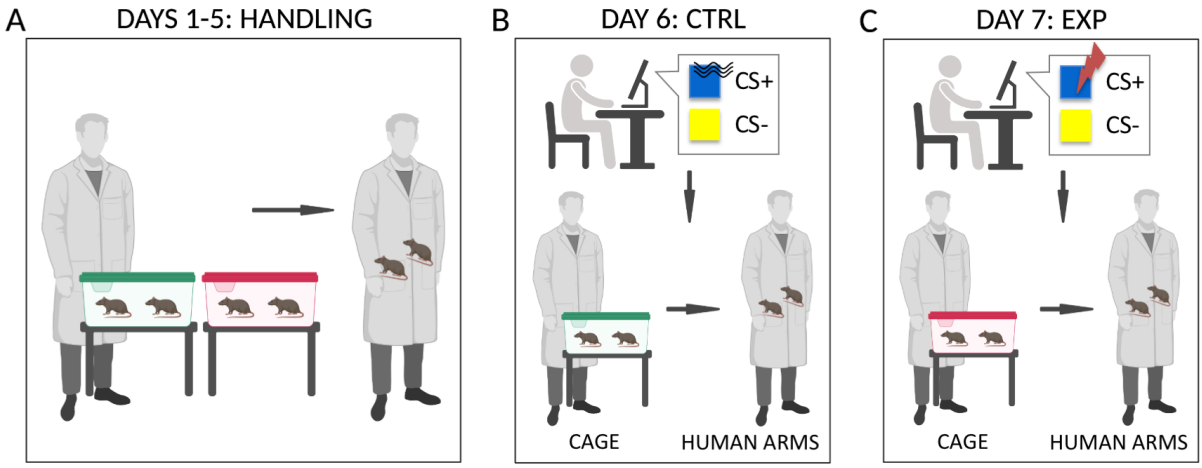


Fig. 1. Experimental design. (A) During the first five days every caregiver handled four rats (2 sessions involving 2 rats): first they kept their hands on the cage for 40 s and then took the rats into the arms and handled them for 2 min. (B) On day 6 mild vibrations were applied to the caregiver during the computer task and only rats from the control (marked in green) cage were handled. (C) On day 7 uncomfortable electric shocks were applied to the caregiver during the computer task and only rats from the experimental (marked in pink) cage were handled.

Analysis of the humans' skin conductance responses

During the computer tasks, the skin conductance responses of the human participants were registered. They were recorded using a Biopac EDA100C amplifier, sampled at 250 Hz. Two 6 mm Ag-AgCl electrodes (TSD 203) filled with 0.5% NaCl electrolyte gel (GEL101) were attached to the distal phalanges of the second and third digits of the participant's left hand.

To analyze skin conductance data, I used PsPM 4.3.0 software (https://bachlab.github.io/PsPM/) running under MATLAB 2020a (MathWorks, Natick, MA, USA). I used a non-linear model for event-related skin conductance responses (SCR). Before the analysis, I visually inspected the signals for artifacts and manually marked missing epochs. I used the default settings for preprocessing: signals were filtered using bi-directional 1st order Butterworth filters, with 5 Hz low-pass and 0.0159 Hz high-pass cut-off frequencies, and resampled to 10 Hz. I performed no response normalization. The mean values were calculated over the four US and two no US responses for each caregiver in experimental and control condition. The mixed model Anova with one between- (Group) and one within-subject (Stimulus) factor was run in the Scipy package v. 1.9.3.

Analysis of the rats' brains

Two hours after the interaction, rats received a lethal dose of morbital (133.3 mg/ml sodium pentobarbital, 26.7 mg/ml pentobarbital), and were transcardially perfused with ice-cold 0.1 M PBS (pH 7.4, *Sigma*) and 4% (wt/vol) paraformaldehyde (POCh) in PBS (pH 7.4). The brains were removed and stored in the same fixative for 24 h at 4°C, and subsequently immersed in 30% (wt/vol) sucrose at 4°C. The brains were then slowly frozen and sectioned at 40 μm on a cryostat. Coronal brain sections containing the amygdala were collected for immunohistochemistry.

The immunohistochemical staining was carried out on free-floating coronal brain sections. At first sections were incubated in PBS (pH 7.45, Gibco #18912014) overnight at 4°C, then washed three times again in PBS. Next, sections were incubated for 10 minutes in 0.3% H_20_2 in PBS, and then washed two times with PBS. After that, sections were incubated with a primary antibody (anti-c-Fos, 1:1000, abcam #ab190289) in PBST (0.02% Trition X-100, Chempur #498418109) and 3% NGS (Normal Goat Serum, Vector Laboratories, #S-1000-20) for 48h at 4°C. Later, brain slices were washed 3 times with PBST and incubated with goat anti-rabbit biotinylated secondary antibody (1:1.000, Vector Laboratories #BA-1000) in PBST for 2h in Room Temperature. After that, sections were washed three times with PBST and incubated with avidin-biotin complex (1:1.000 in PBST, Vector Laboratories ABC kit #PK-6100) for 1h, and then washed three times in PBS. The immunostaining reaction was developed by using the oxidase-diaminobenzidine-nickel method. The sections were incubated in distilled water with diaminobenzidine, urea hydrogen peroxide (Sigmafast #D4293-50SET) and 0.5M nickel chloride for about 5 mins, until the desired effect, and then reaction was immediately stopped by three washes in PBS. The c-Fos positive nuclei turned to dark brown. Following staining, sections were mounted on sides, dried under the hood, dehydrated in xylene and coverslipped with Entellan™ new (Sigma #107961).

The c-Fos positive nuclei were counted using ImageJ (NIH) software. As two slices were chosen from each rat brain and I did not take lateralization into account (S. Kim et al., 2012), four amygdalae were analyzed in each rat brain. Out of 144 amygdalae that I initially planned to analyze (4 amygdalae x 2 rats x 2 groups x 9 caregivers), 21 were assessed as damaged and were excluded from the analysis. In the remaining dataset, five main amygdala nuclei (basal, lateral, central medial, central lateral, medial) were distinguished on each slice. Due to the imperfect condition of the slices, it was not possible to analyze all five nuclei in each and every slice but it was done for the vast majority. The amygdala nuclei were delineated manually (Fig 3B) based on the corresponding sections from the rat brain atlas (Paxinos &

Watson, 2013). Pixels with a value in a 40-255 range were identified as c-Fos positive nuclei. The area (in mm^2) and the number of the c-Fos positive nuclei within each nucleus were exported and the mean density was calculated for each nucleus (number of cells divided by the area, the conventional unit: cells/mm^2).

To calculate the mean c-Fos expression in the five amygdala nuclei, ten categories involving information about the nucleus and the group were created (e.g., basal-exp, basal-ctrl, lateral-exp etc.). The observations that entered the analysis were the values of mean density for every nucleus in every single amygdala. A repeated measures ANOVA was run and FDR correction was applied for the pairwise comparisons. The order of taking rats into the arms was found to have no impact on the results. To calculate the mean c-Fos expression in the centromedial and basolateral nuclei, the areas of nuclei and the number of c-Fos positive cells were summed within the two complexes (basolateral = basal + lateral, centromedial = central medial + central lateral + medial). Based on such sums, mean density was calculated in the two main amygdala divisions. For each division the difference between the experimental and control group was calculated using independent samples t-test in the Scipy package v. 1.9.3.

Analysis of the rats' behaviors

The analysis of the rats behavior was done using BehaView software (http://www.pmbogusz.net/?a=behaview). The following behaviors were coded and analyzed: approach, avoidance, exploration, human exploration, hiding under the human's armpit, responding to the human's activity, freezing, hiding in the other rat's body, interaction with the other rat, waiting. Only the most frequent behaviors (exploration, human exploration, hiding under the human's armpit) were used in the analysis. A mixed model ANOVA was done separately for the 40-s period in the cage and the 120-s period in the arms. For the 'cage' phase the between factors were caregiver and group, the within factor was behavior. For the 'arms' phase the between factor was group, the within factors were behavior and time point (initial 60 s vs. final 60 s).

Analysis of the USV

All subtypes of 50 kHz rat calls were recorded using an UltraSoundGate Condenser Microphone CM16 (Avisoft Bioacoustics, Berlin, Germany) that was positioned 25–30 cm above the floor of the cage. This microphone was sensitive to frequencies of 15–180 kHz with a flat frequency response (± 6 dB) between 25 and 140 kHz. It was connected to

UltraSoundGate 416H (Avisoft Bioacoustics, Berlin, Germany), and then to the computer. The recordings were conducted using Avisoft-RECORDER software.

Due to technical problems the USV recordings were collected from rats handled by five caregivers only. The recorded data were processed using the RAT-REC PRO 5.0 software (custom-made). The signals were processed through a fast Fourier-transformation (FFT; 1024, Hamming window) and displayed as color spectrograms. Each signal was manually marked with the section label included in the automated parameter measurement. Various parameters were determined automatically, including the number of USV calls, the total calling time (s), the mean call length (s), the frequency bandwidth (kHz), the number of gaps, the mean gap length (s), and the mean peak frequency (kHz). Taking into account that dopaminergic system plays role in the processing of both appetitive and aversive states (Bromberg-Martin et al., 2010; Lammel et al., 2011; Zweifel et al., 2011), I have analyzed FFT spectrograms in the whole recorded frequency spectrum (10–130 kHz) to evaluate occurrences of not only "50-kHz appetitive", but also "22-kHz aversive" calls. Detailed analysis of the FFT spectrograms showed the absence of 22-kHz (alarm calls) in the presented model. Data recorded within the 0-1 min, 1-2 min and 2-3 min windows were used for the statistical analysis. As data were collected from the pairs of rats (and not the rats individually), 15 samples (5 caregivers x 3 timepoints) were included in each group. The mean call length and the mean peak frequency were compared between groups using Mann-Whitney U tests in the Scipy package v. 1.9.3. When calculating the mean frequency, 0 values were omitted.

2.2. Experiment 2: human-human fear contagion

Participants

48 pairs of human participants were recruited to the study. They were supposed to be friends, knowing each other for at least 3 years and each of them had to score at least 30 out of 60 points in the McGill Friendship Questionnaire - Respondent's Affection (Mendelson & Aboud, 1999) to be eligible for the study. They were mostly students, aged between 18 and 30 years, right-handed (due to the lateralization-related issues), and native or fluent Polish speakers. Additional requirements involved not being a student or a graduate of either psychology or cognitive science, not suffering from neurological disorders or other medical conditions precluding MR scanning or electrical stimulation, and not taking psychoactive drugs.

Only males were studied, as the original protocol (Haaker, Golkar, et al., 2017) was validated on the male group. Also, our previous studies (Szczepanik et al., 2020), as well as the rat studies that I planned to refer to, involved male subjects only. Investigating sex-related differences would be an interesting extension of the described research but here I focused on further validation of the modified protocol, as well as the possibility to refer to the analogous animal studies. We assumed that non-heterosexual orientation of observers could be related to the involvement of romantic feelings and specific patterns of directing attention, thus we recruited exclusively heterosexual participants only. Within pairs, one participant was assigned the role of a demonstrator and the other one - an observer. Only the observers underwent the fMRI procedure and the results obtained from their group were of our main interest. In the analyzed sample, the mean age of the observers was 22.4 years (SD = 2.8), the mean length of the observer-demonstrator friendship was 8.6 years (SD = 4.9), and the mean observers' score in the McGill Friendship Questionnaire was 50.7 (SD = 9.1). All participants received financial remuneration of 100 PLN (∼23 EUR) for their participation.

Experimental setup, task and stimuli

Data presented here were collected during an experiment on observational fear learning, where together with the team, we adapted the protocol of Haaker, Golkar et al. (2017) for live observation of demonstrator-observer interaction (Szczepanik et al., 2020). The experiment involved two groups of participants who, during the first phase, observed either their friends or stranger subjects undergoing the classical fear conditioning task, and during the second phase the effects of fear learning were measured (Kaźmierowska et al., 2022). The thesis presents only the data collected from the observers watching their friends being conditioned (N = 48). A similar fMRI experiment involving a between-group design (n_1 = 21 and n_2 = 22; Haaker, Yi, et al., 2017) was considered in order to estimate groups' sizes that provide sufficient statistical power. The number of recruited participants was additionally increased, taking into account the lowered ratio of the contingency-aware participants in a real-time observational fear learning procedure (Szczepanik et al., 2020). The protocol was approved by the Ethics Committee of the Faculty of Psychology at the University of Warsaw (decision from 28 November 2017). The procedure complied with the Ethical Principles of Psychologists and Code of Conduct published by the Polish and the American Psychological Associations.

In the MRI scanner, the observer watched a live streaming (without sound) on an MR-compatible monitor through a mirror box placed on the head coil. The demonstrator sat in a

small room adjacent to the MR room and a GoPro Hero7 camera provided video transmission (Fig. 2B). The room walls were covered with gray acoustic foam to minimize distractors.

The stimuli used in the task were the same as the ones used in the human-rat procedure (see above). The colored squares were presented centrally on the demonstrator's screen and covered a half of its height. Stimulus presentation was controlled using Presentation v19.0 software (Neurobehavioral Systems, Berkeley, CA, USA). Cutaneous electrical stimulation, applied to the ventral part of a forearm of the demonstrator, was used as the unconditioned stimulus. Stimulating electrodes were placed above the *flexor carpi radialis* muscle so that even low-intensity stimulation caused involuntary muscle flexion, visible to the observer. The demonstrators individually adjusted shock intensity to be unpleasant but not painful (for details see the description of the human-rat procedure above).

The demonstrator watched 24 CS+ and 24 CS- displayed on the screen in pseudo-random order, with a given CS repeated at most twice in a row. Each CS lasted 9 s, half of the CS+ were reinforced with the US. The US reinforced the first and the last presentation of CS+. The US started 7.5 s after the CS onset to allow the demonstrator's reaction to co-terminate with the CS. The CS- was never reinforced. The intertrial intervals (ITIs) lasted randomly between 10 and 15 s, with a fixation symbol (+) displayed centrally on the screen (Fig. 2C). When this task was over, the observers underwent a similar task themselves, which is not of importance for the thesis.

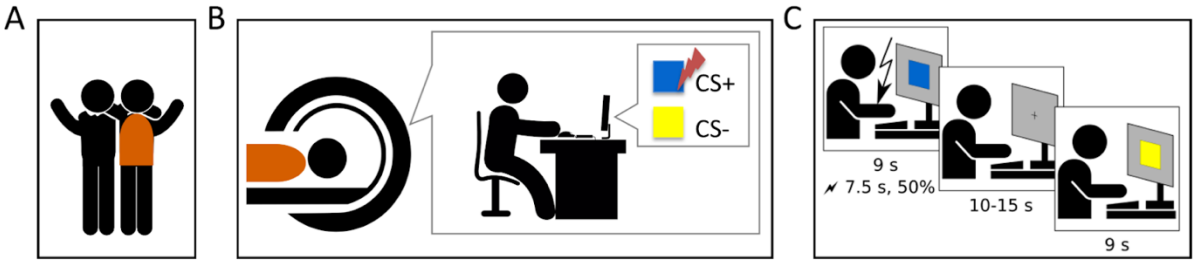


Fig. 2. Experimental design. (A) In the neuroimaging experiment pairs of friends were invited to the lab. (B) The observer was lying in the fMRI scanner and watching his friend (the demonstrator) performing the fear conditioning task. (C) The task consisted of two squares presented one by one, one of which was repeatedly paired with an uncomfortable electric shock applied to the forearm.

The modifications introduced to the original protocol (Haaker, Golkar, et al., 2017) aimed at increasing its ecological validity, which is claimed to be critical in research focusing

on social interactions (Bottenhorn et al., 2019; Matusz et al., 2019). We believed that modifying the procedure toward a more naturalistic one could tell us how observational fear learning occurs in real life, with authentic emotions being expressed. For the purpose of adapting the protocol, we decided to invite pairs of participants and involve them both in the experimental procedure. Instead of using a prerecorded video of an actor, one of the friends was asked to become a live demonstrator. Additionally, in order to create a more relevant situation, we recruited pairs of friends (Szczepanik et al., 2020). These changes enabled a better (although still imperfect) comparison of our human experiment and the previous rat studies (in which subjects are cage mates).

Procedure

Upon their arrival to the laboratory, the participants received brief information about the experimental procedure, including the possibility of receiving aversive electrical stimulation. Next, the participants gave informed consent and filled in safety screening forms. The roles of a demonstrator and an observer were then randomly assigned to the participants by giving two color-coded envelopes. Then the participants were isolated - the demonstrators were invited to a room adjacent to the MR room.

Subsequently, the observers were informed that they would watch their friends performing a task involving the presentation of colored symbols and the administration of unpleasant electrical stimulation. They were also told that afterwards, they would do the same task themselves. After receiving the instruction, the observers had stimulation and skin conductance electrodes attached and went to the MR room. In the scanner, the subjects had sham leads connected to the stimulation electrodes attached to make receiving electrical stimulation believable.

The demonstrators were informed that they would perform a task involving the presentation of colored symbols and administering unpleasant, but not painful, electrical stimulation. We asked the demonstrators to react to the stimulation in a natural yet noticeable manner. The demonstrators watched a recording with a model reaction. After receiving the instruction, the demonstrators had stimulation and sham skin conductance electrodes attached. Afterwards, the demonstrators adjusted stimulation intensity (see the human-rat procedure description). The experimenter adjusted the camera's position to ensure that the observer could see the demonstrator's face, hand, and computer screen and turned on video transmission. The observer received a brief reminder: ‘in this part of the study, you will observe your friend performing a certain task’ and the MRI scanning started. After completion of the observational

stage, the observer performed a similar task that is out of scope of this manuscript. At the end, all the participants were debriefed about the study.

Behavioral measures

McGill friendship questionnaire - respondent's affection

During an online recruitment of pairs of friends, we used the McGill Friendship Questionnaire - Respondent's Affection (Mendelson & Aboud, 1999); translated by A. Kaźmierowska, P. Pączek, and A. Schudy. It consists of 16 positive statements describing feelings for a friend and satisfaction with the friendship, rated along a 9-point scale ranging from -4 (*very much disagree*) to 4 (*very much agree*). One item (no. 9) was omitted from the questionnaire due to human error. A score of 30 points was a threshold for inclusion in the study.

State anxiety inventory

To measure participants' anxiety, we used the State Anxiety Inventory (Spielberger et al., 1983); Polish adaptation (Spielberger et al., 2012). It is a self-report scale consisting of 20 items. Participants rate statements related to how they feel at a given moment using 4-point Likert scales. Each participant completed the scale twice (at the beginning and the end of the experiment).

Evaluation of the demonstrator's expression (the observational US)

To control how the observers perceived the demonstrators' behavior, we used a set of questions suggested by Haaker, Golkar et al. (2017). At the end of the experiment, we asked the observers to rate: how much discomfort the demonstrator experienced when receiving the electrical stimulation, how expressive the demonstrator was, how natural the demonstrator's reactions were, and how much empathy they felt for the demonstrator. Additionally, we asked the observers to rate the degree of unpleasantness attributed to the demonstrators. Finally, the observers scored the degree to which they identified with their friends. All ratings used a 10-point Likert scale, ranging from 0 (*not at all*) to 9 (*very much*), except for the unpleasantness rating, which used a 5-point Likert scale ranging from 1 (*very unpleasant*) to 5 (*very pleasant*).

fMRI data acquisition

The MRI data were acquired on a 3T Siemens Magnetom Trio scanner equipped with a 12-channel head coil. At the beginning of a session, a T1-weighted anatomical image was

acquired using an MPRAGE sequence with 1 × 1 × 1 mm resolution and the following parameters: inversion time TI = 1100 ms, GRAPPA parallel imaging with acceleration factor PE = 2, acquisition time TA = 6 min and 3 s. After acquiring the anatomical scans, two functional imaging runs followed: the observational and direct task. The first run contained 362 volumes. Each functional volume comprised 47 axial slices (2.3 mm thick, with 2.3 × 2.3 mm in-plane resolution and 30% distance factor) that were acquired using a T2*-sensitive gradient echo-planar imaging (EPI) sequence with the following parameters: repetition time TR = 2870 ms, echo time TE = 30 ms, flip angle FA = 90 degrees, field of view FoV = 212 mm, matrix size: 92 × 92, interleaved acquisition order, GRAPPA acceleration factor PA = 2.

fMRI data preparation – preprocessing

The fMRI data were preprocessed using fMRIPrep 1.4.0 (Esteban et al., 2019a; Esteban et al., 2019b), based on Nipype 1.2.0 (Gorgolewski et al., 2011; Gorgolewski et al., 2019) and Nilearn 0.5.2 (Abraham et al., 2014). At the beginning of the fMRIprep pipeline, the anatomical images were corrected for intensity non-uniformity with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.2.0 (Avants et al., 2008), and used as an anatomical reference. The anatomical reference was then skull-stripped with antsBrainExtraction (from ANTs) and segmented using fast from FSL 5.0.9 (Zhang et al., 2001). Finally, the anatomical images were normalized to the MNI space through nonlinear registration with antsRegistration (ANTs 2.2.0). The ICBM 152 Nonlinear Asymmetrical template version 2009c was used (Fonov et al., 2009).

The functional images were preprocessed in the following manner. First, a reference volume was generated using a custom methodology of fMRIPrep. This reference was co-registered to the anatomical reference using flirt from FSL 5.0.9 (Jenkinson & Smith, 2001) with the boundary-based registration cost-function (Greve & Fischl, 2009). Head-motion parameters with respect to the functional reference volume (transformation matrices and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt from FSL 5.0.9 (Jenkinson et al., 2002). The functional scanning runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox & Hyde, 1997). Next, the functional images were resampled into the MNI space (voxel size after normalization: 2 x 2 x 2 mm). All resamplings were performed in a single interpolation step (composing head-motion transform matrices and co-registrations to anatomical and output spaces) using antsApplyTransforms (ANTs). Finally, the functional images were smoothed with a 6 mm FWHM 3D Gaussian kernel using spm_smooth (SPM 12 v7487, Wellcome Centre for Human

Neuroimaging, London, UK). Framewise displacement (FD) and the derivative of root mean square variance over voxels (DVARS) were calculated by fMRIPrep for each functional scan, both using their implementations in Nipype and following the definitions by (Power et al., 2014). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. For more details on the fMRIprep pipeline, see fMRIPrep's documentation at https://fmriprep.org/en/latest/workflows.html.

fMRI data analysis

To analyze data, I used a mass univariate approach based on a general linear model. I used SPM 12 software running under MATLAB 2020a (MathWorks, Natick, MA, USA). First-level models contained four types of events in the observational learning stage: CS+, CS-, US, and no US (i.e., lack of US during 50% of CS+). The observational CS were modeled as instantaneous events (i.e., CS onset), while the observational US/no US events were 1.5 s (i.e., from US onset to CS offset). In addition to the event regressors, I had six motion parameters (translation and rotation) as regressors of no interest. I added one delta regressor for each volume annotated by fMRIPrep as a motion outlier.

For the purpose of this manuscript, only the observational stage was analyzed and the US > no US was the primary contrast of interest. I estimated beta values on the first-level and used them in the second-level analysis employing a paired t-test design. For the amygdala analysis, I thresholded the second-level statistical maps using small volume correction, for each amygdala mask separately, with a $p = .05$ threshold. The anatomical ventrolateral and dorsomedial amygdala masks (Bielski et al., 2021) were combined and treated as a single ROI. I also investigated each of the amygdala divisions separately. Since it was reported that the functional connectivity patterns between the ventrolateral and basolateral amygdala as well as between the dorsomedial and centromedial amygdala were found to be similar, I decided to use general labels commonly used in animal research (McDonald, 1998). For the additional analysis verifying the US > no US activations within the brain network related to both observation and imitation of actions, the meta-analysis by Caspers et al. (2010) was used, and the observation-imitation mask (resulting from the conjunction of the observation and imitation masks) was derived from the corresponding Neurovault collection (https://identifiers.org/neurovault.collection:824). The statistical maps were thresholded using a small volume correction within the observation-imitation mask, with a $p = .05$ threshold.

3. Results

3.1. Experiment 1: human-rat fear contagion

Only one out of nine caregivers participating in the study reported not working with rats before, but this person had a large experience in working with mice. The rest of the caregivers reported to have experience in working solely with rats or with rats and mice. The self-report characteristics describing the caregivers' experience in working with rodents are presented in Tab. 1.

Table 1. Results of the questionnaire assessing the caregivers' experience in working with rodents

	M	SD
Length of work with rodents	11.9	6.7
	ME	IQR
Proficiency in handling (1-5 scale, 1: very low, 5: very high)	4.0	1.0
Frequency of performing different types of tasks in the lab (0-5 scale, 0: never, 5: very often)	ME	IQR
Performing behavioral experiments	4.0	2.5
Performing surgeries	4.0	2.0
Performing laboratory procedures (e.g., stainings)	4.0	2.5
Analysis of behavioral data	4.0	2.5
Analysis of data of different type (e.g., molecular)	3.0	2.5
Reading literature, planning	5.0	1.0

I do… (1-7 scale, 1: definitely not, 7: definitely yes)	ME	IQR
care about habituation when running an experiment	7.0	2.5
not feel discomfort when I anesthetize animals	5.0	2.5
recognize when an animal is scared/relaxed	6.0	1.0

M: mean, SD: standard deviation, ME: median, IQR: interquartile range. Ratings refer to the animal that the caregiver declared to have the biggest experience with (rat or mouse).

When the rats were habituated (Fig. 1A), they interacted with caregivers who underwent either the fear conditioning (Fig. 1C) or the sham procedure (Fig. 1B). Using skin conductance response, I confirmed that the fear conditioning, compared to the sham procedure, induced a stronger physiological response in the caregivers [a repeated measures ANOVA with Group and Stimulus factors: Group x Stimulus interaction ($F(1, 8) = 32.47$, $p < .001$, $\eta_g^2 = .15$); pairwise comparisons with FDR correction: US-EXP > US-CTRL ($p < .001$) and EXP-US > EXP-noUS ($p < .001$); Fig. 3].

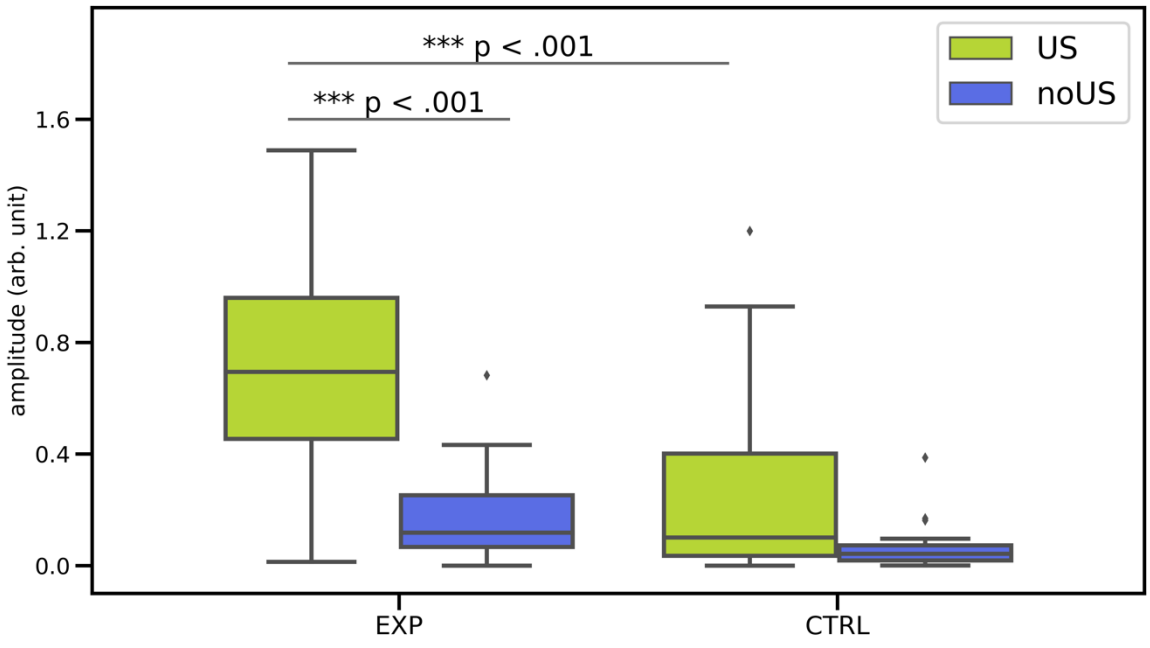


Fig. 3. Skin conductance response of the caregivers during the fear conditioning (EXP) and control (CTRL) task. US condition marks the electric stimulation occurrence, no US condition refers to the expected but not occurring stimulation. Error bars extend to data points placed no further than 1.5*IQR (interquartile range) beyond the 1st quartile and above the 3rd quartile.

Next, I analyzed the rats' behavior during the interaction with caregivers: during 40 s in the home cage (when the caregivers held their hands on the cage, phase 1) and the subsequent 120 s in the arms of the caregivers (phase 2). In phase 1 I measured how much time the rats explored the cage and stayed close to the caregivers' hands. In phase 2 I compared how much time the rats spent on walking on the caregivers' arms and sniffing his body (human exploration), and how much time they tried to hide in the caregivers' armpit. I found that rats tested with the fear-conditioned caregivers explored the human's hands significantly less and instead spent more time exploring the cage [a mixed model ANOVA (within-subject factor: Behavior, between-subject factors: Group, Caregiver) for phase 1: Group x Behavior interaction ($F(1, 12) = 9.54$, $p < .01$, $\eta_g^2 = .38$; the effect of group on the duration of the human exploration ($F(1, 22) = 14.6$, $p < .002$), pairwise comparisons with FDR correction; Fig. 4A].

Additionally, the analysis of the ultrasonic vocalizations (USV) in the subgroup of rats indicated that during the human-rat interaction mean USV episode duration decreased in animals interacting with fear conditioned caregivers [$U = 546.5$, $p = .042$, $n_{exp} = 30$, $n_{ctrl} = 30$; Fig. 1E]. The number of USV episodes also tended to be lower in these rats [number of episodes: $U = 538$, statistical trend $p = .06$, $n_{exp} = 30$, $n_{ctrl} = 30$; total duration of the USV episodes: $U = 541.5$, statistical trend $p = .05$, $n_{exp} = 30$, $n_{ctrl} = 30$]. The rats in both groups vocalized in the similar frequencies of 50-60 kHz [the experimental group: M = 60.80 kHz, the control group: M = 57.05 kHz, Fig. 4B]. Taken together, the rats interacting with fear conditioned caregivers decreased their contact with humans and reduced their ultrasonic vocalization.

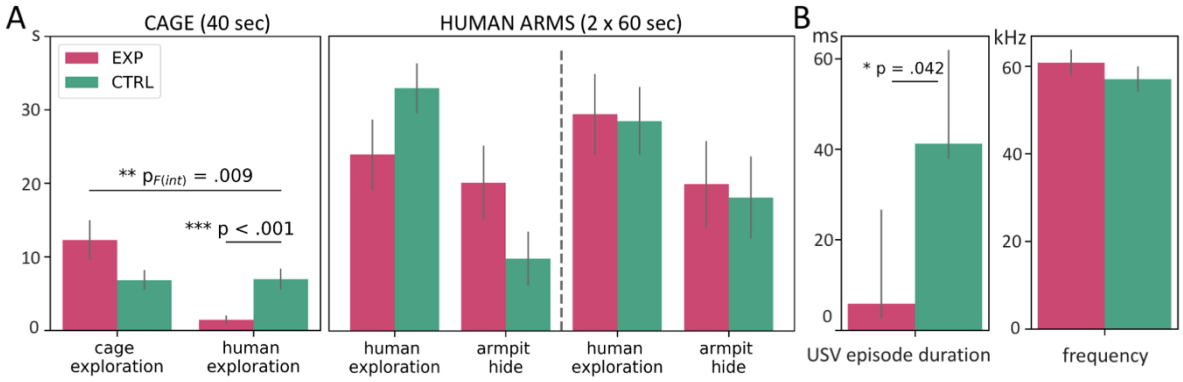


Fig. 4. Rats' behavioral results. (A) Rats' behavior during 40 s in the cage with the caregivers holding their hands on the cage (phase 1) followed by the periods during which the humans handled the rats (phase 2, divided into two 60-s blocks). Rats tested with fear-conditioned caregivers interacted less with the human's hands and spent more time exploring the cage. The dashed line divides the arms phase into two 60-s periods. Error bars indicate SEM; $n_{exp} = 18$;

n_{ctrl} = 18. (B) Mean durations of a single USV episode (n_{exp} = 15, n_{ctrl} = 15; USV from 5 pairs of rats measured in 3 timepoints) and the USV frequency (n_{exp} = 3, n_{ctrl} = 9). Error bars indicate SEM.

Then, I investigated activation of the amygdala of rats interacting with the caregivers subjected to fear conditioning or the sham procedure. I found increased expression of c-Fos, a marker of neuronal activation, in the amygdala of rats handled by the fear-conditioned caregivers compared to those handled by the humans subjected to the sham procedure [the mixed model ANOVA with two between- (Group, Human) and one within-subject (Nucleus) factors: main effect of the group ($F(1, 13) = 11.63$, $p = .005$, $\eta_g^2 = .28$); Fig. 5A].

Further, I investigated the activation of the separate nuclei of the amygdala. I found that the basal nucleus and the lateral division of the central nucleus were more active in rats interacting with the fear conditioned caregiver than with the caregiver subjected to the sham procedure [the repeated measures ANOVA with one Category factor involving the information about both the group and the nucleus: main effect of the category ($F(9, 72) = 20.19$, $p < .001$, $\eta_g^2 = .35$), pairwise comparisons with FDR correction: $p = .03$ for both basal ($d = .63$) and central lateral ($d = .47$) nuclei; Fig. 5B, C]. I found a similar trend in the medial ($p = .05$, $d = .63$) and the lateral ($p = .06$, $d = .66$) nuclei of the amygdala.

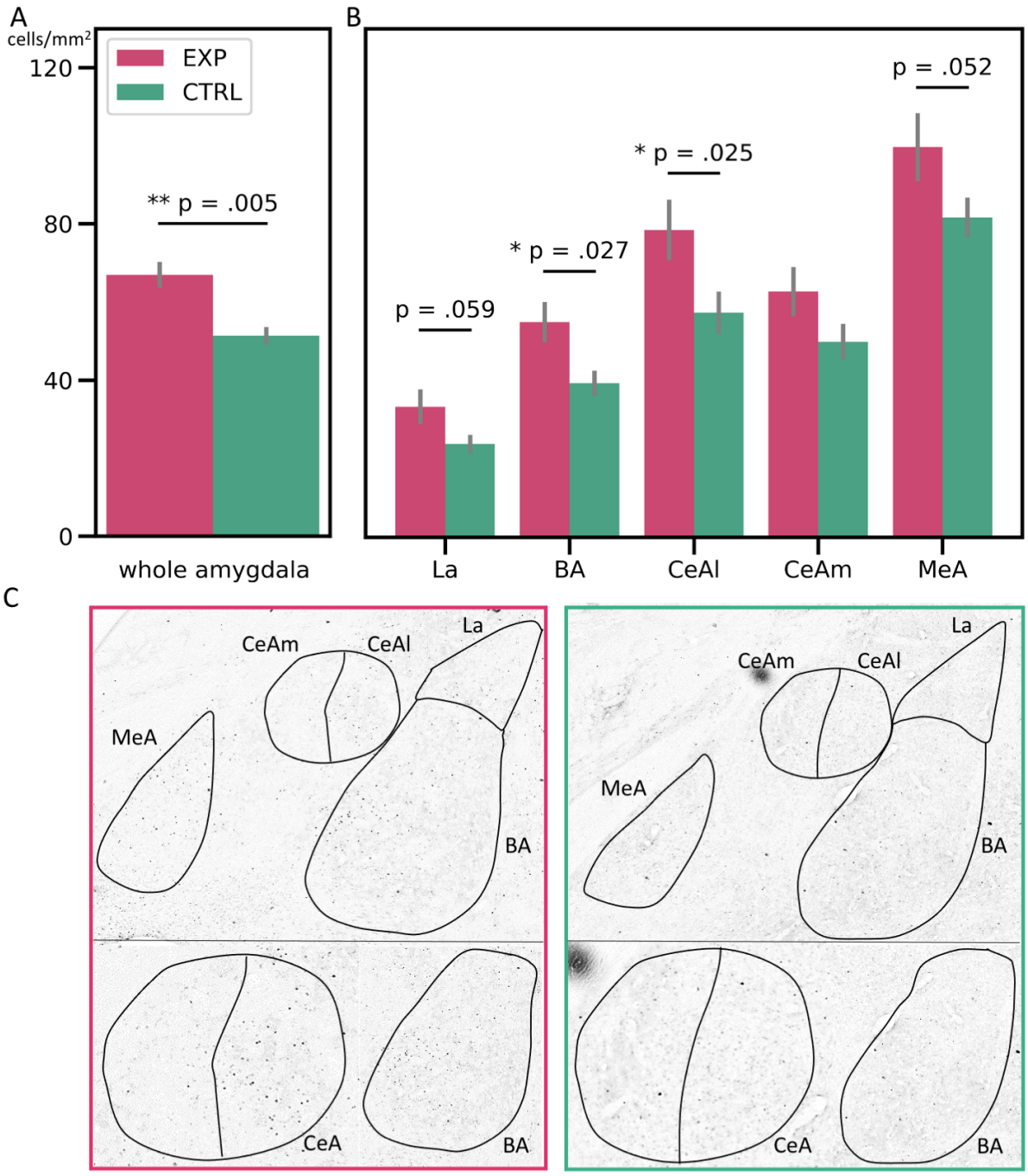


Fig. 5. (A) Mean density of c-Fos positive nuclei in the amygdala following interaction with caregivers; $n_{exp} = 250$, $n_{ctrl} = 290$. (B) Rat amygdala activations in five main amygdalar nuclei: La - lateral, BA - basal, CeAl - central, lateral division, CeAm - central, medial division, MeA - medial; $n_{La\text{-}exp} = 41$, $n_{La\text{-}ctrl} = 49$, $n_{BA\text{-}exp} = 55$, $n_{BA\text{-}ctrl} = 61$, $n_{CeAl\text{-}exp} = 52$, $n_{CeAl\text{-}ctrl} = 60$, $n_{CeAm\text{-}exp} = 52$, $n_{CeAm\text{-}ctrl} = 61$, $n_{MeA\text{-}exp} = 50$, $n_{MeA\text{-}ctrl} = 59$; n indicates the number of brain sections analyzed in 18 rats in each group. Error bars indicate SEM. (C) The sample brain sections showing c-Fos expression in the rats interacting with fear conditioned caregivers (left panel) and with caregivers subjected to the sham procedure (right panel). The upper part shows five

main amygdalar nuclei. In the lower part the central (central lateral + central medial, CeA) and basal (BA) parts are zoomed in.

3.2. Experiment 2: human-human fear contagion

To investigate whether human-human fear contagion results in a similar pattern of amygdala activation as the one we found in the human-rat fear contagion, I used the observational fear conditioning procedure (Kaźmierowska et al., 2022; Szczepanik et al., 2020). It involved an interaction of a pair of friends, one of whom (the observer) was watching the other (the demonstrator) undergoing the classical fear conditioning task (Fig. 2A, B, C; see also the Methods section).

In this procedure demonstrators` performance modulated physiological arousal and resulted in conditioned fear responses in the observers (Kaźmierowska et al., 2022). Here, the demonstrators' performance was rated by the observers as natural, expressive, and showing discomfort. The observers identified with their friends and felt empathy towards them (see Fig. 6 for the ratings of the demonstrators' performance). The shocks administered to the demonstrators were perceived by the observers as very unpleasant (ME = 1.5, IQR = 1.0, on a 1-5 scale, 1: very unpleasant, 5: very pleasant). The observers' anxiety level was similar before and after the experiment [t(47) = -.10, p = .92]

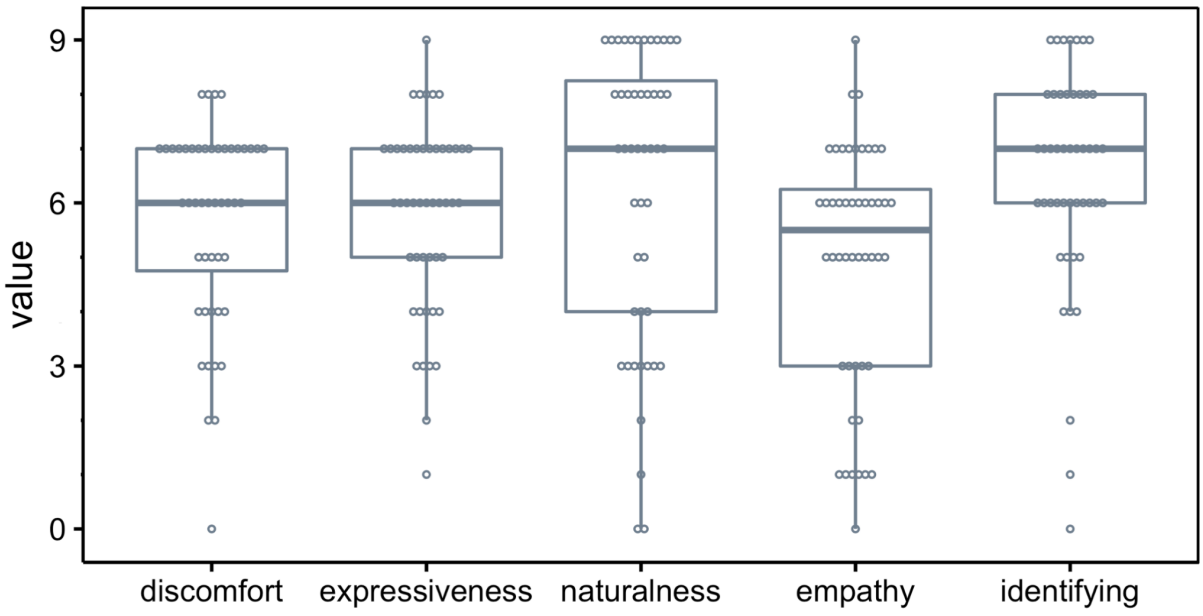


Fig. 6. The observers' ratings of the demonstrators' performance. Error bars extend to data points placed no further than 1.5*IQR (interquartile range) beyond the 1st quartile and above the 3rd quartile.

I compared activation of the amygdala when the subjects observed the friend receiving an electric stimulation (unconditional stimulus, US) to the periods without stimulation (no US). Using the small volume correction approach, I found significant clusters within the bilateral amygdalae mask (44 voxels' cluster on the left side and 36 voxels' cluster on the right side). Further, I found significant activations in the two main subparts of the amygdala, the basolateral and centromedial divisions (Fig. 7; Tab. 2). Additionally, I tested for the activations in regions related to observation and imitation of actions, including the inferior frontal gyrus, the superior parietal lobule, and the fusiform gyrus, and found that activations in these areas accompanied the amygdala activation during observation of a friend receiving electric stimulation (see the Appendix for these results).

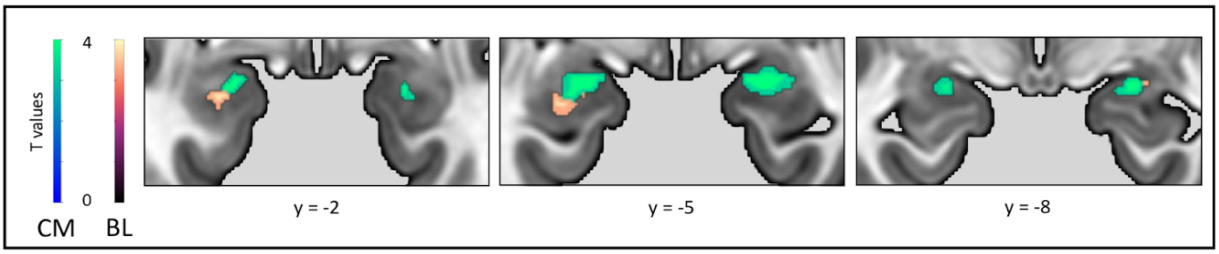


Fig. 7. Fear contagion between humans. Centromedial (CM, green) and basolateral (BL, orange) amygdala were activated in the observers; US > no US contrast, small volume corrected within the CM and BL masks.

Table 2. Results of direct comparison of the US > no US contrast.

Region	Extent	t-value	X	Y	Z
US > no US					
Left amygdala	44	5.65	-22	-2	-20
Right amygdala	36	5.61	22	-6	-14
Left centromedial amygdala	30	5.65	-22	-2	-20
Right centromedial amygdala	32	5.61	22	-6	-14
	1	3.44	26	-0	-24
Left basolateral amygdala	14	4.53	-24	-2	-22

Right basolateral amygdala	2	3.76	24	-0	-24
	1	3.66	24	-8	14

p- and t-values presented were obtained using FWE (familywise error) correction at a voxel (peak) level $p < .05$ within small volume correction within bilateral amygdala, bilateral centromedial amygdala, and bilateral basolateral amygdala masks. Each row corresponds to a significant cluster of voxels.

3.3. Shared perspective

I investigated the homologous parts of the amygdala in rats and humans: the centromedial and basolateral parts. Rats data were aggregated: central lateral, central medial and medial nuclei were treated together as the centromedial division, while basal and lateral nuclei were counted as the basolateral division. I found that both parts of the amygdala were activated in the rats interacting with fear conditioned caregivers [the centromedial amygdala: $t(111) = -2.20$, $p = .03$, the basolateral amygdala: $t(114) = -2.57$, $p = .01$] (Fig. 8A). Similarly, during the human-human interaction the reaction to the US applied to the partner was significantly greater compared to the no US (control) condition in both the centromedial [$t(46) = 4.24$, $p < .001$] and basolateral [$t(46) = 2.79$, $p = .008$] amygdala (Fig. 8B).

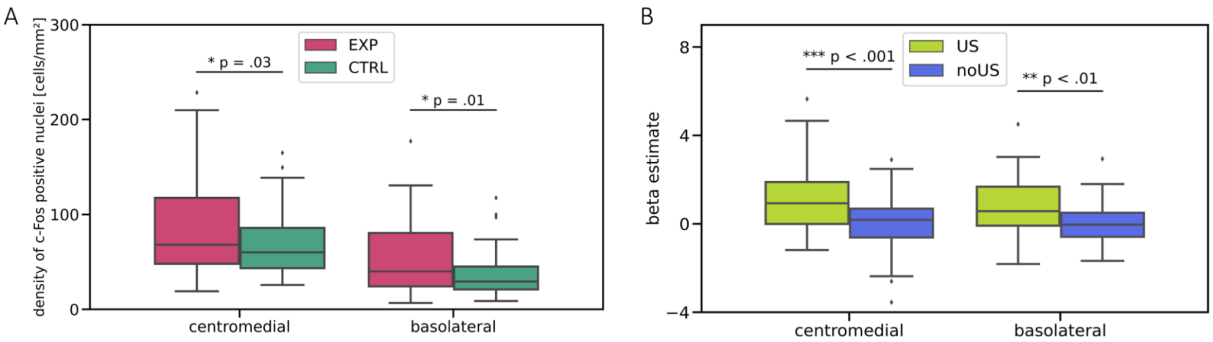


Fig. 8. Fearful partner activated the centromedial and basolateral amygdala in rats (human-rat interaction) and humans (human-human interaction). (A) The mean c-Fos expression was higher in the rats interacting with fear conditioned caregivers (EXP) compared to the rats interacting with caregivers subjected to the sham procedure (CTRL). (B) In humans, the BOLD signal was increased in response to the US applied to the interaction partner compared to the no US condition. Error bars extend to data points placed no further than 1.5*IQR (interquartile range) beyond the 1st quartile and above the 3rd quartile.

4. Discussion

This thesis has described two experiments. The first one, involving humans and rats, aimed at investigating the possibility of the human-rat fear contagion. The interspecies emotional contagion between humans and rats has not been tested before. Moreover, none of the existing studies on the interspecies emotional contagion (investigating other species) has looked at the brain mechanisms underlying this phenomenon. In the described study, activations in different amygdala subnuclei during the human-rat interaction were tested. Additionally, behavior and ultrasonic vocalizations of rats were assessed.

The second experiment involved pairs of human friends and employed fMRI to investigate whether both main divisions of the amygdala activate during fear contagion in humans. Although the amygdala as a whole has previously been shown to activate during the observational fear acquisition in humans, I aimed at testing the involvement of its two major parts - the basolateral and centromedial nuclei. Known to be morphologically and functionally different, both have been indicated as crucial for the processing of directly acquired fear in both rats and humans. This experiment was meant to be the link between the previous rat-rat studies and the human-rat study described above. The obtained results were supposed to open a discussion of the potentially common brain circuitry underlying fear contagion within humans, within rats, and between both these species.

Summary of the findings and their interpretation

In the human-rat experiment, I found increased c-Fos expression in the amygdala of rats interacting with fear-conditioned caregivers, compared to those handled by caregivers subjected to the sham procedure. This result indicates a successful transfer of fear from humans to rats. The amygdala' nuclei that responded particularly strongly were the basal nucleus and the lateral division of the central nucleus. The trend-level differences in the c-Fos expression were also found in the lateral and the medial nuclei of the amygdala. I also showed that when the c-Fos expression is aggregated and compared between the two main amygdala divisions - basolateral and centromedial - both of them show elevated activations. These findings indicate that both of the two main amygdala divisions are involved during the rats' interaction with fearful caregivers. Based on the previous findings which showed how the fear circuit works, it is probable that the information about fear first entered the rats' basolateral complex of the

amygdala, and was further sent to the centromedial complex. These results thus suggest that the processing of the humans' fear in the rats' amygdala involved the typical brain response that is also employed when rats share signals of fear with their conspecifics. What it implies is that the humans' fear signals are understandable for rats, and that the brains of rats are wired to process the fear-related information derived from humans in the similar manner as the signals of fear sent by conspecifics.

The neural findings were supported by the behavioral results. I found that during the first 40 seconds of the interaction, when rats were still in the cage but the caregiver held his hands on it, rats from the experimental and control group behaved differently. Those interacting with the fear-conditioned caregivers showed decreased human exploration compared to those interacting with caregivers who underwent the sham condition. Importantly, the 'experimental' rats did not freeze, but chose to explore the cage instead of approaching the human. Thus, their decision to withdraw from the interaction with caregivers was fast, and so the fear signal must have been evident to rats from the very beginning. When taken in the arms of the caregivers, 'experimental' rats still tended to explore them less, at the same time displaying more hiding behavior compared to the 'control' rats. These differences were not statistically significant though. During the last 60 seconds in the caregivers' arms, rats from both groups showed similar levels of both the human exploration and the hiding behaviors. This pattern of temporal dynamics suggests that the rats' reaction to the caregiver's fear was the strongest at the beginning of the interaction, but it quickly decreased. The rats never freezed - neither in the cage, nor in the caregivers' arms. Their active behavior is in line with the previous reports on the rats' behavior during the remote fear contagion paradigm, in which they show increased risk assessment behaviors (Andraka et al., 2021; Knapska et al., 2006). Risk assessment is an information-gathering behavior displayed in potentially threatening aversive situations (Blanchard et al., 2011). In a home cage it is expressed by means of increased cage exploration. It may be supposed that the rats, when in a cage, gathered information while avoiding a close contact with a caregiver, and when in the arms, started to explore a caregiver. Thus, in this uncertain situation, while receiving signals about a potential threat, they remained active, increasing chances for the threat detection.

I also found that rats from both groups vocalized with a similar mean frequency, around 50-60 kHz. Calls of this frequency are known as the indices of positive affective states (Burgdorf et al., 2000; Knutson et al., 1998, 2002), as opposed to the 22 kHz vocalizations, which are the alarm calls and are typical for the direct, strong experience of aversive events (Carrillo et al., 2019; Fendt et al., 2021; Litvin et al., 2007; Tonoue et al., 1986) but see

(Andraka et al., 2021). I noticed that the mean duration of a single ultrasonic vocalization was shorter in the rats interacting with fear-conditioned caregivers compared to the rats from the control group. Also the number of calls tended to be lower in the 'experimental' rats, but this difference was not significant. Altogether, these results show that although no typical ultrasonic aversive responses were observed in rats interacting with fear-conditioned caregivers, their positive calls were decreased, which indicates a less positive affective response in this group compared to the rats from the control group. This is in line with the previous reports showing that reduced 50-kHz calling occurs in the presence of aversive stimuli (Burgdorf et al., 2000; Knutson et al., 1998, 2002).

Finally, I looked at the amygdala activations during the observational fear learning in humans. I found that the amygdala was activated in the observers watching their friends receiving aversive electric stimulation. Not only did it activate as a whole, but also its two major divisions - the basolateral and centromedial nuclei - were activated. Given that these activations occurred in response to the social unconditioned stimulus - the demonstrator's body expression of fear - I propose that it reflects fear contagion in the observers. This finding is further supported by the additional analysis, which revealed that the areas involved in the observers in our study were similar to those that have previously been reported to be implicated in the observation and imitation of others' actions (Caspers et al., 2010). Voxels belonging to the inferior frontal gyrus, the lateral occipital cortex, and the temporal occipital fusiform cortex have been shown to activate during both observation and imitation in various paradigms, and here they also activated in the US > no US contrast, suggesting the activation of mirror neurons in the observers during observational fear acquisition. Together with the amygdala response, these activations constitute evidence for fear contagion in the observers (de Gelder et al., 2004). It is important to note that the used paradigm had previously been modified in terms of ecological validity. The observers watched their friends in real time, which was supposed to create a naturalistic context. Indeed, the observers' ratings of the demonstrators' behavior revealed that they assessed their friends' performance as natural and expressive. They also stated that they had perceived the discomfort of the demonstrators, that they identified and empathized with them, and that the observed shocks seemed to be very unpleasant. Taken together, these ratings indicate that the observers' feelings resonated with those of the demonstrators, which supports the idea of the emotional contagion taking place during the observational fear acquisition.

Social cues of fear are processed in the amygdala

While the vast majority of scientific evidence has demonstrated the crucial role of the human amygdala in fear processing, the recent meta-analysis of the neural signatures of human fear learning (Fullana et al., 2016) has indicated no involvement of the amygdala in this process. Crucially, only direct fear-conditioning studies were analyzed, and the reaction to the CS+ > CS- contrast was taken into account. Following LeDoux (2014), the authors have differentiated conscious fear from implicit defensive response to threat, and argued that their analysis captured the former rather than the latter. Cortical activations observed in place of the amygdala responses have been indicated as supporting evidence. Amygdala activations could thus be considered characteristic for the automatic process of fear contagion, which occurs in the early acquisition of fear (LaBar et al., 1998). Conversely, the prolonged exposure to the CS-US association, which is usually the case during the learning procedures, may be related to the habituation of the amygdala (Quirk et al., 1997), the effect that has been found in response to the emotional stimuli (Fischer et al., 2003; Phillips et al., 2001; Wright et al., 2001). Given that the fMRI experiment described here did not measure the participants' reactions to direct threat, and the measured responses were related to the relatively quick appearance of the social US (1.5 s), the observed amygdala activation was indicative of the automatic process of fear contagion, and not the classical fear conditioning.

In line, all of the fMRI human observational fear learning studies that have been conducted so far reported the amygdala involvement in this process (Haaker, Yi, et al., 2017; Kaźmierowska et al., 2022; Lindström et al., 2018; Olsson et al., 2007). The recent study involving the human participants with impaired basolateral amygdala has also demonstrated its crucial relevance for the social experiential learning (Rosenberger et al., 2019). The amygdala's reactivity has also been shown following the administration of oxytocin (Gamer et al., 2010; Lischke et al., 2012; Quintana et al., 2019; Wang et al., 2017), which is a neuropeptide involved in important psychosocial functions. Notably, oxytocin has been found to increase trust (Kosfeld et al., 2005), enhance fear recognition in dynamic displays (Fischer-Shofty et al., 2010), and improve inferring about emotional states from subtle facial expressions (Domes et al., 2007). These findings indicate the particular role of the amygdala in processing social emotional cues, and are further supported by the reports emphasizing the significance of the amygdala activation in response to emotional face expressions (Fried et al., 1997) and complex social scenes (Oya et al., 2002). While it remains unclear 'what psychological construct would best capture whatever it is that is engaging the amygdala' (Adolphs, 2010), it has consistently

been shown to activate in response to stimuli that are salient, relevant, and unpredictable (Anderson & Phelps, 2001; Bach et al., 2008; Ewbank et al., 2009; Herry et al., 2007), and these characteristics are usually associated with processing of the social cues.

Finally, the amygdala is known to be involved in processing various emotions, not only fear. It has consistently activated in response to the facial expressions of happiness, sadness, anger, and disgust (Diano et al., 2017; Tettamanti et al., 2012). It has also been found to process stimuli of different emotional valence and arousal (Ball et al., 2009; Hamann et al., 2002; Winston et al., 2005). The subset of neurons in the basolateral amygdala has also been shown to send projections to the nucleus accumbens, and enhance the reward-seeking behavior (Ambroggi et al., 2008). The question thus remains, how can one be sure that it was fear that was transmitted between the demonstrator and the observer in the described fMRI experiment. It might be argued that it is not clear whether the demonstrators felt fear when the shock was administered, and consequently, whether the observers felt fear due to the observation. Indeed, the transfer could have involved simply the emotional arousal or stress - not enough specific measures have been employed to clearly demonstrate that the fear contagion occurred. Using tools such as facial EMG, fear-potentiated startle or even a questionnaire asking about the emotions felt, would have strengthened the inferences. However, in the light of the gathered data, I argue that it is highly probable that the fear-conditioning procedure evoked fear in the demonstrators, who not only received very unpleasant electric shocks but also were told to react in a 'natural yet noticeable manner'. Thus, their fear reactions were likely to signal the threatening information to the observer. What is more, observational fear acquisition has previously been shown in studies employing skin conductance response as a standard index of conditioned response in humans, reflecting physiological arousal in response to the observed threat (Golkar et al., 2015; Golkar & Olsson, 2017; Szczepanik et al., 2020). In the human-human study, the observers confirmed that they perceived the demonstrators' discomfort as high, and they rated the perceived shock's intensity as very unpleasant. The observers' perception of the watched scene also suggested that they empathized with their friends. At the same time, prior to the task the observers were informed that the shocks administered to their friends were not painful, which suggests that the measured response did not involve empathy for pain. Rather, the lower-level empathy-related process - emotional contagion - was involved.

Rodents and humans process fear in a similar manner

Certain similarities between the humans' and rodents' neural processing of the aversive emotional content have previously been demonstrated on the molecular level. For example, the study by Soliman et al. (2010) has found that a single-nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) results in similar behavioral phenotype in humans and knock-in mice. BDNF has previously been shown to mediate synaptic plasticity associated with fear learning (Chhatwal et al., 2006; Rattiner et al., 2005). Both humans and mice with the allele coding for the BDNF variant involving methionine displayed impaired extinguishing of a fear-conditioned response. In mice, this was indexed by an increased percentage of time freezing, and in humans, as an elevated SCR to CS that was no longer paired with US. Additionally, these behavioral effects have been mapped onto the brain circuits known to be crucial for fear processing. Namely, an elevated recruitment of the amygdala and diminished activations in the ventromedial prefrontal cortex (vmPFC) have been identified during the extinction phase in Met allele carriers, indicating impaired learning of the safety cues. This linkage of molecular and neuroimaging evidence has thus provided strong evidence for a cross-species translation from the mouse to the human brain with regard to fear processing.

Parallel human and mice studies on the fear acquisition and extinction during adolescence period have also revealed similar fear-extinction behavioral patterns in both species (Pattwell et al., 2012). Again, impaired extinction learning was indexed by means of percentage of time freezing in mice and SCR in humans. Based on the behavioral similarities between humans and mice, the authors investigated c-Fos activity in the vmPFC, a structure crucial for fear extinction, and found diminished activation of the infralimbic cortex (a ventral portion of vmPFC) of the adolescent mice during the extinction phase. Moreover, electrophysiological recordings in the vmPFC area revealed a mechanism of synaptic plasticity underlying fear regulation, whose impairment may explain decreased fear extinction in adolescent mice. Similarly, human research has indicated that the vmPFC controls fear expression during fear extinction (Fullana et al., 2018; Motzkin et al., 2015). Other studies also indicated parallels between the brain mechanisms in rodents and humans, e.g., a common gene regulating fear processing in the amygdala in mice and humans with posttraumatic stress disorder (Andero et al., 2013), and the importance of the fatty acid amide hydrolase inhibition for the enhanced fear extinction in both mice and humans (Mayo et al., 2020). Together, these findings suggest that the neural mechanisms of fear are similar in rodents and humans. Moreover, they suggest the translational potential and possibility of developing new treatment

strategies in rodents. The rodent studies might guide neuroimaging investigations, and human results might be thoroughly interrogated in rats in order to study the details of molecular and neuronal mechanisms (Milad et al., 2006).

The results showing that the basolateral and centromedial amygdala activate during the rat-rat (Knapska et al., 2006), human-human, and human-rat fear contagion indicate a potentially common brain circuit involved in the within-species fear transfer in both humans and rats, as well as in the inter-species fear contagion. This hypothesis has previously been based on direct evidence coming from the rodents' brain (increased c-Fos expression in the amygdala), as well as converging behavioral observations from rats (increased freezing or risk assessment) and humans (elevated SCR and FPS) undergoing the fear contagion paradigm. The experiments described in this thesis provide additional evidence supporting this hypothesis.

First, the basolateral and centromedial amygdala have been identified as the neural correlates of fear contagion in humans. In human research, the functional relevance of different amygdala nuclei has previously been shown in several contexts. For example, their differential activation has been reported following the administration of oxytocin under different emotional conditions (Gamer et al., 2010). It has also been shown that the central and basolateral amygdala orchestrate the process of forming beliefs about others' trustworthiness (Sladky et al., 2021), and that damage to the basolateral nucleus results in an impaired learning from social experience (Rosenberger et al., 2019). Furthermore, different patterns of the functional connectivity have been found for the basolateral and centromedial nuclei of the human amygdala (Bielski et al., 2021; Rausch et al., 2016; Roy et al., 2009). Still, there have not been many human studies investigating the functional relevance of the amygdala subparts, and the described study is the first to show their involvement in the context of the observational fear acquisition and fear contagion in humans. The presented results also concur with the amygdala activations reported by the rodent studies.

Second, the interspecies study investigating a human-rat interaction has been conducted for the first time. It enabled examining the involvement of different amygdala nuclei in the process of the rats' tuning into the emotional state of the caregivers. The direct manipulation of the rat's emotional state by means of the interaction with an emotionally aroused human resulted in the pattern of the amygdala activations, which strongly resembles the one that rats employ when communicating threat to each other, supporting the hypothesis about a common brain circuit processing socially acquired fear.

According to the view proposed by Keysers et al. (2022), emotional contagion is an evolutionary adaptation, which prepares animals for danger by using others as sentinels. In

relation to the cross-species interactions, this theory could be extended and explain the common neural mechanisms enabling the interspecies communication of threat in terms of the importance of sharing the emotional states of other species for one's own benefit. This would imply that the evolution of a common brain system underlying the communication of threat between species might have been determined by the need of receiving information important for survival without experiencing threat directly. The Keyser et al.'s view emphasizes the straightforward motive underlying development of the empathy-related behaviors in rodents: sharing the distress of others simply enables saving one's own skin. Such an explanation differs from the romantic view on human empathy, often identified with selfless helping. While the higher-order forms of empathy, e.g., prosocial behavior, may in fact reflect such logic (but this has not been determined), the basic process of fear contagion seems to involve a neural circuit that is conserved across rats and humans, and possibly other mammals. Thus, the described results favor the Keyser et al.'s theory and open the discussion on the universality of the neural system enabling the cross-species communication of threat.

The reported findings are of basic nature, but their potential applications should also be considered. Fear acquisition constitutes a central point of anxiety disorders, and learning of fear through social means has been shown to be as effective as direct fear learning (Lindström et al., 2018; Olsson et al., 2007). The human and rodent vmPFC studies reviewed above indicate that rodents can be used as model animals to test new therapeutic solutions. Given that fear contagion is a basic process involved in social learning of fear, one may expect that its thorough understanding could help develop better treatment strategies for patients with anxiety disorders. It has been known that the CS-US association is formed in the amygdala (Kim & Jung, 2006; LeDoux, 2000; Maren, 1999), and this area has been indicated as one of the core regions that pharmacotherapy should target (Faria et al., 2012; Izumi et al., 2018). The presented results expand the knowledge on the amygdala nuclei involved in the social transmission of threat in humans. Moreover, they provide further evidence for the similarity of the human's and rat's brain. Learning about the mechanisms underlying fear acquisition in rats may thus have important implications for understanding how the pathological fear is acquired in humans, and how it might be cured.

Similarities and differences between the human-rat and human-human paradigms

Both experiments described in this thesis employed paradigms for studying the social transfer of fear. Both relied on naturalistic, ecologically valid procedures, mimicking real-life

situations. Only male individuals participated in both experiments, and the demonstrators were well-known to the observers. Regarding familiarity, in the human-rat study, rats were habituated to their dedicated caregivers during five consecutive days preceding the experimental and control interactions, and thus the caregivers could be considered familiar to them. In the case of the human-human study, a subgroup of the sample studied in a previous experiment (Kaźmierowska et al., 2022) was selected, so that only pairs of longtime friends were investigated. In the case of rodent studies, it is a common practice to house pairs of rats in the home cages - they are social species and such a setting positively influences their well-being. Prior to the experiment's beginning, rats usually undergo a habituation to the cage and the experimenters' hands. During this period, rats become familiar with each other, so that upon the experiment's start, they are not considered strangers any more. This suggests that also previous rat-rat studies involved a similar level of familiarity between the participants, and thus my results may plausibly be compared to those reports.

However, it is worth noticing that the human-rat and human-human paradigms differed in several ways. While rats were involved in a physical interaction with caregivers, humans in the fMRI study were sitting in separate rooms. Such paradigms seemed most ecological, as observation is the most common way of social learning in humans, while interactions are most frequently studied in rat-rat paradigms. For the human-rat study, the physical interaction seemed most appropriate. The physical contact between rats and caregivers was provided, so that the relevant information could be transmitted with the highest possible probability. Resulting from the differences in paradigms, the olfactory channel was most probably involved in the human-rat fear contagion (which is usually the case in rodent research (Arakawa et al., 2011; Ferretti et al., 2019; Scheggia et al., 2020; Sterley & Bains, 2021), and the visual channel was crucial for the human-human fear transmission. Designs involving placing both humans in one room (to enable both visual and olfactory communication) or humans talking about the aversive task that one of them just did (enabling both channels and an interaction), could be better comparable to the one used in the human-rat experiment. However, they would also introduce additional sources of variance. Thus, given the complexity and novelty of the real-time observational fear learning procedure, I argue that the designs that were employed were the most ecological ones. Usage of the described fMRI design also had an important advantage: it allowed for an observation that smell is not necessary for the fear contagion to occur between humans.

An important difference between the experiments involves the level of inferences that can be drawn. While the results of the fMRI study have shown what the fear contagion looks

like between humans, it is worth noting that the results presented here show the human-rat but not the rat-human transfer. Obtaining analogous results in the rat-human study would provide additional evidence for a shared mechanism of fear contagion between humans and rats. Finally, there is a difference in the nature of measures used by the experiments. The c-Fos expression provides a single-cell resolution informing about the number of neurons activated in response to the certain manipulation. The fMRI method offers an indirect investigation of the neuronal activations, and as such is much less precise compared to the immunohistochemistry.

Limitations and future directions

Besides the differences between the human-human and human-rat paradigms, and the already mentioned constraints resulting from them, several important limitations of the described work should additionally be addressed. First, it might be argued that not sufficient measures of the fear contagion were employed in the fMRI study. In particular, lack of the EMG recordings enabling inferring about facial mimicry is an important caveat. What is more, the GSR or FPS measurements could have been provided to characterize the psychophysiological responses of the observers and complete the fMRI results. Moreover, self-descriptive measures of experienced emotions could clarify whether the participants actually felt fear. However, the additional analysis showing the involvement of brain areas related to both observation and imitation of actions constitutes important evidence for the fear contagion. Similar findings have previously been shown by de Gelder et al. (2004), who have argued that such activations, together with the amygdala response, may be indicative of fear contagion. Second, both experiments would benefit from a wider range of brain areas investigated. The amygdala was selected as a major region of interest, but both human and rodent studies have indicated other structures, primarily the ACC, as activating during fear contagion, observational fear acquisition, and empathy for pain. It thus seems an important candidate for further studies of the brain circuits involved in fear contagion between humans and rats. Further, the obtained USV results should be treated with caution due to the loss of data. Replicating the human-rat experiment while enlarging the sample size would be valuable. Other important directions for the future studies include controlling the channel of the human-rat transmission of fear, investigating the transfer involving the female rat population, and testing the impact of the caregiver's sex on the fear contagion effectiveness. The experimenter's sex has been indicated as an important factor influencing the study results (Chapman et al., 2018), and based on the

previous reports (Faraji et al., 2021; Sorge et al., 2014) it might be expected that the baseline level of rats' fear response would be decreased if the human caregivers were females.

Speaking of the experimenter's impact on the results, the human-rat study's findings have important implications for rodent research in general. If rats are sensitive to the human's fear, it is possible that they could also share other emotions. Even if these emotions are not induced for the experimental purposes (as was done in the human-rat study), a simple interaction that usually occurs between the experimenter and animals at different stages of the experiment, might result in an unintentional emotional transfer, which might impact the results. While one might argue that providing a control condition could help overcome this limitation, this is true, but only as long as both the conditions are performed close in time (so that the experimenter's emotional state is similar across both). Studying the experimental and control groups on different days could be problematic in that sense. Alternatively, the experimenter's emotional state should either be assessed prior to each interaction with a studied animal, to control for potential confounds, or the fully-automatized experimental procedures that do not require contact with an experimenter should be employed.

In the future studies, it would be valuable to test whether the transfer of other emotions would also be possible between humans and rats. Social signals of fear seem to be most important from the evolutionary perspective, but other emotions might also carry meaningful messages. Thus, a human-rat interaction involving a transfer of e.g., happiness could be performed. In the light of the Keysers et al.'s (2022) theory explaining the origins of the emotional contagion, receiving information about the other's happiness could be interpreted as a safety signal. Similarly, the transfer of sadness, disgust, anger, pain and surprise could be considered informative. However, conducting such studies would require defining the neural and behavioral indices specific for certain emotions.

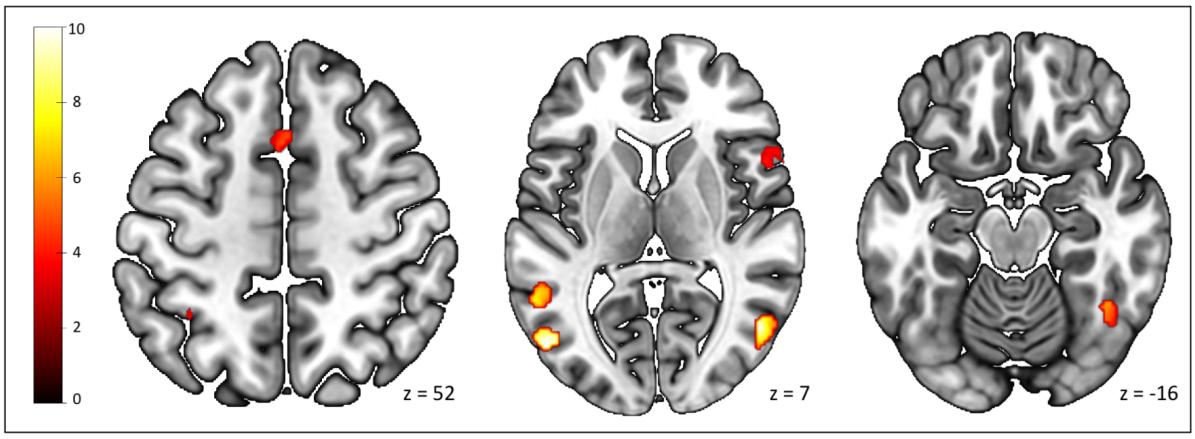
Having obtained the first cross-species neural evidence indicating the successful fear contagion, it would also be interesting to learn whether it is possible during the cross-species interactions between other animals. Interactions between humans and other mammals could thus be investigated. Dogs seem to be a good point to start with, taking into account a large number of behavioral studies showing emotional contagion between humans and dogs. What is more, a non-invasive imaging of the awake dog's brain is possible using fMRI (Berns, 2022; Karl et al., 2020; Thompkins et al., 2018). The finding that is particularly interesting in this context is the recent report showing that dogs watching a positive social interaction of their caregiver and another conspecific react with increased amygdala activation compared to watching their non-social, neutral interaction (Karl et al., 2021). Due to ethical reasons, the

results of the dog studies do not provide as direct neural evidence as rodent studies do. However, observing the amygdala activation following fear transfer from humans to dogs, and possibly other mammals, could suggest the existence of a brain circuit underlying fear contagion that is shared across mammals.

Concluding remarks

The experiments described in this thesis have shown that: 1) rats are sensitive to the human's fear, 2) during interaction with a fear-conditioned human, basal and central amygdala of rats become activated, 3) observational acquisition of fear in humans involves basolateral and centromedial amygdala. These results suggest that humans and rats might share a common brain mechanism allowing for emotional communication within and between species. I interpret these findings using the theory proposed by Keysers et al. (2022), and argue that a common brain circuit underlying fear contagion could have evolved to enable interspecies communication of the emotional signals that are crucial for survival.

Appendix



Supplementary Figure 1. Activations within the observation-imitation mask derived from the meta-analysis of regions involved in the observation and imitation of another person's action (Caspers et al., 2010). US > no US contrast, small volume corrected within the mask representing conjunction of the observation and imitation conditions. The activated areas involved in both observation and imitation of actions include the lateral occipital cortex, the temporal occipital fusiform cortex, the inferior and superior frontal gyri, and the superior parietal lobule.

Supplementary Table 1. Activation peaks during observation of a friend in the fMRI experiment, US > no US contrast, small volume corrected within the mask of regions that were previously reported to activate both during observation and imitation of another person's action. Table shows local maxima more than 4 mm apart. Last column lists labels from the Harvard - Oxford atlas. x, y, z - MNI space peak coordinates in MNI space

cluster	x	y	z	t	voxel	label
1	50	-64	6	10.61	174	Lateral Occipital Cortex, inferior division
2	-50	-72	10	10.47	130	Lateral Occipital Cortex, inferior division
	-46	-74	4	9.30		Lateral Occipital Cortex, inferior division
	-44	-76	0	8.82		Lateral Occipital Cortex, inferior division
3	-54	-46	12	8.29	91	Supramarginal Gyrus, posterior division
	-58	-50	10	8.21		Supramarginal Gyrus, posterior division
4	46	-68	-8	7.56	98	Lateral Occipital Cortex, inferior division
	42	-54	-14	6.19		Temporal Occipital Fusiform Cortex
5	54	18	16	7.11	146	Inferior Frontal Gyrus, pars opercularis
	54	16	20	6.74		Inferior Frontal Gyrus, pars opercularis
	56	22	12	5.83		Inferior Frontal Gyrus, pars opercularis
	52	14	24	5.69		Inferior Frontal Gyrus, pars opercularis
	60	16	6	4.00		Inferior Frontal Gyrus, pars opercularis
6	2	12	56	5.89	36	Superior Frontal Gyrus
	8	12	58	5.44		Superior Frontal Gyrus
7	-34	-50	52	3.72	5	Superior Parietal Lobule

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Own publications

Authors who equally contributed to a publication are marked with *

1. **Kaźmierowska, A. M.**, Kostecki, M., Szczepanik, M., Nikolaev, T., Hamed, A., Wypych, M., Marchewka, A., Knapska, E. (under review). Human-rat and human-human fear contagion involves the same subnuclei of the amygdala.
2. **Kaźmierowska, A. M.***, Szczepanik, M.*, Wypych, M., Droździel, D., Marchewka, A., Michałowski, J. M., Olsson, A., Knapska, E. (2022). Learning about threat from friends and strangers is equally effective: an fMRI study on observational fear conditioning. *NeuroImage, 263*, 119648.
3. Szczepanik, M.*, **Kaźmierowska, A. M.***, Michałowski, J. M., Wypych, M., Olsson, A., Knapska, E. (2020). Observational learning of fear in real time procedure. *Scientific reports, 10*(1), 1-10.
4. **Antosz, A. M.**, Imbir, K. (2017). Effects of the emotional properties of words and a manipulation of mindset on performance of an ambiguous task. *Journal of Cognitive Psychology, 29*(2), 151-168.