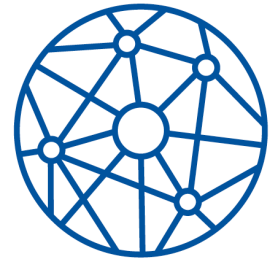


Kraków, 04/17/2023



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FACULTY OF PHILOSOPHY  
INSTITUTE OF PSYCHOLOGY

REVIEW OF ANNA MARIA KAŻMIEROWSKA'S DOCTORAL THESIS  
"THE SAME SUBNUCLEI OF THE AMYGDALA ARE ACTIVATED WHEN  
FEAR CONTAGION OCCURS BETWEEN HUMANS, AND BETWEEN  
HUMANS AND RATS"

SUPERVISED BY

PROF. EWELINA KNAPSKA, PH.D., D.SC.

AND

PROF. JAROSŁAW M. MICHAŁOWSKI, PH.D., D.SC.

**Przemysław Babel, PhD  
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Anna Maria Kaźmierowska's doctoral thesis, "The same subnuclei of the amygdala are activated when fear contagion occurs between humans, and between humans and rats," aimed to test 1) whether cross-species (human-rat) fear transfer occurs, 2) which amygdalar nuclei are activated in rats during human-rat fear contagion, and 3) whether the same parts of the amygdala are activated during human-human fear contagion. These are very innovative aims. So far, the problem of fear transfer from humans to rats has not been investigated on the behavioral or brain level. Also, the brain mechanisms of fear contagion between humans and rats and between humans have not been compared. The thesis's aims are also very relevant as fear is involved in many mental health problems; thus, a better understanding of its acquisition mechanisms may significantly contribute to

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the development of effective strategies for preventing and managing fear-related problems.

The thesis reports the results of an original, unpublished experimental study and the results of an analysis of a subgroup of participants from a previously published experimental study for which this PhD candidate served as the first author. In the first study, behavior and amygdala activation in two groups of rats were compared: one group was handled by non-feared humans; the other group was handled by feared humans. This study showed that, through handling, fear was successfully transferred from humans to rats, which was confirmed on behavioral and brain levels. Importantly, this study also showed that both basolateral and centromedial divisions of the amygdala were activated in rats which were handled by feared humans. The brain responses of persons observing their friends undergoing a fear conditioning task were analyzed in the second study. It was found that in humans, similar to the rats from the first study, both the basolateral and centromedial divisions of the amygdala were activated when these persons were observing fear being induced in their friends. The author concludes that the results suggest a common brain circuit involved in fear contagion.

The introduction section of the thesis not only justifies the aims of the thesis and the hypotheses to be tested but also provides an overview of the



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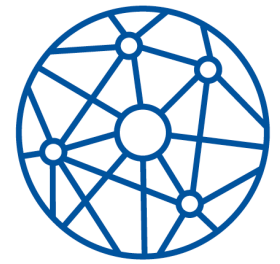
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methods applied in the studies conducted by the author. Moreover, the introduction discusses previous research results and theories of emotional contagion. However, the introduction does not clearly differentiate between emotional contagion and observational learning of emotions, especially between fear contagion and observational fear learning. This is a crucial issue as the two studies reported in the thesis differ substantially in their methodology. Although fear conditioning was applied in both studies, the rats in the first study did not observe fear conditioning in humans; in the second study, however, humans did observe fear conditioning in other humans. The question then arises whether fear contagion was actually induced in both studies, but the introduction does not shed any light on this question.

The second issue that is lacking in the introduction is a discussion of the differences between fear and anxiety. This is another crucial issue as it is generally difficult to differentiate between fear and anxiety, and both concepts seem to overlap. However, on both the psychological and neurobiological levels, these are two different concepts, and one of the main criteria that is used to differentiate between them is threat certainty vs. uncertainty. In both studies reported in the thesis, not all conditioned stimuli were paired with an unconditioned stimulus, thus it is not clear whether fear or anxiety was actually induced. The importance of this issue is also highlighted by the fact that the State Anxiety Inventory was used to



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measure anxiety in the second study, whereas the intention was to induce fear. Unfortunately, the fact that neither the introduction nor the discussion deals with the differences between fear and anxiety does not help to dispel my doubts.

The methods section is well-written, and the methodology of the first experiment is perfect. I especially like the idea of pairing the color with mild vibrations in the control condition in contrast to pairing the other color with uncomfortable stimulation in the experimental condition. Also, I fully appreciate the fact that psychology or cognitive science students or graduates were excluded from the second experiment and that the manipulation check (evaluation of the demonstrator's expression) was conducted. It should also be highlighted that including only males in the second study is well justified.

However, there are also significant limitations of the methods applied. First, no sample size calculation was provided for the first experiment. The sample size of the second experiment is reported to be based on a previous study, but no actual sample size calculations are provided. Second, as mentioned above, it is not clear whether fear was actually induced in both studies because threat uncertainty rather than certainty was present due to the fact that not all conditioned stimuli were followed by unconditioned stimuli. Third and most importantly, the methods of both studies differ in



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so many aspects that it makes it very difficult or even impossible to compare their results. The author has discussed most of these differences in the methods and discussion sections, but one issue that is not discussed seems crucial: as I have already mentioned above, the rats in the first study did not observe fear conditioning in humans, whereas the humans in the second study did observe fear conditioning in other humans. Although it seems that pure fear contagion may have been induced in the first experiment, observational fear learning may have been applied in the second study. Although, as stated in the introduction, emotional contagion is a basis for observational learning of emotions, they are not exactly the same phenomena.

The studies' results are appropriately analyzed. The discussion is in-depth even though it shares some limitations with the introduction, i.e., it does not refer to the difference between emotional contagion and observational learning of emotions, or to the difference between fear and anxiety. Anyway, I like the discussion very much as it goes far beyond the description of the results found and relates them not only to previous studies' findings but – more importantly – to the theoretical approaches.

The thesis is very concise but includes all the required information. It has a standard and proper layout, including the introduction, the methods, the results, the discussion, the appendix, and the bibliography. The references



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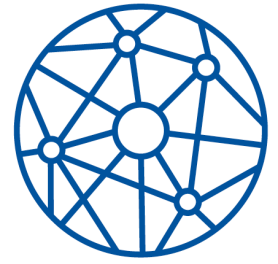
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are relevant to the thesis topic and include most of the essential publications in the field. The thesis has been carefully and nicely designed and edited. I have not noticed any language or editorial problems, which is quite rare in the case of doctoral theses prepared as manuscripts.

To conclude, despite some critical issues I have raised above, the thesis under review is very strong. It provides an original solution to a scientific problem and demonstrates the author's general theoretical knowledge in neuroscience and her ability to conduct research work independently. Thus, I have no hesitation in concluding that Anna Maria Kaźmierowska's doctoral thesis, "The same subnuclei of the amygdala are activated when fear contagion occurs between humans, and between humans and rats," meets the criteria for doctoral theses specified in article 187 of the Act of 20 July 2018: The Law on Higher Education and Science and the Appendix 1 to the Regulations of the Scientific Council of the Nencki Institute of Experimental Biology of the Polish Academy of Sciences.



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Hamburg, 25.04.2023

**Evaluation of the PhD thesis "The same subnuclei of the amygdala are activated when fear contagion occurs between humans, and between humans and rats " submitted by Anna Maria Kaźmierowska.**

The work of the thesis has been completed in the Laboratory of Brain Imaging and Laboratory of Emotions Neurobiology of the Nencki Institute of Experimental Biology Polish Academy of Sciences and was supervised by Dr Ewelina Knapska Ph.D., D.Sc. and Dr Jarosław Michałowski, Ph.D., D.Sc.

Social groups of humans, as other social animals, enable individuals to learn about challenges and opportunities in their environment. Such social learning is based on the integration of others' responses and behaviour to thrive as an individual and as a group. In particular, the sharing of emotional responses, emotional contagion, provides the basic function that allows to make sense of socially observed responses, adapt our own responses and to engage in empathic and pro-social behaviours.

In her Ph.D. thesis, Anna Maria Kaźmierowska, aims to investigate the brain mechanism underlying the interspecies fear contagion between humans and rats. Specifically, the Ph.D. project first focuses on the behavioural (goal 1) and then on the neural correlates (goal 2) of human-rat fear contagion that is followed by a cross-species comparison between rat and human neural activation during fear contagion in observational threat learning (goal 3). These innovative and ambitious research goals reflect the excellent quality of this Ph.D. project.

The thesis is organized in a clear and for the reader transparent way. The thesis starts with a definition of emotional contagion and clear distinction of emotional contagion from other social processes (like imitation). The description of the state of research is used to introduce

theoretical models that link emotional contagion with empathic responses (“Russian doll model” and “combination model”) and carves out the prerequisites for emotional contagion taking place. The thesis further lays out the connection between emotional contagion and observational threat learning and highlights the distinction that is used in the thesis between subjective emotional states (such as fear) and defensive responses.

In this introduction, Anna Maria Kaźmierowska, is presenting the state of research on emotional contagion in rodents and humans in a comprehensive way. The linkage of the individual results towards a coherent picture enables the reader to further follow the interspecies emotional contagion that is described for dogs, horses, goats, mice and rats.

This description of the current state of research is further focused on the underlying neural processes that involve the amygdala, and highlights an excellent and differentiated picture of the functions that are mediated by the amygdala (and which are not). The introduction is than finalizing by describing the connection between emotional contagion, empathic processes and observational learning of fear, before the research methods are introduced.

The introduction is excellent to make the point that previous research could not provide direct evidence for rats being responsive to induced states of fear in humans and if the neural substrates underlying emotional contagion in the amygdala are comparable between rats and humans.

This thesis aimed to coherently and innovatively test how emotional contagion of fear is transmitted from humans to rats and if amygdala subnuclei are comparable between both species during emotional contagion of fear.

The research methodology is well suited to the aims of the thesis and provides the opportunity for innovative advances by combination of single cell c-fos staining in rats and neuroimaging of brain responses in humans. Furthermore, the employment of ecological valid learning situations in both the human to rat and the human to human transfer goes well beyond the current literature.

The first study of the thesis employed a design that allows to examine behavioural responses in rats to physical contact with caretakers that either underwent a fear conditioning procedure, as compared to a control task. The results are presented in a clear fashion and provide a rich and comprehensive picture of the rats’ changes in risk assessment and vocalization, based on the preceding experience of the caretakers. The caretakers that underwent fear-conditioning were explored less (instead the cage was explored) and vocalizations decreased. This change in behavioural responses was paralleled by an increase in c-fos in the basal and central nuclei of the amygdala.



Hence, this first study could reveal a specific influence of the induced emotional state in the human that is changing behaviour in the rat, mediated by activation of amygdala subnuclei.

The second study within this thesis extended the focus towards human to human emotional contagion during observational threat learning within pairs of friends. This study revealed in a transparent manner that amygdala responses, specifically in the basolateral and centromedial division, were activated when observing the friend being exposed to unpleasant electrical stimulation (via a live-video feed). These findings partly confirm the results of the first study, but also extend their insights.

Importantly, Anna Maria Kaźmierowska, combined the results across species and provided a shared perspective for the activation of amygdala subnuclei. This innovative translation of results revealed that homologous part of the amygdala, the centromedial and basolateral parts, are active in both, humans and rats during emotional contagion.

The thesis provides clear and adequate conclusions drawn from these results, by advancing the current state of research with evidence of cross-species emotional contagion that underlies similar activation of subnuclei of the amygdala in rats and humans. One highlight of these conclusions is that these results provide a link between prior studies of emotional contagions from rat to rat and from human to human.

These findings are discussed within the thesis in the context of previous findings and how they extend the current state of the research. The discussion further provides excellent and detailed linkage between the results obtained in the studies and previous work. The discussion is very well balanced in stating the evidence that can be drawn from the results, but carefully assessing the limitations (e.g., assessing affective ratings of the demonstrator or physiological responses of the pairs) and the differences between results that can be obtained in humans and rodents.

The discussion compiles the evidence in an excellent manner to sketch future research and this thesis thereby lays a cornerstone for revealing the mechanisms that underlie interspecies communication. It further highlights the point that this thesis reveals practical implication for handling of laboratory animals, which reflects the all-encompassing and integrative perspective that this thesis takes.

This thesis provides an original solution to the scientific problem to understand the emotional contagion between species and about the similarity between neural processes across species, which opens several opportunities for future research. It further underlines shortcomings and limitation that are important to follow-up.

The doctoral dissertation demonstrates Anna Maria Kaźmierowska overall theoretical knowledge of the field and ability to conduct independent scientific work.

**I recognise this thesis as outstanding**, based on the innovative and stringed experimental set-up that employs ecological valid situations in rats and human. The complementing methodological techniques across species demand a broad and versatile understanding and are mastered exceptionally well in these studies. The logic interpretation of the results and the fine balance between evidence and limitation is a true advancement of field by this outstanding doctoral thesis.

In sum, I recommend graduating Anna Maria Kaźmierowska and recognise the thesis as outstanding.



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Vienna, April 27, 2023

**Evaluation of the thesis by Anna Maria Kaźmierowska**

I read the thesis by Anna Kaźmierowska with great interest. Overall, this is work performed at high scholarly standards that makes an important contribution to the literature on the neural basis of fear processing and interspecies fear transmission. The thesis also shows a great deal of commitment to the work and the research by the candidate, who as alluded to in the introduction seemed to have to overcome several significant hurdles to successfully complete the research and the thesis. Thus, congratulations to what I overall would regard as a great achievement!

The thesis consists of an introductory chapter, two empirical chapters, and an overall discussion. In the introductory chapter, the candidate outlines some of the conceptual background and the corresponding research that motivated the empirical work performed and described in the two following empirical chapters. The intro chapter generally attests to the extensive knowledge the candidate acquired throughout the thesis, both in terms of the research topics and the methodologies used. The literature review covers both non-human animal and human research and appears as both extensive and relevant. If I wanted to be critical, I would suggest that some more attention could have been given to how specifically the various topics and phenomena are related to each other (and how this may inform or be relevant to the ensuing empirical work). For instance, how exactly do vicarious fear learning, emotional contagion and empathy for pain relate? While the first taps into learning processes, the second is part of the response during such learning processes, but then the third is generally regarded as an other-oriented emotional response. How precisely could such an other-oriented response inform the learning process and by means of which neural computations? Is it “problematic” in this context that the majority of empathy for pain studies (in humans) does not show involvement of the amygdala, but of other structures such as the MCC/ACC and the anterior insula? How could the neural responses in the insula inform the fear learning processes and result in fear transmission, even outside a learning process, more generally? What could have been helpful here, for instance, is a process- or conceptual model that outlines more explicitly how the phenomena are connected.

The empirical work is exciting and provides novel and compelling first neural evidence on inter-species (rat-human) fear responses. The work has been meticulously performed and designed and fulfills high scholarly standards. I have a few comments, though, geared towards a general reflection - none of them really touch upon the “technical” aspects of the work, but rather upon the “big picture” implications of the overall approach, and what we can learn from this study.

First, I am a big advocate of comparative work and especially of direct within-study comparisons between species. The question (to me, at least) often is, though: what is the theoretical rationale of using the specific comparative approach? Do we mainly want to gain insights into evolutionary mechanisms? Or is the focus instead on interspecies signal/information transmission? What are the main hypotheses we want to test? And how has the work been planned to connect to such an overarching framework and the specific hypotheses? Playing devil's advocate, in the present context, one could ask oneself why rats should not respond to fear expressed by their human handlers? After all, they spend considerable time together (I assume), and thus will learn from and about each other. So what specifically do we learn, beyond assessing and demonstrating this for the first time (which in itself of course is a great achievement that I do not want to downplay). Would one e.g. predict that lab rats differ from their wild counterparts, who develop and live with minimal human interaction? After all, joint rearing, but not genetic/subspecies relatedness have been shown to be key for promoting prosocial behavior (e.g., work by Ben-Ami Bartal & colleagues). So, to be even more provocative, maybe the findings are not so much about interspecies interaction, but rather about animals having had joint experiences and interindividual "learning histories", or not?

Second, but certainly connected to the first comment, I was left wondering about the rationale of some of the experimental design choices, and how they connect to the overall approach and main aims of the work. If the main aim was to better understand interspecies interaction/fear transmission and its neural underpinnings, wouldn't it have been better to use a full-factorial design where rats interact also with other rats, and humans also perceive rats in fear? Such a design would undoubtedly increase the specificity of the findings regarding the question of how two species interact and pick up fear signals compared to their own species - but of course it may be far beyond the scope of a dissertation (still, comparisons to existing data from the dissertation lab or other labs/the literature would have been worthwhile to compare the rat-human data to rat-rat data). A related question would be how specific the findings are for social fear transmission. The current design does not tell us much about whether the responses in the amygdala are specific to fear transmitted by another animal or whether they domain general responses to fear-inducing stimuli.

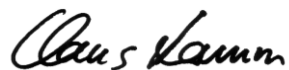
Third, focusing only on the amygdala and ignoring the many other areas involved in fear responses and their transmission seems a missed opportunity. Both in terms of a more holistic picture of how "similar" the responses of rats and humans really are, but also in terms of control analyses with which one could show if the amygdalar responses are causal/essential for the fear response, or what other brain areas may drive them; for instance, looking at areas such as the ACC or the insular cortex, and how they are connected to the amygdalar responses, would seem key to gain a more exhaustive picture of what it is exactly that the rat picks up from the human, and how that affects the rats' behaviors. However, I frankly lack the expertise to evaluate whether such "whole-brain analyses" are possible with the c-fos technique used in rats. Incorporating a network-oriented approach would also allow to corroborate claims on "sameness" of the amygdalar nuclei across rats and humans; alternatively, comparative-anatomical information approaches could have been used to establish homology.

Finally, an appealing element of the work is that the rat and human designs are closely matched (as the same conditioning procedure is used in both rat-human and human-human interactions); however, upon closer inspection and reflection they are really somewhat different. For instance, the rat has no specific information on what specific stimulus triggered the fear response in the human, and the rat design is not embedded in a vicarious fear learning setting where the rat could even find out about what was the trigger and how it could be relevant for itself; in addition, the rat and the human do not interact while the humans get the painful shocks, but afterward, so most likely any fear transmission is related to other mechanisms (such as persisting heightened arousal, olfactory cues etc.) as in the human design, where the focus is on immediate neural responses to pain being

induced in their friends. Of course, this is a high-level comment, and I am fully aware of how challenging it is to develop and design experimental settings that allow direct comparison across species, especially in two species that differ so widely in terms of their perception and behaviors.

Of note, some of these issues are to a certain extent addressed as limitations in the concluding discussion, so I acknowledge the candidate's awareness of these limitations and their capacity to discuss and consider them in the context of her empirical work. As a minor concluding comment on the discussion, which I overall found well-balanced and transparent in discussing the limitations, but also the strengths of the work, I suggest being careful with statements such as on p. 54 "rats' tuning into the emotional state of the caregivers". This sounds like some anthropomorphism slipped through, and I am pretty sure this was not the intention of the candidate. But we simply do not (and maybe even cannot ever) know whether the animals "tuned into" the emotion state, or simply showed a behavioral response to it, which would seem the more parsimonious explanation.

In summary, and despite my extensive comments, this is great and highly relevant work, and the first study, at least to my knowledge, that looks at neural correlates of interspecies fear transmission. I look forward to discussing some of the issues raised with the candidate during their defense.

A handwritten signature in black ink that reads "Claus Hamm". The signature is written in a cursive, flowing style.

Professor of Biological Psychology  
Member of the Austrian Academy of Sciences