The impact of workplace bullying and repeated social defeat on health and behavioral outcomes: A biopsychosocial perspective

Dhaksshaginy Rajalingam

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2020

UNIVERSITY OF BERGEN

The impact of workplace bullying and repeated social defeat on health and behavioral outcomes: A biopsychosocial perspective

Dhaksshaginy Rajalingam

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 09.12.2020

Year: 2020

Title: The impact of workplace bullying and repeated social defeat on health and behavioral outcomes: A biopsychosocial perspective

Name: Dhaksshaginy Rajalingam

Print: Skipnes Kommunikasjon / University of Bergen

Table of contents

Scientific environment

The present PhD thesis is a part of the overarching research program and Toppforsk project called "Workplace bullying – from mechanisms and moderators to problem treatment" led by professor Ståle Valvatne Einarsen at the Department of Psychosocial Science, University of Bergen. The project is jointly financed by the Norwegian Research Council and the University of Bergen, with the National Institute of Occupational Health (STAMI) and Diakonhjemmet Hospital in Oslo, as co-partners. The work presented in this thesis was completed under the supervision of my main supervisor Professor Johannes Gjerstad (STAMI/ISP), and my co-supervisors Professor Ståle Valvatne Einarsen (ISP, head of FALK), and Professor Morten Birkeland Nielsen (STAMI/ISP). All data analyses and laboratory work presented in this thesis was conducted at the laboratory facilities at STAMI, Department of Work Psychology and Physiology in Oslo, from 2017 to 2020. During these three years, I have been employed at the Department of Psychosocial Science (ISP), yet having my daily work at STAMI. In addition, I have been a member of the Bergen Bullying Research Group also known as Forskningsgruppe for Arbeidsmiljø, Ledelse og Konflikt (FALK) and the Graduate School of Human Interaction and Growth (GHIG) both at the Faculty of Psychology, University of Bergen.

Acknowledgments

First of all, I would like to express my gratitude to my supervisors, Professor Johannes Gjerstad, Professor Ståle Valvatne Einarsen, and Professor Morten Birkeland Nielsen for giving me the opportunity to work on this interdisciplinary project. I feel privileged to have been guided by you in this process! Thank you for all the time and resources you have devoted to my PhD project. I am grateful for all that you have done! It has been three incredible years with experiences I would never have been devoid of.

I want to thank Johannes for your consistent guidance and support. I appreciate the opportunity you gave me and for letting me be a part of the inspiring environment at STAMI. Thank you for taking the time to discuss and for the critical reading of my thesis. Your dedication has been a great motivation for me.

Thank you, Ståle, for introducing me to the field of workplace bullying. Thank you for including me in your Toppforsk/FALK group at the Faculty of Psychology at UiB. Thank you for your guidance, support and I am grateful to you for sharing your knowledge. Thank you for the critical reading of my thesis and for your excellent ability to keep having an eye for the details, while still retaining the big picture! Your insight and dedication have been a great inspiration for me.

Morten, thank you for all that you have taught me about methodology and for sharing your knowledge about the bullying research field. Also, thank you for your creative ideas and for always being supportive and positive. You have been inspiring!

Thank you to Ingeborg Nymoen, and Henriette Nyberg for great discussions and all the time we have spent together at the animal facility and in the lab. I would not have managed without you!

Thank you to my colleagues at STAMI; Daniel Pitz Jacobsen, Anne-Mari Gjestvang Moe, Tiril Schjølberg, Mina Baarnes Eriksen, and Oda Helgesen Ramberg for all the excellent work, for always being supportive and for giving a helping hand whenever I needed it. Also, I would like to thank everyone in the neighboring group, Toxicology, for your helpfulness and willingness to answer my questions.

I would also express my gratitude to the members of Toppforsk and FALK. You have all been very including, inspiring, and provided me with a helping hand whenever I needed it. Thank you! Also, I would like to thank the administration at ISP, in particular Helga Marie Meling, Anlaug Lid, and May-Britt Sande for always being available and answering my questions throughout these years. You made it easy and possible for me to work in Oslo, although being affiliated to the University of Bergen.

Thank you, Erik Dissen, for teaching me the immune cell isolation protocol and for teaching me all that I know about flow cytometry. I am forever grateful!

Lastly, I would like to thank my family and friends for always being supportive and encouraging. Menan, thank you for always believing in me, encouraging me, and for keeping me sane!

Dhaksshaginy,

Oslo, July 2020

Abbreviations

ACTH	Adrenocorticotropic hormone
ADRB2	β_2-adrenergic receptor
ANS	Autonomic nervous system
ARRB2	β-arrestin-2
BBB	Blood-brain-barrier
CORT	Cortisol/corticosterone
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
DEX	Dexamethasone
DNA	Deoxyribonucleic acid
E	Epinephrine
GABA	Gamma-aminobutyric acid
GAS	General adaptation syndrome
HPA	Hypothalamic-pituitary-adrenal
HSCL	Hopkins symptom checklist
IL	Interleukin
miRNA/miR	MicroRNA
mRNA	Messenger RNA
NAQ	Negative acts questionnaire
NE	Norepinephrine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NOS1	Nitric oxide synthase 1
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1
PFC	Prefrontal cortex

PNS	Peripheral nervous system
POMC	Pro-opiomelanocortin
PVN	Paraventricular nucleus
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
SIT	Social interaction test
SNP	Single nucleotide polymorphism
SNS	Sympathetic nervous system
TNF	Tumor necrosis factor

Abstract

Workplace bullying is a severe problem that needs further investigation from a range of disciplines. Yet, during more than twenty years of research on workplace bullying, few studies have addressed the bullying phenomenon from a biological perspective. Hence, the purpose of this thesis was to learn more about how stressors such as workplace bullying in humans and repeated social defeat in rats affect the physiological and psychological mechanisms of the body, seeing the latter as an animal model of bullying among humans.

The purpose of this thesis was, therefore, to advance our understanding of how workplace bullying leads to severe health problems in those targeted. As such, the present research addresses individual susceptibility when exposed to workplace bullying and examines causative effects and mechanisms on the relationship between exposure to workplace bullying and subsequent health outcomes.

The first paper addressed the potential moderating effect of the miR-146a genotype on the association between exposure to workplace bullying and insomnia through psychological distress, using a nationally representative survey of Norwegian employees. The findings showed that the relationship between distress and insomnia induced by exposure to bullying was stronger among GG genotype individuals compared with GC/CC genotype individuals.

The second paper addressed the neuro-immune changes initiated by exposure to prolonged social stressors. Thus, an animal model of repeated social defeat – the resident-intruder paradigm – was implemented. The animal data demonstrated stress-induced health effects, including reduced weight gain, hypothalamic-pituitary-adrenal (HPA) axis changes, and an increased inflammatory profile of the isolated splenic myeloid cells.

The third paper addressed the changed expression of the β2-adrenergic receptor (ADRB2) during prolonged exposure to stressors and its role in the association between exposure to workplace bullying and anxiety. A moderating effect of the ADRB2 genotype on the workplace bullying-anxiety relationship in humans was also observed. Moreover, in vivo and in vitro experiments demonstrated reduced ADRB2 gene expression induced by the stress hormone norepinephrine (NE) and a stress-induced switch from an anti-inflammatory to a pro-inflammatory state of the immune cells.

In conclusion, the findings of the present thesis indicate that persistent social stressors in the form of workplace bullying may lead to subjective health complaints such as insomnia and anxiety by promoting a state of low-grade systemic inflammation. Also, the findings from the animal model of repeated social defeat suggest that the systemic inflammation may be a consequence of the missing functioning of the "breaks" of the sympathetic nervous system (SNS) and HPA axis. The persistent inflammatory state following exposure to persistent social stressors, causing excess production of pro-inflammatory cytokines, seems to cause dysregulation and mal-adaptation of biological mechanisms central in the stress response system leading to physiological and psychological changes that may be damaging for overall health and well-being. Thus, the present thesis demonstrates a clear link between exposure to persistent social stressors, genetic factors, and severe health problems in targets of bullying.

List of Publications

The present thesis is based on the following publications:

Paper I. **Rajalingam, D.**, Jacobsen, D.P., Nielsen, M.B., Einarsen, S., & Gjerstad, J. (2019). Exposure to workplace bullying, distress, and insomnia: the moderating role of the miR-146a genotype. *Frontiers in Psychology,* **10**, 1204. doi: 10.3389/fpsyg.2019.01204

Paper II. **Rajalingam, D.**, Nymoen, I., Jacobsen, D.P., Eriksen, M.B., Dissen, E., Nielsen, M.B., Einarsen, S., & Gjerstad, J. (2020). Repeated social defeat promotes persistent inflammatory changes in splenic myeloid cells; decreased expression of β-arrestin-2 (ARRB2) and increased expression of interleukin-6 (IL-6). *BMC Neuroscience,* **21**, 25. doi: 10.1186/s12868-020-00574-4

Paper III. **Rajalingam, D.**, Nymoen, I., Nyberg, H., Dissen, E., Nielsen, M.B., Einarsen, S., & Gjerstad, J. (2020). Workplace bullying increases the risk of anxiety through a stress-induced β2-adrenergic receptor mechanism. Submitted for possible publication in *Stress. The International Journal of the Biology of Stress.*

1. Introduction

Since the time of our primal ancestors, exposure to stressors have been a part of our everyday life. The primitive humans needed to hunt for food, escape from predators, and defend their territories to survive. As such, the type of stressors they encountered would often be physical and often episodic in nature. In contrast, humans in our time face stressors that are mainly psychological, ongoing, and often social in its nature. The evolution of stress may, therefore, reflect the changes in human lifestyles. Today, people spend a significant part of their day at the workplace outside of the family group. As such, working outside the home has become an important and closely interrelated aspect of our lives. Accordingly, it is not surprising that humans today commit themselves to high goals, particularly in their working life, where tough competition both within and between one's organization may be a reality. The hectic lifestyle, with demanding work tasks can be tiring. Under such circumstances, irritation and frustration may be provoked among colleagues, consequently promoting to tensed working environments. It is also important to recognize that when at work, we are part of a group of individuals who have been assigned to each other by an employer and not by individual choice. Also, we are under the supervision and power of managers and leaders.

Even if interpersonal conflicts at work can be positive, i.e., being constructive and promote new ideas (Tjosvold, 1991), conflicts of a negative and prolonged nature may have a damaging effect on those who are involved. Exposure to occasional single acts of incivility may gradually escalate to systematic and frequent exposure to social stressors at work if not solved - the latter describing a phenomenon often referred to as workplace bullying. Existing literature demonstrates that such ongoing social stressors at work are risk factors for developing health problems, e.g., depression, anxiety, and sleep problems (Einarsen & Nielsen, 2015; Nielsen et al., 2017; Nielsen et al., 2014; Reknes et al., 2016). Despite the evidence provided for measures like prevalence, outcomes, and predictors of workplace

bullying, there is so far only a limited understanding of how systematic exposure to workplace mistreatment leads to detrimental health effects among those targeted. Both physiological and psychological processes determine health when facing such stressors. As such, further investigations of the biological mechanisms affected by bullying behaviors are required to improve our knowledge about the bullying phenomenon and also to increase our understanding of the relationship between exposure to bullying and its adverse and well-documented health outcomes (Brousse et al., 2008; Hogh et al., 2012; Jacobsen et al., 2019).

1.1. The objective of this thesis

In a little over three decades, we have been witnessing immense growth in the literature on prevalence, antecedents, and outcomes of workplace bullying, for review see (Neall & Tuckey, 2014). The extensive literature has provided an understanding of the bullying phenomenon. However, the number of studies investigating the underlying mechanisms of workplace bullying to explain how and when bullying occurs is limited (Nielsen & Einarsen, 2012; Trépanier et al., 2013). This thesis aims to examine the underlying biological mechanisms on the relationship between exposure to workplace bullying and health outcomes. In this, we will use human data, an animal model of repeated social defeat and in vitro cell culture experiments to increase our understanding of the bullying phenomenon and the underlying biological mechanisms leading to the physiological and psychological effects on targets of bullying.

Bullying is a complex social phenomenon that may be characterized by a range of factors – depending on whether we focus on the perpetrator or the target – at multiple levels, e.g., individual-, group-, organizational-, and cultural level (Einarsen, 2020; Notelaers et al., 2018). The understanding of the causal relationship of bullying and other variables is, therefore, beneficial when developing theoretical models and effective interventions

(Nielsen & Einarsen, 2018). The choice of methodology and study design will thus be critical for attaining valid and reliable findings of the bullying phenomenon. So far, except for some qualitative interview approaches (Baillien et al., 2009; Strandmark & Hallberg, 2007), the majority of studies in this field have relied on quantitative methods, in particular, surveys and questionnaire data with self-report only and often using cross-sectional study designs (Nielsen & Einarsen, 2012; Nielsen et al., 2010) and for review see (Neall & Tuckey, 2014). Few studies have included more objective biological variables or employed experimental designs. Also, the majority of studies conducted before 2001 focused mainly on examining the linear associations between antecedents, bullying, and outcomes, for review see (Rai & Agarwal Upasna, 2018). As a result, the number of studies examining underlying and intervening mechanisms of the relationship between bullying and its associated variables is insufficient, for reviews see (Nielsen & Einarsen, 2018; Rai & Agarwal Upasna, 2018). Investigating moderating and mediating factors and examining whether these factors attenuate or promote bullying or its aftermath, the latter being the focus of the present study, may enrich and extend our theoretical understanding of the phenomenon (Frazier et al., 2004).

The association between exposure to workplace bullying and the subsequent adverse health outcomes, i.e., psychological and psychosomatic health complaints (psychological distress, low sleep quality, anxiety, depression, musculoskeletal complaints, and physical illness) has been convincingly documented and is well-recognized (Berset et al., 2011; Glambek et al., 2018; Niedhammer et al., 2015; Nielsen & Einarsen, 2012; Nielsen, Harris, et al., 2020; Vie et al., 2012). Although there are some studies examining social and psychological moderators and mediators on the bullying-health relationship, for review see (Rai & Agarwal Upasna, 2018), the knowledge on the underlying biological mechanisms affected by bullying exposure and the understanding of biological mechanisms explaining how bullying may develop into adverse health effects in targets of bullying, is scarce.

In this thesis, we try to overcome the shortcomings mentioned above by integrating survey data from a human study involving biological moderators in the form of genotypes, an animal model of repeated social defeat implemented to study behavioral and physiological outcomes, and in vitro cell culture experiments to examine possible underlying biochemical causations between exposure and health-related outcomes.

The use of questionnaires may provide valuable information about exposure to workplace bullying, depending on the subject's appraisal of the situation, and its relation to psychological and psychosomatic outcomes. By including intervening and conditional factors, it is possible to explain in more detail how and when bullying is associated with health. However, despite the many advantages of such a method, it may be implausible to identify causative processes as previously described. Moreover, conducting experimental studies in humans to investigate the cause-effect relationship between workplace bullying and health outcomes may violate both ethical and legal frameworks that function to prevent research misconduct. Also, it is impossible and unethical to harvest tissues such as the brain, spleen, and bone marrow (BM) from humans. It may, for that reason, be difficult to investigate the physiological effects and mechanisms of how bullying in humans is related to health outcomes. Due to these limitations, we implemented an animal model of repeated social defeat to explore the underlying mechanisms of prolonged exposure to social stressors and the subsequent physiological and behavioral effects. The animal study was performed in two rounds in our lab, in which the second round included in this thesis was a refinement of the initial animal study conducted by Jacobsen et al. (2019).

A considerable advantage of conducting animal studies is the ability to control the conditions, i.e., only one or a few variables are changed at a time, in order to conclude on cause-effect relationships with greater certainty. Moreover, examination of tissues that are vital for biological processes such as for the stress response, e.g., brain, heart, spleen, adrenal gland, BM and blood, may be facilitated by implementing animal experiments due

to the limitations with humans as mentioned above. Animals models and, in particular, rodent animal models have made an immense contribution to our understanding of human health concerning drug testing, but also to increase our understanding of the pathophysiology of human diseases. Hence, the use of animals in research stands out as an invaluable benefit. Information gathered from animal studies may be translated into humans, although with some care as there are cases where information may be partially or entirely lost during translation, for review see (Attarwala, 2010), to provide more clarity and understanding, in this case, of the bullying phenomenon. At the very least, it may provide us with hypotheses that may be used in studies on humans.

Humans and rats have anatomical and physiological similarities, e.g., similar organs, similar nervous systems, and both use corresponding hormones, e.g., norepinephrine (NE) and glucocorticoids, to regulate body functions (La Perle & Dintzis, 2018; Snyder et al., 2018). Also, studies show that the response to stressors is relatively conserved among mammals, for review see (Joëls et al., 2018; Joëls et al., 2012; McEwen, Bowles, et al., 2015). Estimations indicate that approximately 90 % of the rat genes have orthologues – homologous gene sequences found in different species – in the human genome (Gibbs et al., 2004). Similar to humans and other mammals, rats are social creatures that prefer being with other individuals. They live in large colonies with a hierarchical structure where they engage in a range of social behaviors, e.g., grooming, exploration, play, aggression, and sexual behavior (Barnett, 1958). Hence, there are also some very basic social similarities with humans. Despite these similarities, however, it is apparent that humans are not rats and vice versa. Both species have different genetic backgrounds making them unique. Animal models are, however, extensively used in research as they are the closest whole complex organism to study.

In the present study, an animal model of repeated social defeat – the resident-intruder paradigm – was implemented to study the physiological and behavioral effects of prolonged

exposure to psychological and social stressors. The resident-intruder paradigm of repeated social defeat is often used to model exposure to psychological stressors in rodents as it results in the emergence of anxiety-like behavior and potential mal-adaptive changes in the neuroendocrine responses (Finnell et al., 2017; Koolhaas et al., 2013; Wohleb et al., 2011). This model encompasses the three critical features of the bullying definition, i.e., prolonged and repeated exposure to stressors in which there is a power imbalance between the two parties involved (Einarsen et al., 2011), which will be elaborated in more detail in a later subsection. Hence, the resident-intruder paradigm of repeated social defeat was regarded to be highly relevant as a model to study mechanisms involved in the pathophysiology of exposure to persistent psychological stressors.

The main purpose of this thesis, was as mentioned, to increase our knowledge about the underlying biological mechanisms of the relationship between workplace bullying and the development of adverse health problems, as seen from a biological or rather biopsychosocial perspective. Data collected from humans (questionnaires and saliva samples), rats exposed to repeated social defeat, and in vitro cell culture experiments were used to address how workplace bullying "*gets under the skin"* and may act to develop the detrimental and well-documented health effects. Moreover, the allostatic load model will be used as the theoretical framework to link persistent exposure to stressors with adverse health and well-being.

1.2. Workplace bullying – a brief background

The workplace bullying phenomenon was initially described by the American psychiatrist Carroll M. Brodsky in his book entitled *The Harassed Worker (1976)*. Here he presented a variety of cases where employees at all organizational levels affirmed to have been systematically mistreated by coworkers or superiors while at work with negative consequences regarding productivity, health, and well-being. Unfortunately, Brodsky did

not receive much attention for his pioneering work until it was rediscovered years later by another pioneer Heinz Leymann and the members of the Bergen Bullying Research group (Einarsen, 1994; Einarsen, 1991). In his book *Mobbing: Psychological Violence at Work (1986)*, Leymann described the concept of bullying among adults at the workplace – a phenomenon in parallel to ideas put forward by two pioneers in the field at that time; Peter-Paul Heinemann and Dan Olweus, who researched bullying among children in the schoolyard (Heinemann, 1972; Olweus, 1978). Leymann argued that the issue of workplace bullying had less to do with those involved and had rather to do with organizational factors such as deficits in work design, psychosocial work environments, and leadership (Leymann, 1996).

The growing awareness of the issue of bullying and harassment at work initiated extensive research initially in the Scandinavian countries, i.e., Norway (Einarsen et al., 1994; Einarsen & Skogstad, 1996), Sweden (Leymann, 1996) and Finland (Björkqvist et al., 1994; Vartia, 1996), but quickly spread to rest of Europe (Demirel & Yoldaş, 2008; Hubert & van Veldhoven, 2001; Kirchler & Lang, 1998) and America (Dingfelder, 2006; Keashly, 1997; Meyers, 2006). Despite being referred to as the "research topic of the 1990s" (Hoel et al., 1999), a meta-analysis conducted by Nielsen et al. (2010) revealed that the greatest number of studies (81.8 %) were published between 2000-2008 in which the majority of the studies (60 %) originated in Europe.

Over the past thirty years, the research field underwent a shift in focus and content, which was reflected by the rising multidisciplinary interest on the topic. While the initial investigations had a psychological perspective with attention on the nature, causes, and frequency of the bullying phenomenon, the research interest moved towards being focused on health-related issues. Consequently, understanding the link between exposure to bullying and severe health problems, i.e., depression, anxiety, and post-traumatic stress disorders, became of importance (Einarsen & Nielsen, 2015; Malinauskiene & Einarsen,

2014; Niedhammer et al., 2015). From there on, the interest evolved towards approaching the bullying issue from an organizational, national, and cross-cultural perspective (Harvey et al., 2007; Heames & Harvey, 2006; Skogstad et al., 2007). Moreover, intertwining theories from both conflict and stress fields have been essential in order to explain why bullying occurs and why the consequences of such exposure can evolve to become so detrimental to target health and well-being (Einarsen, 2011).

1.3. Defining workplace bullying

Despite the substantial advances that have occurred in the field, the researchers have met on challenges in developing an agreeable concept and a definition of this multicausal and complex phenomenon (Einarsen et al., 2011). Among the different labels and terms used interchangeably (which will not be elaborated here) the most commonly used are "workplace bullying" and "harassment" in English- and French-speaking countries, respectively, and "mobbing" along with national specific terms in European countries (Einarsen, 2020). However, irrespective of the different usages in each country, a considerable agreement regarding the concept within the European research community may be found.

Despite the existence of different bullying definitions, Einarsen and colleagues (2011), presented a definition that is well-established and commonly used within the European research tradition:

> "Bullying at work means harassing, offending, socially excluding someone or negatively affecting someone's work task. In order for the label bullying (or mobbing) to be applied to a particular activity, interaction, or process, the bullying behavior has to occur repeatedly and regularly (e.g., weekly) and over a period of time (e.g., about six months). Bullying is an escalating process in the course of which the person confronted ends up in an inferior position and becomes the target of

systematic negative social acts. A conflict cannot be called bullying if the incident is an isolated event or if two parties of approximately equal strength are in conflict". This definition emphasizes three main features of bullying, which implies that the negative behaviors are systematic, persistent over a prolonged time, and involves a power imbalance between the two parties involved (Einarsen, 2020).

Bullying is about the negative and unwanted behaviors that last for months and years rather than days and weeks (Einarsen, 2020). As have been discussed earlier (Einarsen, 1999; Leymann, 1990; Leymann, 1996) and again highlighted by Rosander and Blomberg (2019), there seems to be a discrepancy as to whether bullying is the process that leads to becoming a target or whether bullying is something that occurs when becoming a target. The essence of this problem may be due to the different ways of assessing and framing bullying (Rosander & Blomberg, 2019). However, Einarsen et al. (2011) suggested that any exposure to negative acts that are systematic and occurs over an extended time should be referred to as bullying.

The nature of the behaviors involved in bullying may be distinguished as (1) work-related as opposed to person-related bullying, (2) passive and indirect behaviors versus active and direct behaviors, and (3) psychological versus physical aggression (Einarsen, 2020). While unmanageable workload, giving unreasonable deadlines, excessive monitoring of work, and being assigned to meaningless or even no tasks at all are referred to as work-related bullying behaviors, examples of person-related bullying behaviors may be excessive teasing, making insulting remarks, spreading rumors, persistent criticism, and intimidation. These mentioned behaviors may further be regarded as either being passive and subtle, i.e., gossiping, spreading rumors, and social isolation, or as active and direct, i.e., verbal threats and verbal aggression (Einarsen, 1999; Einarsen et al., 2009). Although earlier studies involved physical behaviors in their categorization of bullying (Leymann, 1996; Vartia,

1991), there is an increased recognition among researchers nowadays that behaviors engaged in workplace bullying are mainly psychological of nature (Einarsen, 2020).

As recognized by Leymann (1990), some of the behaviors mentioned above may be experienced at a single occasion at the workplace and will not be referred to as bullying. It is the frequency and duration of the exposure to such negative behaviors that matter. This stresses the importance of the escalation process – from being exposed to single acts of incivility to becoming a target of severe bullying – in which the negative behaviors evolve to be more intense and personalized over time (Ågotnes et al., 2018; Zapf & Gross, 2001). While the initial stages of ongoing bullying involve work-related behaviors, the final stages of severe and extreme bullying involve behaviors that are person-related, e.g., emotional abuse (Escartín et al., 2009; Rodríguez-Carballeira et al., 2010; Rosander & Blomberg, 2019). During this escalating process, the target may perceive oneself as incapable of stopping the negative behaviors (Einarsen et al., 2011; Einarsen & Skogstad, 1996; Olweus, 1993; Zapf & Einarsen, 2005). Irrespective of a pre-existing or evolved imbalance of power, the frequency and persistence of the negative behaviors may, in the end, become unbearable and tending to drain the coping resources of the target, regardless of personal coping strategies (Nielsen et al., 2017). The person ending up in the inferior position may feel powerless, and at this point, the target may face severe trauma and suffer from numerous mental and somatic symptoms (Hansen et al., 2011; Hogh et al., 2012; Jacobsen et al., 2018; Nielsen et al., 2014). Hence the aftermath of such exposure is detrimental and traumatic for the target.

1.4. Measuring workplace bullying

The commonly used methods to measure exposure to bullying at work are both self-reports, the self-labeling method, and the behavioral experience method (Nielsen et al., 2010; Nielsen et al., 2009). When applying the self-labeling method, the participants are given a

single-item question in which they are asked if they have been bullied or not, within a specific period of time (Nielsen et al., 2011). In some studies, the definition of bullying is presented to the respondents, which gives an advantage as both researchers and respondents acquire a similar understanding of the phenomenon (Nielsen et al., 2011). Even though the method does not need much space in a questionnaire and is easy to administer, the researchers do not get an insight into the nature of the bullying behaviors. Also, since the method is subjective and measures whether the respondent has been bullied or not, personal thresholds may influence their experience of being bullied (Nielsen, 2020; Nielsen et al., 2009).

Another commonly used measurement method is the behavioral experience method such as the Leymann Inventory of Psychological Terror (LIPT; (Leymann, 1990)), the negative acts questionnaire (NAQ/ NAQ-R; (Einarsen et al., 2009; Einarsen & Raknes, 1997)) and the Workplace Aggression Research Questionnaire (Harvey & Keashly, 2003). The respondents are here presented with various types of unwanted negative behaviors (without mentioning the label "bullying") that can be interpreted as bullying if they repeatedly occur over time. In the inventory, they are also asked to report the frequency of exposure to such behavior, e.g., in the case of NAQ; *"Never," "Now and then," "Monthly," "Weekly,"* and *"Daily."* Thus, the method takes the nature, frequency, and duration of the bullying phenomenon into consideration but does not explicitly address power distance between the target and perpetrator. However, by including a single item question following the NAQ inventory, i.e., "*If you have been exposed to one or more behaviors in the list above, did you find it difficult to defend yourself against this exposure?"* it is possible to measure whether the respondent can defend him or herself against the negative behavior (Nielsen et al., 2017). A study doing so showed, however, that the latter variable had little impact and explanatory value as the exposure escalated. Compared to the self-labeling method, the behavioral experience method is regarded to be less subjective in the sense that the respondents do not need to label their experience as bullying. Furthermore, it measures the

full range of exposure from the occasional instances to systematic exposure and victimization from bullying, falling under the more strict definition presented above. In the studies comprising this thesis, we employ the term exposure to bullying behaviors when referring to this.

Apparently, there are both advantages and disadvantages with the two above mentioned methods, and they both tend to emphasize different aspects of the bullying phenomenon (Nielsen, 2020). Moreover, several studies demonstrate that the choice of method may affect the prevalence measured, i.e., behavioral experience method report a higher prevalence of workplace bullying as compared to the self-labeling method (Nielsen et al., 2010; Nielsen, 2020; Nielsen et al., 2009). Thus, it is important to be aware of the differences when implementing the methods and not compare studies using different methodological approaches.

Although both methods (the self-labeling method presented with the bullying definition) were included in the questionnaire collected from the respondents, only the responses from the NAQ inventory were used in paper I and III included in this thesis. The reason being that this method provides a less subjective measure of workplace bullying and avoids subjectivity bias. Also, there is a higher risk of missing out on some targets of bullying with the self-labeling method, as some do not label themselves as targets (Nielsen et al., 2009). On the contrary, here we measure the whole range of exposure, including instances falling outside the strict definition, looking more at bullying as an escalating process existing on a continuum from not exposed to highly exposed.

1.5. Workplace bullying and health outcomes

Cross-sectional (Harb et al., 2019; Jacobsen et al., 2019; Jacobsen et al., 2018; Török et al., 2016; Vie et al., 2012), and longitudinal studies (Einarsen & Nielsen, 2015; Glambek et al.,

2018; Hoprekstad et al., 2020; Niedhammer et al., 2015; Nielsen et al., 2013), but also a few qualitative studies (Baillien et al., 2009; Strandmark & Hallberg, 2007) report a positive association between prolonged and systematic exposure to bullying behaviors and physical and mental health problems (Nielsen et al., 2014; Verkuil et al., 2015). Studies indicate that workplace bullying has a strong influence on mental health in the form of intrusive thoughts, avoidance behavior, and hyperarousal (Hogh et al., 2012). In light of the cognitive appraisal theory (Lazarus & Folkman, 1984), it is believed that the association between bullying and mental health is through cognitive factors, e.g., attributions and interpretation (Nielsen et al., 2014), suggesting that the effect of bullying on health depends on how the target experiences, evaluates and resists bullying behaviors, i.e., coping strategies (Dehue et al., 2012; Hewett et al., 2018).

Exposure to strong stressors such as bullying has shown to challenge the fundamental beliefs about one's own worth and the world as meaningful and benevolent (Hamre et al., 2020; Mikkelsen & Einarsen, 2002; Rodríguez-Muñoz et al., 2010). Going through a bullying process, assumptions become shattered, which is assumed to cause constant worrying, rumination, and negative thoughts. The psychological stress imposed on individuals exposed to bullying may lead to dysregulation of neurocircuits in the brain, for review see (McEwen, 2017; McEwen & Gianaros, 2011; Radley et al., 2015). This may involve neurocircuits that control the regulation of sleep (Henderson et al., 2017; D. W. Lee et al., 2016; Olini et al., 2017) – important for recovery (Berset et al., 2011; Demsky et al., 2019; Kallestad et al., 2015) – and emotions that may lead to mental health problems, e.g., depression and anxiety, following exposure to persistent stressors (Nielsen et al., 2013; Schutte et al., 2014). Also, prolonged exposure to psychological stressors has been associated with allodynia – increased sensitivity towards pain – (Alexander et al., 2009; Crettaz et al., 2013; Sawicki et al., 2019), which may support previous findings on the association between bullying and physical health problems (Glambek et al., 2018; Jacobsen et al., 2019; Jacobsen et al., 2018; Vie et al., 2012).

Despite the clear association between bullying and its effect on health, there may be individual differences and risk factors, i.e., genetic dispositions, that may moderate the impact of bullying behaviors on health and well-being, for review see (Nielsen & Einarsen, 2018; Rai & Agarwal Upasna, 2018). Individual differences at the genetic level involve variation due to the inheritance of two alleles – one from each parent. Genes that play crucial roles in specific biological systems, e.g., hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), the immune system, and in brain neurocircuits, may affect how individuals react to strong stressors such as bullying. Although genetic differences may explain differences in susceptibility and vulnerability among individuals, studies indicate that the significance of psychological factors that theoretically should act to buffer the relationship between bullying and outcomes diminishes when the bullying behaviors are of high intensity (Nielsen et al., 2008; Vie et al., 2011; Vie et al., 2012). Still, knowledge about genetic variation may improve our understanding of the underlying biological mechanisms that are involved in the bullying-health relationship. Examination of genes that are central in the stress response systems, and, which explains the bullying-health relationship to some degree, may improve our understanding of how molecular mechanisms at the cellular level leads to pathophysiology and the development of negative health problems. As a result, improved knowledge of how bullying at work develops into detrimental health effects may be achieved.

As briefly mentioned, most of the studies to date have been self-report studies with cross-sectional study design, even though some prospective studies exist, see also (Nielsen et al., 2014). The nature of the study designs so far has, therefore, made it challenging to conclude on cause-effect relationships between bullying and other variables. For instance, although negative health problems, e.g., sleep problems, have been reported by individuals exposed to bullying behaviors, there is still a basis for a reciprocal relationship between bullying and health issues, see also (Nielsen & Einarsen, 2012). Individuals with deprived sleep quality will most likely function poorly at work, which further may provoke irritation and

frustration among colleagues. Also, as the variables, i.e., exposure and outcome, are collected at the same time, conclusions about causality cannot be made (Munnangi & Boktor, 2020). Therefore, due to the limited understanding of cause-effect relationships, research designs that can provide knowledge on this aspect should be preferred. Such designs may include experimental study designs that are performed under highly controlled conditions, i.e., animal studies or cell-culture experiments.

Altogether, workplace bullying has a strong influence on health and well-being, as reported by those exposed (Einarsen & Nielsen, 2015; Harb et al., 2019; Niedhammer et al., 2015). To understand the effects of bullying on health, we need to examine physiological processes that are affected, particularly those involved in the stress response, e.g., HPA axis and the SNS. It will also be important to look for theoretical biological models of stress to address the bullying phenomenon and its effects on health.

1.6. Allostatic load

The main theoretical framework in this thesis is the *allostatic load model*, proposed by Bruce McEwen and Eliot Stellar (1993). The model provides a theoretical basis to understand the relationship between stressors and adverse health outcomes by which it distinguishes between the protective and damaging consequences of the response to stressors (McEwen, 2005). The model is a reinterpretation of the *general adaptation syndrome (GAS)*, which was proposed by Hans Selye, who also introduced the concept of stress (Selye, 1936). With his model, Selye proposed a physiological response that takes the form of a series of three stages that could explain the response to a stressor (McEwen, 2005). In the first stage, which he called "the alarm reaction," primary mediators, i.e., epinephrine (E), NE, glucocorticoids, and cytokines, are released through the activation of the SNS and the HPA axis to reinstate homeostasis. The second stage, "the resistance," is when homeostasis is restored. If the stressor persists, the final stage of "exhaustion" follows,

and the adaptive responses cease (Selye, 1950). However, in the light of new and updated knowledge about stress, one may understand that the different stress responses may activate differently based on the type of stressor, e.g., acute stress activates the SNS ("fight-or-flight" response) whereas longer-lasting stressors activate the SNS as well as the slower activated HPA axis, an aspect lacking in the GAS model. Also, both the protective and damaging consequences inflicted on the body by the same stress response mediators (McEwen, 2000) has not been taken into consideration by the GAS model. Hence, it may be regarded that the allostatic load model fit well to explain the physiological and psychological changes that occur following exposure to workplace bullying.

The term "homeostasis" was initially coined by physiologist Walter Cannon (1926) to describe a relatively constant internal environment of systems that are essential for life, e.g., pH, body temperature, glucose level, and oxygen tension. Homeostasis may be maintained at different levels, e.g., whole-body level, the organ level, and at the cellular level, in which sensors, i.e., receptors, monitors the physiological value and relays the information to the brain, which compares the physiological value to the normal range (Ferrè et al., 2012; Kobayashi, 2015). In situations where the value deviates from the normal range, the brain initiates behavioral and physiological responses to reinstate homeostasis (McEwen, 2017). According to the allostatic load model, the system achieving stability through adaptation is termed *allostasis* (McEwen, 2005). Whereas allostasis gives protection to the body, the same systems may cause damage to the body and lead to disease when overused and dysregulated, referred to as *allostatic overload* (McEwen, 2012a).

When exposed to a stressor, the stress response systems of the body, e.g., the SNS and the HPA axis, secrete mediators, e.g., NE and glucocorticoids, respectively, to help the body adapt and reinstate homeostasis. When these mediators are secreted in a balanced manner, the activated systems are turned off through negative feedback mechanisms when the stress exposure is over (Herman et al., 2012; Osterlund et al., 2016). However, if the exposure to

stressors persists and is long-term as during workplace bullying, the activated systems may not be turned off. The continuous activation of the systems may result in dysregulated functions of the uncontrollably secreted mediators (McEwen, 2007a). Chronic stressors may, therefore, cause wear and tear on the body, i.e., allostatic overload, which may progress and develop into diseases (Hering et al., 2015; Wiley et al., 2016), for review see (Silverman & Sternberg, 2012).

The allostatic load model centers on the brain as the interpreter and responder to the environmental challenge (McEwen, 2000, 2012a, 2017). The subjective appraisal of the situation is what determines how the body reacts. If the situation is perceived as threatening, the brain may initiate behaviors to handle the threat ("fight-or-flight response). Accordingly, the allostatic load model does also take into consideration the individual differences in vulnerability to developing diseases following exposure to a stressor.

1.7. The concept of stress

The term "stress" is central to the present study. It may be defined as a "non-specific response of the body to any demand of change," and may, as such, refer to both the environmental challenge to an organism's homeostasis as well as the biological response to such a challenge (Moberg, 1987; Selye, 1975). However, throughout this thesis, a "stressor" will be referred to as the external environmental challenge, while the biological response will be referred to as the "stress response." In the present study, the social stressor inflicted on the organism will be denoted as workplace bullying in the case of humans and as repeated social defeat in the case of animals, i.e., rats. The term "stressor" will not be referred to when discussing the in vitro cell culture experiments. As will be described later, the in vitro cells were exposed to stress hormones, i.e., NE and dexamethasone (DEX, a synthetic glucocorticoid), to resemble the activation of the stress response following exposure to chronic stressors. Thus, only the physiological effects following exposure to

the stress hormones were examined at the cellular level. The exposure to stress hormones will, therefore, be referred to as a treatment, e.g., NE- or DEX- treated cells.

As briefly described in the prior subsection, stress has been defined as a state in which homeostasis is threatened or perceived to be so (Asarian et al., 2012; Fink, 2009; McEwen, 2007b). A stressor may, in nature, be physical, e.g., injury, hot/cold temperature or pain, or psychological, e.g., events, situations, individuals, or comments that are interpreted as negative or threatening. All living organisms have a complex set of mechanisms to maintain an internal steady state (homeostasis) of physical and chemical conditions when exposed to a stressor, for review see (Kotas & Medzhitov, 2015). When homeostasis is disturbed, various physiological and behavioral adaptive responses become activated through the brain to keep the dynamic equilibrium of certain variables, e.g., pH, temperature, concentrations of ions, and blood sugar level, within respective set-points (Koolhaas et al., 2011; McEwen, 2012b, 2017). Even if external adverse effects continuously challenge the homeostasis, the equilibrium is, for the most part, re-established and kept in check through adaptation – allostasis. However, if stressors are persistent, as in the case of workplace bullying, and the demands on the organism surpass the available energy and adaptation capacity, a state of allostatic overload may lead to mal-adaptive processes (McEwen, 2000; Merkulov et al., 2017; Olini et al., 2017).

In case of exposure to a psychological stressor, the elicited response may be positive or negative depending on the subject's appraisal of the situation (Han et al., 2017; Harvey et al., 2010). A positive response in which the stressor is perceived as manageable may give rise to positive feelings of excitement, meaningfulness, and strength to the organism (Gibbons et al., 2008; Rudland et al., 2020). Such a response is regarded to be beneficial for health and well-being, also referred to as eustress. The negative response to a stressor is regarded as distress and is associated with physiological and psychological changes that are negative to health and well-being (Alhurani et al., 2018; Yin et al., 2019; Zhang, Ge, et

al., 2018). Although earlier stages of bullying may be interpreted as less harmful on the target, the repeated and persistent exposure to bullying behaviors will cause distress through promoting a state of allostatic overload (Nielsen et al., 2017).

1.8. The stress response

The stress response is subserved by the stress system, which is situated both in the central and the peripheral nervous system, for review see (Charmandari et al., 2005). The immediate response to a threat is characterized by the activation of the locus coeruleus (LC) – a nucleus in the brainstem giving rise to extensive NE-containing projections throughout the brain – which releases NE to several stress-related limbic forebrain regions, e.g., amygdala, bed nucleus of the stria terminalis, medial prefrontal cortex (PFC) and the lateral septum (brain regions involved in behavioral and emotional responses) upon acute stress exposure (Ding et al., 2014; Giustino et al., 2020; McDevitt et al., 2009). The LC-NE system in the brain is, therefore, central in the acute stress-induced behavioral changes such as anxiety-like behavior and fear (Arnsten et al., 2015; Borodovitsyna et al., 2018; McCall et al., 2015). The LC-projections also relay signals to brain structures such as the paraventricular nucleus of the hypothalamus (PVN) (Wohleb et al., 2011). Activation of the PVN upon acute stress exposure initiates transmission of signals to pre- and post-ganglionic sympathetic nerve fibers of the autonomic nervous system (ANS) that innervate the adrenal gland and spleen, respectively (Cano et al., 2001; Kesse et al., 1988). The principal effectors, i.e., E and NE (Figure 1), are released in the circulation and to tissues from the adrenal medulla and the sympathetic nerve fibers, respectively, to stimulate motor and hormonal tissues to initiate a "fight-or-flight" response (Flak et al., 2014). The acute response to threat is, hence, characterized by physical and physiological changes, e.g., elevated heart rate, increased blood flow to muscles, increased muscle contractility and elevated levels of glucose to supply the body with energy and to prepare the body for survival (Bola & Kiyatkin, 2018; Cavallotti et al., 2002; Emrick et al., 2010; Fu et al.,

2013). However, this state of alertness is short-term and ceased by the parasympathetic nervous system (PNS).

With a delay, a slower and longer-lasting neuroendocrine response, i.e., the HPA axis, becomes activated (Figure 1). The PVN also contains neurons that activate the HPA axis through the release of corticotropin-releasing hormone (CRH) (Roman et al., 2017; Wamsteeker Cusulin et al., 2013). By binding to its receptor on corticotropic cells in the anterior lobe of the pituitary gland, CRH stimulates these cells to secrete adrenocorticotropic hormone (ACTH) into the circulation (Deng et al., 2015). ACTH, in turn, binds to its receptor in the adrenal cortex, melanocortin type 2 receptor (MC2R), to stimulate glucocorticoid – cortisol in humans and corticosterone in rodents - synthesis and secretion (Osterlund et al., 2016). Glucocorticoids regulate physiological changes that involve metabolic, e.g., breakdown of glucose molecules, fat and proteins to enable energy mobilization (Christiansen et al., 2007), immune, e.g., both immunosuppressive and immunoregulatory functions (Franco et al., 2019; Xie et al., 2019; Yu et al., 2018), and behavioral processes, e.g., mood and cognitive behavior (Savas et al., 2020; van Donkelaar et al., 2014) and for review see (Vyas et al., 2016), through binding to its ubiquitously expressed intracellular receptor. Also, glucocorticoids play an essential role in regulating the magnitude and duration of HPA axis activation through a negative feedback mechanism (Goncharova et al., 2019; Thrivikraman et al., 2000). As such, activation of both the SNS and HPA axis is generally followed by counteractive and adaptive mechanisms to reinstate homeostasis.

Although the short-term anti-inflammatory effects of the NE and glucocorticoids are well recognized (Auphan et al., 1995; Löwenberg et al., 2005; McNamee et al., 2010), accumulating evidence suggests a pro-inflammatory role of these stress hormones during chronic stress conditions (Cohen et al., 2012; Miller et al., 2008; Powell et al., 2013; R. Yang et al., 2014). When the threat persists, such as in ongoing bullying cases, the demands

may become unbearable. Irrespective of the persons coping resources, the target may feel distressed and powerless at this point, and the coping and adaptive mechanisms may fail to reinstate homeostasis, i.e., allostatic overload (Nielsen et al., 2017).

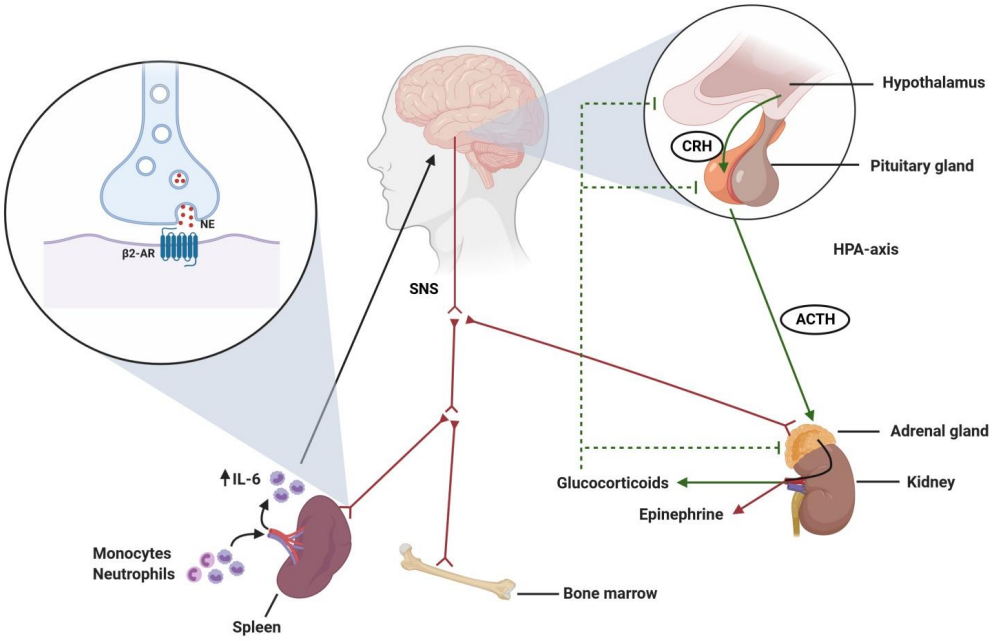

Figure 1. Schematic illustration of the sympathetic and neuroendocrine response to stressors. Exposure to acute stressors activates norepinephrine (NE) containing neurons in the brain and induces activation of the hypothalamus. The hypothalamus transmits signals to the efferent sympathetic pre- and post-ganglionic neurons (red) that innervate the adrenal glands and the spleen, respectively. The adrenal innervation causes the release of epinephrine (E) in the circulation. The sympathetic innervation of the bone marrow (BM) stimulates the egress of immune cells from the BM and alters the morphology of monocytes that may migrate to the spleen. Sympathetic innervation of the spleen may also affect monocyte functions through NE-β2-adrenergic receptor interaction. Prolonged sympathetic activation may, for instance, enhance the release of cytokines, which may pass into the brain and affect neurocircuits important for cognition, emotion, and behavior. Activation of the slower and longer-lasting endocrine response, the HPA axis, following exposure to stressors induces the release of corticotropin-releasing hormone (CRH) from the hypothalamus to the pituitary gland, where the release of adrenocorticotropic hormone (ACTH) is induced. ACTH travels through the circulation and binds to its receptor in the adrenal gland, stimulating the release of glucocorticoids from the adrenal cortex. In addition to the various downstream effects of glucocorticoids, they also exert negative inhibitory feedback (green, stippled lines) on the pituitary and the hypothalamus, thus limiting the magnitude and duration of the HPA axis activation. Similarly, an autoregulatory mechanism of action has been proposed due to the findings of glucocorticoid receptors in the adrenal gland. The figure was created in Biorender.

1.9. The innate immunity

Upon detection of harmful stimuli, e.g., injury, pathogens or irritants, the first line of defense – the innate immune system – initiates a state of inflammation. In this process, tissue-resident immune cells release chemicals (e.g., histamine, bradykinin, and prostaglandins) to promote vasodilation and vascular permeability to allow infiltration of white blood cells as well as fluid, ions and inflammatory proteins (e.g., cytokines and chemokines) into the damaged tissue (Jenne et al., 2013), for review see (Medzhitov, 2008). Macrophages with innate properties, which through phagocytosis[1] remove non-self cells, are an important part of this process. The purpose of this defense mechanism is to eliminate the cause of injury and to clear out dead cells from the site so that the body can initiate restorative processes. As the name implies, the innate immunity is the inborn defense mechanism that acts immediately.

White blood cells – cells of the innate immune system – are produced in the BM and consist of mononuclear leukocytes, i.e., monocytes, lymphocytes, and granulocytes (neutrophils, basophils, and eosinophils) (Ding & Morrison, 2013). Among these cells, monocytes flow through the bloodstream and perform important surveillance functions to ensure antigen detection and effective activation of the immune response (Auffray et al., 2007; Jakubzick et al., 2013). In contrast to granulocytes and lymphocytes, monocytes may differentiate into macrophages or dendritic cells upon tissue infiltration and perform phagocytosis and antigen presentation (J. Yang et al., 2014; Yona et al., 2013). Depending on the signals from their microenvironment, these macrophages may perform a range of effector functions, including phagocytic activity, antigen presentation, and immunomodulation (Gosselin et al., 2014; Lavin et al., 2014). As such, these cells make a crucial contribution

[1] **Phagocytosis** – A process by which a cell uses its plasma membrane to engulf particles such as bacteria, cell debris/fragment, or foreign matter. Phagocytic cells of the immune system consists predominantly of macrophages and neutrophils.

to the activation of the adaptive immune response, thus creating a bridge between the innate and adaptive immunity, for review see (Rivera et al., 2016).

As briefly described, microglia are the principal resident innate immune cells in the central nervous system (CNS), i.e., the brain and spinal cord (Elmore et al., 2014; Ginhoux et al., 2010) and are, as such, critical for maintaining homeostasis of the CNS. Depending on the microenvironment of the brain, which varies between brain regions due to different neuronal subtypes and neurotransmitter profiles, the microglia cells may exhibit a broad diversity of phenotypes and functions (de Haas et al., 2008; Doorn et al., 2015; Grabert et al., 2016). Also, the balance of pro- and anti-inflammatory cytokines may affect the role of microglia activation, which can be protective, i.e., surveilling, maintaining tissue integrity, and restoring the CNS, or damaging, i.e., causing neuronal damage by releasing harmful substances such as inflammatory cytokines and reactive oxygen species (Bellver-Landete et al., 2019; Cserép et al., 2020; Madry et al., 2018; Nimmerjahn et al., 2005; Pais et al., 2008). Consistent with these functions, several studies emphasize the close interaction between microglial cells and neuronal synapses in the brain, signifying the important role of microglia cells during neuronal survival and neurodegeneration (Cserép et al., 2020; De Lucia et al., 2016; Pais et al., 2008; Zhan et al., 2014). This dual role of microglia cells may have an impact on brain activity and mental health when exposed to chronic psychological stressors, i.e., workplace bullying.

The different components of the immune system communicate with each other using signaling molecules such as cytokines and chemokines, and cell-cell interactions to coordinate immune responses (Bruce et al., 2019; Johnson et al., 2019; Kawano et al., 2018). With respect to cytokines, these signaling molecules are necessary to enhance immune activity to protect the body against pathogen invasion. However, during chronic exposure to stressors, excessive and dysregulated production of cytokines, which disrupts the balance of pro- and anti-inflammatory cytokines, may lead to low-grade systemic

inflammation (Miller et al., 2019; Niraula et al., 2018). This systemic condition has shown to increase central sensitization, i.e., increased sensitivity to pain (Jacobsen et al., 2019; Jacobsen et al., 2018; Sawicki et al., 2019), and affect brain neurocircuits that also are involved in regulating sleep and mood (e.g., anxiety and depression) (Niraula et al., 2018; Tang et al., 2018; Yin et al., 2019). Accordingly, further investigation of the immune system during exposure to chronic stressors may provide new insight into how exposure to workplace bullying causes mental health problems.

1.10. The bi-directional neuroimmune communication

The sympathetic nerve fibers innervate most of the organs in the body, including the lymphoid organs, i.e., the BM, thymus, spleen, and lymph nodes (Felten et al., 1985) and facilitate the direct release of NE into the innervated tissues. Since peripheral immune cells express adrenergic receptors (Araujo et al., 2019; Grisanti et al., 2010; Saygin et al., 2018; Wohleb et al., 2011), receptor stimulation may result in functional responses that affect differentiation, migration capacity and inflammatory profile of the immune cells (Bierhaus et al., 2003; Grisanti et al., 2010; Reader et al., 2015).

Prolonged sympathetic signaling has been associated with increased production and release of myeloid cells, which includes monocytes, macrophages, neutrophils, granulocytes, erythrocytes, and platelets, from the BM to the periphery (Dhabhar et al., 2012; Hanke et al., 2012). Studies report that exposure to persistent stressors causes a significant increase in the number of circulating myeloid cells (from now on only concerning monocytes/macrophages), which may be supported by the findings of increased numbers of myeloid cells in the spleen (Engler et al., 2004; McKim et al., 2018). The monocytes released from the BM have been demonstrated to have an enhanced capacity to traffic and induce pro-inflammatory signaling throughout the body (Engler et al., 2004; Hanke et al., 2012; Wohleb et al., 2015). Wohleb et al. (2015) stated that many of the observed pro-

inflammatory effects of chronic stressors are merely a result of enhanced myelopoiesis, i.e., production of immune cells, particularly the cells of the myeloid cell lineage, in the BM. The purpose of the increased production of immature myeloid cells is to provide a rapid but non-specialized immune response (Heidt et al., 2014; Powell et al., 2013). The immature nature of the released monocytes may also be relevant to the development of glucocorticoid-insensitivity (the reduced sensitivity of immune cells to glucocorticoids) since the immature monocytes in the BM are functionally glucocorticoid-resistant (Avitsur et al., 2002). These findings may indicate that prolonged exposure to stressors increases the number of pro-inflammatory myeloid cells in the circulation that may enter tissues and provoke pathological states through promoting inflammation.

Accumulating evidence indicates that pro-inflammatory signaling in the brain affects cognition, mood and behavior (Hodes et al., 2015; Reader et al., 2015; Réus et al., 2015; Wohleb et al., 2011; Wood et al., 2015; Zhang, Ge, et al., 2018). The predominant innate immune cells in the CNS, namely microglia cells, express adrenergic and glucocorticoid receptors and are, as such, sensitive to the physiological stress response mediated by NE and glucocorticoids (Carrillo-de Sauvage et al., 2013; Qian et al., 2011; Sugama et al., 2019; van Olst et al., 2018). It has been demonstrated that exposure to stressors is accompanied by enhanced microglia activation and neuroinflammatory signaling (Frank et al., 2007; Iwata et al., 2016) to influence behavior, for review see (Weber et al., 2017). However, it is believed that microglia cells are not alone in the enhancement of the neuroinflammatory and behavioral responses to stressors. Studies show that peripheral monocytes are recruited to the capillaries in the brain via ligand-receptor signaling, i.e., CX3CL1-CX3CR1 and CCL2-CCR2 (Auffray et al., 2007; D'Mello et al., 2009). It is assumed that the recruited monocytes secrete pro-inflammatory cytokines, which may have an impact on neurocircuits in the brain, which may further affect cognition, mood, and behavior. Also, exposure to stressors has indicated dysfunction of the blood-brain-barrier (BBB), which has been characterized by BBB leakage and inflammation (Dudek et al.,

2020; Welcome, 2020; Wohleb et al., 2014), suggesting that pro-inflammatory components from the periphery may affect the neurocircuits and functions of the brain under chronic stress conditions.

The stress-induced bi-directional communication pathways between the brain and the immune system are, as described above, important for promoting the enhanced neuroinflammatory environment in the CNS and the periphery. Further understanding of the bi-directional communication may help elucidate the relationship between exposure to psychological stressors, i.e., workplace bullying, and the subsequent health problems that affect physical and mental health (Einarsen & Nielsen, 2015; Hamre et al., 2020; Jacobsen et al., 2018; Nielsen et al., 2017; Verkuil et al., 2015). Also, the actions of NE and glucocorticoids transmit signals from the autonomic (SNS) and neuroendocrine (HPA axis) pathways, emphasizing the important role of these mediators in the communication between the CNS and immune system (Engler et al., 2004; Powell et al., 2013; Wohleb et al., 2015; Yin et al., 2019). Thus, investigating the actions of NE and glucocorticoids on the components of the immune system, i.e., myeloid cells, may provide valuable information on the peripheral-to-central immune interaction.

1.11. Stress and mental health

According to the World Health Organization (WHO), mental health has been defined as "a state of well-being in which the individual realizes his or her abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (*World Health Organization*, 2014). Both mental- and physical- health are central factors in achieving the state of well-being in which a person experiences positive emotions, high life satisfaction, a sense of meaning or purpose, and the ability to cope with stress (Fergusson et al., 2015; Kok et al., 2013; Puvill et al., 2016). The reciprocal relationship between mental- and physical- health (Bacon et al., 2015;

Chen et al., 2017; Soysal et al., 2017) has been described and should be emphasized and taken into account when examining the physiological and psychological consequences of exposure to ongoing psychological stressors, as in the case of workplace bullying.

Repeated and persistent exposure to stressors at the workplace has been associated with distress and negative rumination (Giorgi et al., 2016; Hannibal & Bishop, 2014; Nielsen, Christensen, et al., 2020; Nielsen et al., 2012). Exposure to bullying behaviors (e.g., making insulting remarks, spreading rumors, gossiping, persistent criticism, social isolation, giving unmanageable workloads, unreasonable deadlines, or excessive monitoring of work) may cause concerns and worries (Einarsen, 2020). This may result in increased arousal and may eventually develop into sleep problems and negative emotions, i.e., anxiety and depression (Berset et al., 2011; Nielsen et al., 2017; Nielsen, Harris, et al., 2020). The etiology of mental health problems is complex and involve dysregulation of many neurocircuits in brain regions that are important for mood, motivation, reward, and emotions (Capuron et al., 2011; Eisenberger et al., 2010; Miller et al., 2013; Reichenberg et al., 2001).

Accumulating evidence suggests that abnormal inflammatory signaling in the brain following persistent exposure to stressors is associated with subsequent negative mental health and altered behavior – highlighting inflammation as a link between exposure to persistent psychological stressors and the development of subsequent mental health issues (Miller et al., 2013; Reichenberg et al., 2001; Weber et al., 2017). As summarized by Miller et al. (2013), there are three major pathways by which cytokines can access the brain; 1) the humoral pathway in which circulating cytokines enters the brain through leaky regions of the BBB, e.g., in circumventricular organs where the BBB is incomplete or during BBB disruption, (Dudek et al., 2020; Geng et al., 2018; Menard et al., 2017), 2) the neural pathway involving activation of cytokine receptors on nerve fibers that transduce cytokine signals in the brain (Gougeon et al., 2013; Igaz et al., 2006), and 3) cellular route in which CNS-resident immune cells secrete signals upon activation or chemokines in the CNS

recruit peripheral immune cells (Wohleb et al., 2014; Wohleb et al., 2015; Yin et al., 2019). Cytokines in the brain may then affect neurocircuits by influencing and disturbing the synthesis, uptake, and release of neurotransmitters that are necessary to relay signals between neurons. Despite the important roles of cytokines under physiological conditions, e.g., neurogenesis, and long-term potentiation (Bialas & Stevens, 2013; Prieto et al., 2019), the excessive production, and mal-adaptive functions of cytokines following exposure to persistent stressors may cause low-grade systemic inflammation (Miller et al., 2019). Hence, it is plausible that persistent exposure to stressors, as in ongoing exposure to workplace bullying, causing low-grade systemic inflammation may induce harmful effects on brain activity and result in negative mental health. As a matter of fact, blood analyses of patients suffering from mental health illnesses reported upregulation of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF (Dowlati et al., 2010; Tang et al., 2018; Voorhees et al., 2013).

Furthermore, numerous studies show that exposure to prolonged stressors disrupts neuroplasticity in critical brain regions causing structural changes in the brain, i.e., impaired neurogenesis in the PFC and hippocampus and amygdala hyperactivity (Lakshminarasimhan & Chattarji, 2012; Patel et al., 2018; Radley et al., 2008; Rosenkranz et al., 2010; Vyas et al., 2002). Less connectivity between the PFC and different brain areas following exposure to long-term stressors has been associated with reduced cognitive functions (Arnsten, 2009; Liu et al., 2020; Patel et al., 2018; Yuen et al., 2012). As the neurogenesis in the PFC and hippocampus impair during exposure to persistent stressors, orchestration of the brain responses shift from thoughtful reflective PFC to the more rapid reflexive regulation of the amygdala – a brain structure important for regulating emotions such as fear (Giustino et al., 2020). As such, the hyperactive and highly reflexive amygdala, which is present following chronic exposure to stressors, may easily trigger stress responses when sensing danger.

As described, controlled regulation of neurotransmitters – the key functional molecules in the brain – and neuroendocrine functioning is crucial for optimal brain wellness. Disturbance of neurotransmitter balance in brain neurocircuits may lead to the development of mental illnesses (Miller et al., 2013). Decreased activity in the PFC (Steffens et al., 2003; Taylor Tavares et al., 2008), and hippocampus (Campbell et al., 2004), as well as other regions in the brain that are involved in emotion and reward functioning (e.g., nucleus accumbens (Golden et al., 2013), anterior cingulate cortex (Boes et al., 2008) and lateral septum (Brady & Nauta, 1953)), have been associated with anxiety and depression (Iniguez et al., 2014; Liu et al., 2020). Also, increased activity in the amygdala, which may be related to enhanced negative emotion, has been observed in individuals suffering from depression (Sheline et al., 2001; Zhong et al., 2011).

Prolonged exposure to chronic stressors affects, as mentioned above, neurocircuits in critical brain regions. The disrupted regulation of neurocircuits affect cognition and mood, but may also affect behavior. Several studies report that long-term stressors in the form of workplace bullying are related to sleep problems (Berset et al., 2011; Nielsen et al., 2018), which may partly be explained by increased arousal and prolonged physiological activation (Hansen et al., 2011; Hansen et al., 2006). Sleep problems following persistent exposure to stressors have been associated with dysregulation of cortisol (Cui et al., 2018; Wang et al., 2015). As will be described in the next subsection, the mediators of the HPA axis are equally important for sleep regulation. The hyperarousal state following persistent exposure to stressors may, therefore, affect sleep regulation and cause sleep problems (Fernández-Mendoza et al., 2010; Jansson & Linton, 2007).

1.11.1. Insomnia

The understanding of the many functions of sleep is incomplete, and scientists are working to identify and clarify this phenomenon. However, what is clear is that proper sleep is

necessary for optimal functioning and survival (Freiberg, 2020). An altered state of consciousness in which sensory and motor activity is moderately inhibited may characterize sleep, for review see (Arrigoni et al., 2016; Olcese et al., 2018). Additionally, the bodily systems may during sleep be in an anabolic state – involving metabolic processes that use energy to build molecules from smaller units – in which the immune, nervous, skeletal, and muscular systems are restored and recovered (Lucassen et al., 2017; Mackiewicz et al., 2007; Xie et al., 2013), for review see (Briançon-Marjollet et al., 2015). Accordingly, sleep is essential for positive mental health and well-being.

The sleep system, mainly located in the ventrolateral preoptic area (VLPO), induces sleep through the inhibitory actions of the gamma-aminobutyric acid (GABA)-ergic signaling on the ascending arousal system (Gaus et al., 2002; Saito et al., 2018; Wang et al., 2015), for review see (Saper & Fuller, 2017). This ascending arousal system includes neurons that innervate the thalamus and extends to the hypothalamus and the forebrain (Fuller et al., 2011). The neurotransmitters, i.e., acetylcholine, dopamine, histamine, NE, and serotonin, for review see (Schwartz & Roth, 2008), in the ascending arousal system, stimulates wakefulness and, more importantly, inhibit the sleep system (Luo et al., 2018; Ouyang et al., 2004; Zant et al., 2011). The interaction between neurons in the VLPO and neurons from the ascending arousal system reciprocally inhibits each other and operates as a switch that regulates and stabilizes sleep-wake states, for review see (Saper & Fuller, 2017). As described earlier, exposure to acute stressors induces a state of fight-or-flight in which the individual experiences increase alertness and arousal (Purvis et al., 2018; Qi & Gao, 2020). When exposed to persistent stressors, i.e., workplace bullying, regulatory mechanisms may become mal-adaptive. Exposure to chronic stressors, which is associated with long-lasting activation of the stress response, involves prolonged secretion of NE. The persistent secretion may be related to enhanced activation of the ascending arousal system and deactivation of the sleep system – dysregulation of the sleep-wake system – that may advance into sleep problems.

Insomnia is one of the common sleep disorders and involves difficulty in sleep onset, maintenance of sleep, and early morning awakening (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013). The initial stages of sleep involve a reduction of the ACTH and cortisol levels, and this reduction suppresses HPA axis activity, for review see (Baillien et al., 2009; Balbo et al., 2010b). In the later stages, before awakening, HPA axis activity increases, which is evident by enhanced ACTH and cortisol levels (Akerstedt, 2006; Wilhelm et al., 2007), also see for review (Balbo et al., 2010a). As the pathways stimulating wakefulness needs to be inhibited for sleep to occur, it is plausible that elevated activation of the stress pathways, SNS and HPA axis, interfere with the sleep system (Irwin et al., 2016; Rodenbeck et al., 2002).

Despite the dysregulation of sleep systems in the brain following persistent exposure to stressors, the causes of sleep problems are complex and may be multifactorial. However, several studies have now established exposure to workplace bullying as an important precursor for sleep problems (Linton et al., 2015; Litwiller et al., 2017; Nielsen, Harris, et al., 2020; Nielsen et al., 2018). Worrying and rumination, following exposure to workplace bullying, has been demonstrated to be disruptive to sleep (Berset et al., 2011). Sleep problems may in itself also cause further health problems such as anxiety, depression, or other somatic health complaints. As such, sleep problems may be both an outcome and a mediating variable (Nielsen, Harris, et al., 2020). Further examination of these two variables, i.e., exposure to workplace bullying and sleep problems, may help us understand the impact of workplace bullying on other outcomes.

1.11.2. Anxiety

The amygdala is a brain region consisting of multiple interconnected nuclei. It is part of the limbic system and is associated with emotional processing, e.g., fear and other aversive stimuli, but also positive emotion such as reward (Adhikari et al., 2015; Cunningham &

Kirkland, 2013). The amygdala has direct and indirect connections with many brain regions, for review see (Janak & Tye, 2015). The dynamic interactions between the amygdala and PFC are important under physiological conditions in which the PFC limits the activity of the amygdala to prevent inappropriate emotion expression (Motzkin et al., 2015; Quirk et al., 2003; Rosenkranz & Grace, 2001), as previously described.

The symptoms of anxiety, which involves excessive feelings of nervousness, fear, and worry, seem to be a result of dysregulation of amygdala activity. As described earlier, chronic stressors have shown to cause structural alterations of the brain in which neurodegeneration occurs in the PFC and hippocampus, whereas the opposite occurs in the amygdala (Felix-Ortiz et al., 2016; Liu et al., 2020; Patel et al., 2018; Zhang et al., 2019), for review see (Roozendaal et al., 2009). Consequently, exposure to chronic stressors impairs the control of PFC on amygdala activity, and the hyperactive amygdala takes charge.

Moreover, the imbalance of monoamine neurotransmitters in the amygdala, i.e., dopamine, serotonin, and NE, may affect the monoaminergic system – systems involved in the regulation of emotion, arousal, and memory – and has been evident in mental health illnesses such as anxiety (Martin et al., 2009). For instance, elevated levels of NE is associated with symptoms of anxiety (Purvis et al., 2018). Also, the insufficiency of the inhibitory neurotransmitter GABA, which is highly necessary to sustain the inhibitory control of the amygdala under resting state, may explain symptoms of mental illnesses (Almeida-Suhett et al., 2014; Sanders & Shekhar, 1995).

As described, the structural changes in critical brain regions, e.g., amygdala and PFC, and disruption of neurotransmitter systems following exposure to chronic stressors may give rise to abnormal and mal-adapted regulation of the amygdala and PFC. The dominating function of the reflexive amygdala may counteract the slow and attentive regulation of the

PFC, which may be associated with mental health problems such as anxiety (Liu et al., 2020). Irrespective of the stress-induced alterations, genetic variations may also have an impact on the susceptibility and vulnerability of developing mental health issues such as anxiety from ongoing stressors such as workplace bullying. Accordingly, the influence of genetic differences should be taken into account when examining the associations between exposure to workplace bullying and negative mental health, here in the form of anxiety.

1.12. Genetic factors

Although exposure to stressors activates the stress response, there may be individual differences. The subject's appraisal of the situation and coping strategies may influence the effect of bullying on health and well-being (Hewett et al., 2018). These inter-individual variations may again be explained by genetic differences.

Genetic variation between individuals is the presence of differences in the DNA sequence that constitute the genome. Genetic variation is caused by variation in the order of which the bases are incorporated in the DNA sequence. Such variation includes single nucleotide polymorphisms (SNPs), insertions, deletions, and rearrangements. Some genetic polymorphisms, also called mutations, do not change the amino acid sequence of the protein and are therefore called synonymous mutations. Other genetic polymorphisms do change the amino acid sequence of the protein and are referred to as nonsynonymous mutations (Yang & Nielsen, 2000).

A SNP is defined as a single nucleotide substitution occurring in a specific position in the genome and is presented at more than 1 % in the population. SNPs are stable, highly abundant, and distributed throughout the genome, for review see (Fareed & Afzal, 2013; Shastry, 2002). Such variation is associated with diversity in the population, susceptibility, and vulnerability to diseases and individual responses to drugs, for review see (Shastry,

2002). Earlier findings show that individual genetic differences may affect susceptibility to stress (Cousijn et al., 2010).

SNPs occur in genes, including those coding for microRNAs (miRNAs), which are small non-coding RNA molecules that have important protein regulatory functions (Harnprasopwat et al., 2010; Sun et al., 2009). Such miRNAs are 21-22 base pairs in length and suppress gene expression by binding to complementary strands on mRNA molecules, thus preventing translation and production of proteins (El Gazzar et al., 2011). Moreover, the miRNA molecule may even induce degradation of the mRNA molecule through binding to proteins belonging to the Argonaute family – a process called RNA interference (Hammond et al., 2000; Meister et al., 2004). Despite the size of these miRNA molecules, they operate complex regulatory mechanisms that one still lacks knowledge around. However, what is clear is that among the many targets of miRNAs, many of them are involved in inflammatory processes (Davis et al., 2012; H. M. Lee et al., 2016; Lopez et al., 2014; Smalheiser et al., 2012). As such, it may not be surprising that these regulatory molecules may be of importance in chronic stress conditions.

Extracellular miRNAs are found in most bodily fluids, and their aberrant expression is generally observed in diverse diseases and altered physiological states. Previous studies show that the regulation of miRNAs in the circulation may be affected by exposure to stressors (Gidron et al., 2010). Moreover, sympathetic (Hou et al., 2012) and glucocorticoid (Smith et al., 2010) signaling has been shown to affect miRNA expression in the target tissues. Furthermore, several findings, including our own (Jacobsen et al., 2019), suggest that these regulatory miRNA molecules exert important functions peripherally (Pauley et al., 2008; Shu et al., 2019), but also in the CNS – directly or indirectly at the neuro-immune interface (Andolina et al., 2016; Li et al., 2019; Satoorian et al., 2016; Smalheiser et al., 2012). Previous studies also suggest that dysregulation of miRNAs may be associated with mental disorders such as anxiety (Andolina et al., 2016; Haramati et al., 2011), depression

(Lopez et al., 2014; Smalheiser et al., 2012) and sleep problems (Davis et al., 2012; Goodwin et al., 2018). As such, it may be of value to examine genetic variations in regulatory molecules, i.e., miRNAs, which may have functional effects on important biological mechanisms that are affected by persistent exposure to stressors.

2. Aims of the thesis

In spite of the massive global volume of the workplace bullying literature (Einarsen, 2020), few studies address the "how and when" of bullying in its causal relationship to other variables, in our case mental health variables (Nielsen & Einarsen, 2018; Rai & Agarwal Upasna, 2018). For example, the use of questionnaires may provide valuable information about the association between exposure to bullying and the outcome but is implausible to identify causative processes. In addition, it is impossible to harvest tissues to examine the physiological effects of bullying on tissues such as the brain, spleen, and BM from humans.

In this thesis, we, therefore, try to overcome these shortcomings by integrating data from a human study, an animal model, and in vitro cell culture experiments. Earlier observations show that bullying in humans is a strong environmental stressor. Moreover, data from our group show that the resident-intruder paradigm that leads to social defeat in animals may induce behavioral and physiological changes (Jacobsen et al., 2019) that could help to get a better understanding of the health effects of such psychological stressors.

Recent data from our lab show that repeated social defeat increases the expression of several miRNAs (Jacobsen et al., 2019). One of these small non-coding RNAs is the miR-146a – a miRNA playing a central role in inflammation (Saba et al., 2014). In paper I, we follow-up this and address the role of miR-146a on the association between bullying, inflammation, and insomnia in humans.

Also, since bullying is a dynamic process, the use of cross-sectional or longitudinal study designs may not address the development, escalation, and de-escalation of the bullying phenomenon. To understand the causal effects of bullying on physiological and psychological processes, laboratory experiments under controlled conditions may be

necessary. In paper II the effect of repeated social defeat in animals under controlled conditions was examined to address the causal nature between bullying and its correlates.

Since NE is one of the central mediators in the stress response, it was also of interest to investigate the biological mechanisms of its receptor, β2-adrenergic receptor (ADRB2). Previous research shows that psychological stressors such as exposure to bullying in humans and repeated social defeat in animals may result in strong activation of the sympathetic nervous system and activation of the peripheral ADRB2 (Araujo et al., 2019; Powell et al., 2013). In paper III, using three different models; in vivo, in vitro, and in humans, we, therefore, address the effect of these psychological stressors on the function of the ADRB2 receptor.

The overarching aim of this thesis was to investigate behavioral, neuroendocrine, and immunological changes following exposure to stressors in the form of workplace bullying in humans and repeated social defeat in rats, which may provide essential information for further understanding of the effects of bullying exposure in humans. More specifically, we aimed to:

1. Investigate the association between exposure to workplace bullying and insomnia, moderated by the miR-146a genotype rs2910164 – a central regulator during inflammation.

2. Examine behavioral and physiological changes in rats following exposure to repeated social defeat using a resident-intruder paradigm, as an essential animal model employed to possibly better understand the effects of bullying exposure in humans. In this we will:

    a. Examine behavioral consequences of exposure to repeated social defeat employing a social interaction test.

b. Examine expression of genes central in the HPA axis, i.e., Nr3C1 (glucocorticoid receptor), POMC (ACTH precursor), and MC2R (ACTH receptor) in the pituitary and adrenal gland.

c. Examine gene expression of β_2-adrenergic receptor (ADRB2), β-arrestin-2 (ARRB2), and interleukin-6 (IL-6) in isolated myeloid cells from rat spleen.

3. Examine the behavioral consequences of exposure to stressors, in the form of repeated social defeat in rats and workplace bullying in humans, concerning the β_2-adrenergic receptor ADRB2 using three different models; in vivo, in vitro, and in humans.

   a. Examine changes in the β_2-adrenergic receptor gene expression in rats exposed to social defeat.

   b. Examine norepinephrine- and/or dexamethasone-induced changes in the β_2-adrenergic receptor gene expression in a human macrophage cell line (EL-1).

   c. Investigate the association between exposure to workplace bullying and anxiety, moderated by the β_2-adrenergic receptor genotype rs1042714 in a human cohort.

3. Methods

The thesis was based on human, animal, and in vitro cell culture data. The human arm of the project allowed us only to investigate associations between exposure to workplace bullying and health outcomes, and not the causal relationships between workplace bullying and other variables. Hence, an animal model of repeated social defeat was implemented to study the cause-effect relationships between exposure to persistent stressors and the physiological and behavioral changes. Although animal studies may provide valuable information about causative processes in disease states, verification in humans are compulsory (Hackam & Redelmeier, 2006). The in vitro cell culture experiments were performed to investigate the physiological changes in more detail at the cellular level and to support the in vivo findings. Below is a summary of the methods used, and further details may be found in the respective studies.

3.1. Human cohort

A random sample of the Norwegian working population was used to perform the human analyses included in this thesis. With help from Statistics Norway, a total of 5000 subjects between the ages of 18 to 60 from The Norwegian Central Employee Register were randomly selected. The questionnaires were sent through the Norwegian Postal Service, and those of the subjects who gave consent (32 %, 1608 persons) were sent saliva collection kits. Among these, 1204 persons returned their saliva samples. The data were collected at three time points (T1, T2, and T3) over 18-20 months. However, in paper I and III, only the T2 data were analyzed due to a higher rate of missing data in T1 and T3. Finally, 1179 and 1090 subjects were included in paper I and III, respectively.

3.1.1. Control variables

Age (Christensen et al., 1999) and gender (McLean et al., 2011) are variables expected to impact bullying and health. Thus, the T2 measures of these variables were included as control variables in the respective studies.

3.1.2. Exposure to bullying behaviors

Exposure to bullying behaviors at work was measured with the 9-item version of the Negative Acts Questionnaire-Revised (NAQ-R) (Einarsen et al., 2009). This instrument measures exposure to negative and unwanted behaviors during the last six months – of a personal and a work-related nature – that may typically be perceived as bullying when occurring systematic and over time. The items are formulated in behavioral terms and do not present the definition of bullying. Response categories range from 1 to 5 ("never," "now and then," "monthly," "weekly," and "daily"). Cronbach's alpha values, measuring the internal consistency of the items, for this scale was .86 at T2.

3.1.3. Insomnia

The three items reflecting problems with sleep onset, maintenance of sleep, and early morning awakening was used to assess insomnia. The response categories ranged from 1 to 4 ("not bothered," "a little bothered," "considerably bothered," and "seriously bothered"). A composite insomnia score was calculated by adding the score of the three items and dividing the sum by three. The Cronbach alpha for the insomnia scale was .81 in the present study.

3.1.4. Symptoms of anxiety

Five items from the Hopkins Symptom Checklist (HSCL-25) reflecting typical symptoms of anxiety, i.e., "feeling fearful," "nervousness or shakiness inside," "heart-pounding or racing," "trembling" and "feeling tense or keyed up" during the last week were used. Response categories ranged from 1 to 4 ("Not at all," "a little," "moderately," "extremely"). Cronbach's alpha for this scale was .74.

3.1.5. Genotyping

Genomic DNA was extracted from collected saliva samples using an OrageneRNA sample collection kit. SNP genotyping for rs2910164 (paper I) and rs1042714 (paper III) was carried out on a Quantstudio 5 machine, using predesigned TaqMan SNP genotyping assays. Both the miR-146a rs2910164 genotype (GG versus GC/CC) and the ADRB2 rs1042714 genotype (CC versus CG/GG) were included as a dichotomous variable.

3.2. Animal studies

The Norwegian Food Safety Authority approved all animal experiments (application ID: 11671), and the experiments were performed in conformity with the laws and regulations controlling experiments and procedures on live animals in Norway.

A resident-intruder paradigm was applied to study exposure to repeated social defeat in animals. Ten outbred (retired breeders) Long Evans rats (500-550 g) were used as residents, each living with their companion female (200-250 g), (Envigo; USA) in a purpose-made 0.56 m^2 cage. Ten male Sprague Dawley rats (300-400 g) were used as intruders, and ten as controls (Janvier Labs; France), and they were all housed in pairs in a separate room at

the animal facility. All animals were acclimatized to an artificial 12 h light/ 12 h dark cycle for two weeks before the start of the stress conditioning week.

3.2.1. Resident-intruder paradigm

A screening procedure to ensure the dominant behavior of Long Evans males was performed before the stress conditioning week. The rats were selected based on the highest frequency of attacks within 10 minutes of interaction.

One hour before the stress conditioning, the female Long Evans rats were removed from the resident cage. One hour later, the Sprague Dawley rats were placed in the resident cage. The social defeat was defined as submissive supine posture, flight, or freeze behavior (Miczek, 1979). Upon social defeat, or after 10 minutes, the resident and the intruder rat were separated by a perforated plastic wall for one hour. As such, the rats would still be able to smell, see, and hear each other (Figure 2). The intruder rats were introduced to a new resident rat each day of the stress conditioning week to prevent habituation to the dominance establishment with the resident rat. Ten Sprague Dawley rats that served as controls were placed into new empty cages in another room for one hour each day.

During the stress conditioning week, latency until defeat was registered. A median split (75 sec) was used to define the stress exposed subgroups in which long latency (LL) and short-latency (SL) were those who showed defeat behavior later and before 75 sec, respectively.

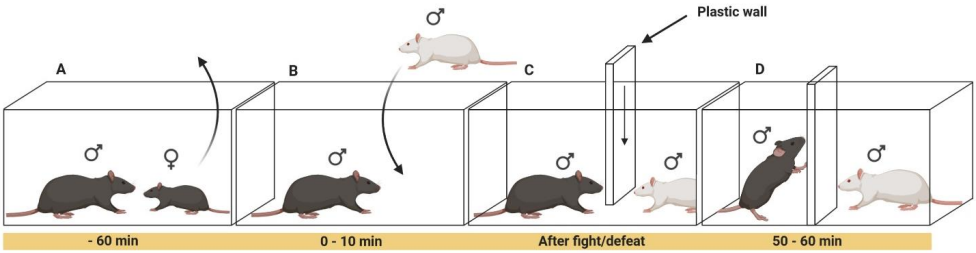

Figure 2. Resident-intruder paradigm. (A) The Long Evans females were removed from the resident cage 60 minutes before the experiment. **(B)** An intruder Sprague Dawley rat (white) was placed in the home cage of a resident male Long Evans rat (black). **(C)** Upon social defeat or after 10 minutes of interaction, a perforated plastic wall was used to separate the resident and intruder rats. **(D)** Sensory interaction was allowed for the remaining time. Both the male Sprague Dawley rat and the female Long Evans rat were returned to their home cages (Illustrated by Nymoen, I.).

3.2.2. Social interaction test (SIT)

A modified version of the social interaction test was implemented to assess the social interaction behavior of the stress-induced Sprague Dawley rats (Kaidanovich-Beilin et al., 2011). The arena was a purpose made box (0.56 m^2) divided into three compartments that were separated by two gated plastic walls. A small wire-like container was placed in each flanking compartment (Figure 3).

The test rat was placed in the middle compartment and allowed for habituation for four minutes. Then, a novel rat of the same strain (did not take part in the resident-intruder paradigm) was placed into one of the containers. The subsequent gates were opened, allowing the rats to move freely between the three compartments for six minutes. The movement and behavior of the rats were recorded by a camera placed above the box. The changes in behavior were examined later by a purpose-made software program (programmed and developed in C by our group).

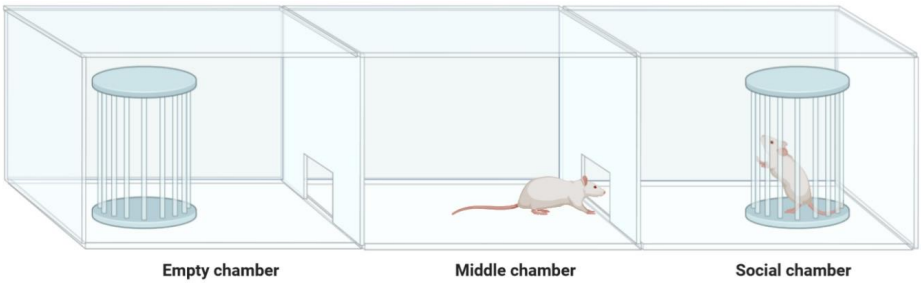

Figure 3. Social interaction test. The test was used to assess behavioral changes following one week of exposure to repeated social defeat. The test arena consisted of a box separated into three chambers by gated plastic walls. The test rat was allowed to habituate the middle chamber for four minutes. Then, a novel rat of the same strain was placed in a small wire-like container in one of the flanking compartments. Subsequently, the gates were opened for six minutes, allowing the test rat to explore all parts of the box. The movement was recorded for later analyses. The figure was created in Biorender.

3.2.3. Blood sampling and tissue harvesting

Following the SIT and one hour of rest in their home cages, the Sprague Dawley rats were sedated with 5 % isoflurane in air in a gas box before being moved to a 3 % isoflurane anesthetic mask. The absence of withdrawal reflexes was considered as adequate for surgery.

Fixation of the animal in a dorsal recumbence position, and a v-cut through the skin and abdominal wall and subsequent opening of the thoracic cage exposed the heart and enabled blood withdrawal. Portions of the blood were immediately placed in liquid nitrogen and sent to the Norwegian Institute of Public Health (NIPH) for analysis of NE and CORT levels (Bergh et al., 2018).

Following euthanasia by dislocation of the neck, tissues such as the pituitary gland, adrenal glands, spleen, and BM were harvested and frozen on liquid nitrogen and later frozen at – 80 ^{o} C for later analyses, e.g., gene expression analyses (qPCR).

3.2.4. Enrichment of splenic myeloid cells

The harvested spleen tissue was processed and homogenized to make a single-cell suspension. Isolation of mononuclear cells was by density centrifugation, and subsequent labeling of a myeloid cell-specific marker, OX41 (SIRP α), enabled purification of myeloid cells from the rest of the mononuclear cell fraction. The immuno-magnetic bead separation allowed only OX41-biotin positive cells to bind to the streptavidin coupled magnetic beads through biotin-streptavidin interaction. The final cell suspension consisting of OX41 positive myeloid cells were further quality controlled by a multicolor flow cytometry analysis (details may be found in the paper). Due to potential unspecific antibody binding, cell-type-specific surface markers for B cells, T cells, and NK cells were used to detect possible contamination in the myeloid cell-enriched samples.

3.3. Cell culture experiments

The human macrophage cell line EL-1 was seeded as suspensions of 0.5 x 10^{6} cells/well in 6 well plates and exposed to 100 nM NE for 24 h and/or 100 nM DEX for 3 h. After 24 h, cells were separated from the surrounding medium by centrifugation. The conditioned medium was collected, and the cell pellet was directly lysed prior to storage at – 80^{o} C. RNA was isolated from lysed cells to perform gene expression analyses of the ADRB2 gene. Luminex analysis of the conditioned cell medium was performed to measure cytokine release from EL-1 cells.

3.4. Statistical analyses

3.4.1. Human data

Statistical analyses were conducted with IBM SPSS 25.0 and PROCESS v3.1 (paper I and III). The level of significance was set to $p<0.05$. Exposure to bullying behaviors at work, insomnia, and symptoms of anxiety were calculated as the mean score of the nine items in the NAQ inventory (paper I and III), the three items reflecting sleep problems (paper I) and the five items in the HSCL inventory (paper III), respectively.

To investigate the mediating and moderating effects on the association between exposure to bullying behaviors and subsequent sleep problems (paper I), a moderated mediation regression analysis was conducted (PROCESS, model 14). Here, we tested for the linear associations between exposure to negative social acts and insomnia via distress and the interaction between distress and miR-146a genotype rs2910164 (GG versus GC/CC) with regard to insomnia. Likewise, moderation analysis was conducted (PROCESS, model 1) to test for interactive effects of exposure to negative social acts and the ADRB2 genotype rs1042714 (CC versus CG/GG) with regard to anxiety (paper III).

3.4.2. Animal data and in vitro cell culture experiments

The data were shown by representative examples and mean ± standard error of the mean. Statistical analyses were conducted with Sigmaplot 14.0, and the level of significance was set to $p<0.05$.

In paper II, the differences in body weight, social interaction, locomotion, gene expression levels, and differences in the percentage of splenic myeloid cells between exposed and control groups were analyzed using Student's t-test.

In paper III, the in vivo data of the rats were analyzed with linear regression (Sigmaplot 14.0), whereas the in vitro data from EL-1 cells were analyzed by linear mixed models (StataCorp 2019. College Station, TX: StataCorp LLC). In all mixed models, treatment was included as a fixed effect, with control as a reference category. Furthermore, all mixed models included a random intercept for triplicates to take into account the dependency between these observations.

4. Results

4.1. Paper I

Based on the established link between stress-induced inflammation and sleep, and the fact that miR-146a has a central role in inflammation, we wanted to address the role of miR-146a genotype rs2910164 on the relationship between workplace bullying and insomnia through distress. As elaborated in the paper, the G allele was associated with low expression levels of the anti-inflammatory miR-146a. Thus, it was hypothesized that the miR-146a rs2910164 G allele would strengthen the relationship between exposure to workplace bullying and insomnia through distress.

The direct associations between the predictor and outcome variable demonstrated a significant association between exposure to workplace bullying and insomnia, after adjusting for age and gender ($b = 0.55$; $p < 0.001$). When including the mediator (distress) and the moderator (miR-146a GG versus GC/CC genotype) in the analyses, the findings demonstrated that exposure to workplace bullying had an indirect association with insomnia through distress. An interaction term showed that this indirect effect was stronger among individuals with the GG genotype (B = 0.31; 95 % CI: 0.23 – 0.41) compared with individuals with the GC/CC genotype (B = 0.16; 95 % CI: 0.08 – 0.023).

Thus, the moderated mediation analysis demonstrated that exposure to negative social acts was indirectly associated with insomnia, through distress in which individuals with the miR-146a GG genotype had a strengthened effect on the indirect relationship between exposure to negative social acts and insomnia compared with individuals having the GC/CC genotype. The present study, therefore, emphasizes the importance of taking biological factors into account since genetics causes individual differences in vulnerability and

susceptibility to diseases and may be of importance during treatment and rehabilitation of targets of bullying.

4.2. Paper II

The aim of paper II was to examine the physiological and behavioral effects of exposure to persistent stressors, i.e., workplace bullying. For this reason, an animal model of repeated social defeat was conducted. While ten Sprague Dawley rats were exposed to a resident bully rat for one hour each day for one week, ten control rats were placed in empty cages.

The resident-intruder paradigm changed the behavior of the intruder rats as the number of rats demonstrating subordinate defeat behavior increased for each passing day. Behavioral assessments (SIT) following the conditioning week showed increased locomotion in stressor exposed rats compared with control rats. Moreover, the resident-intruder paradigm significantly attenuated body weight gain in stress exposed rats compared with control rats. Gene expression analyses of isolated myeloid cells from the spleen showed significant downregulation of the ADRB2 and β-arrestin-2 (ARRB2), and an increase in IL-6 expression in stress exposed rats compared with control rats.

Overall, these results suggest that exposure to repeated social defeat in rats is a potent stressor that triggers neuroendocrine and immunological changes that may affect behavior.

4.3. Paper III

The aim of paper III was to examine the behavioral consequences of exposure to stressors concerning the NE targeted receptor, ADRB2. This paper was partly a follow-up of the ADRB2 findings in paper II. The reduced expression level of ADRB2 on enriched myeloid

cells from the spleen was further examined and supported by genotyping analyses on the human cohort and in vitro cell culture experiments using the EL-1 cell line.

When subgrouping the rats exposed to stressors in two, with respect to latency until defeat, the expression of ADRB2 in isolated myeloid cells from rat spleen gradually decreased with increasing stress exposure, i.e., SL subgroup < LL subgroup < control group. Median split (75 sec) was used to define the stressor exposed subgroups; long latency (LL), and short-latency (SL). Similarly, data from the in vitro cell culture experiments showed that cells exposed to NE and DEX – stress hormones of the SNS and HPA axis, respectively – showed a decrease in ADRB2 expression compared with control cells. Moreover, the analyses of secreted cytokines in the external environment of the cell showed a significant increase of MCP-1 levels following NE and DEX treatment compared with cells in the control condition.

Furthermore, analyses of the human data, concerning the ADRB2 genotype rs1042714, showed a significant linear association between exposure to negative social acts and anxiety. Interestingly, the inclusion of the interaction term (NAQ*ADRB2 genotype) revealed a moderating effect in which subjects with the CC genotype had a stronger relationship between exposure to negative social acts and anxiety compared to carriers of the G allele. As elucidated in paper III, prolonged exposure to NE, as in the case of prolonged activation of the SNS, is associated with low membrane-bound receptors and attenuated immunosuppression. As such, these data suggest that the G allele (retain more membrane-bound receptors during long-term NE exposure) contributes to the maintenance of the NE driven immunosuppressive processes, thus dampening the damaging health effects that are promoted by persistently activated inflammatory processes.

To sum up, the study shows that exposure to persistent social stressors trigger the immune system through an ADRB2 associated mechanism and also links the low membrane-bound

ADRB2 rs1042714 C allele genotype to stress-induced anxiety. The findings suggest that exposure to workplace bullying may promote anxiety and threaten well-being through an ADRB2 associated mechanism.

5. Discussion

The central objective of this thesis was to understand the mechanisms underlying the consistently observed detrimental health effects of bullying behaviors by employing human data, animal data, and in vitro cell culture experiments. This section comprises a general discussion of the main findings in the three papers and will also include methodological considerations, implications, and suggestions for future research.

5.1. Discussion of results

5.1.1. Insomnia and miR-146a genotype (paper I)

The findings in paper I show that the relationship between exposure to workplace bullying and insomnia through distress is moderated by the miR-146a genotype in which the magnitude of this relationship is strengthened in individuals with the miR-146a genotype GG compared with those having the GC/CC genotype.

The comprehensive understanding of the workplace bullying phenomenon and its associations to variables such as insomnia may be multifactorial and is far from completely understood. However, based on theoretical reasoning, it is conceivable that both the perspective of the world as meaningful and benevolent and the views of self as worthy and capable of controlling external events may be challenged in targets of bullying (Hamre et al., 2020; Mikkelsen & Einarsen, 2002; Rodríguez-Muñoz et al., 2010). When these fundamental thoughts are contradicted, such situations may easily cause worries and rumination, and it can be challenging to avoid thinking about the negative experiences (Finne et al., 2011; Kivimäki et al., 2006). Such mental distress has already been proposed as a risk factor for sleep problems (Fernández-Mendoza et al., 2010) and as an intervening

factor in the relationship between workplace bullying and sleep problems (Berset et al., 2011; Magee et al., 2015; Nielsen, Harris, et al., 2020).

As previously described, prolonged activation of the stress response systems, i.e., SNS and HPA axis, following persistent exposure to psychological stressors such as in the case of workplace bullying, has been associated with dysregulation of neurocircuits in the brain (Radley et al., 2008; Zhang et al., 2019), for review see (McEwen, 2017; Radley et al., 2015). Also, findings in rodent models demonstrate dysregulation and excessive production of inflammatory cytokines following exposure to chronic stressors (Miller et al., 2013; Sawicki et al., 2019; Zhang et al., 2019), for review see (Wohleb et al., 2015). This allostatic overload may lead to chronic inflammatory conditions in the body – low-grade systemic inflammation – that has been associated with sleep problems (Motivala, 2011). Moreover, genetic variability may explain differences in coping strategies as well as the differences in vulnerability and susceptibility to diseases (Hewett et al., 2018; Vie et al., 2012). Therefore, studying genetic variation regarding the bullying-health relationship may be of importance with respect to clinical purposes, e.g., treatment and rehabilitation of targets of bullying. Based on the reasoning above, i.e., the link between stress-induced inflammation and sleep, there were grounds to examine the role of miR-146a rs2910164 in the relationship between exposure to workplace bullying and insomnia through distress.

As elucidated in paper I, the miR-146a is well-known for its anti-inflammatory effects during the innate immune response where it acts as a molecular brake on the NF-κB signaling pathway (Gao et al., 2015; Hou et al., 2009; Li et al., 2015). Examinations of the prefrontal cortex (PFC) of depressed suicide victims have reported reduced levels of miR-146a (Smalheiser et al., 2012), suggesting that miR-146a may be involved in stress-induced mental health disorders. MiR-146a expression levels in monocytes have been reported to be lower in patients with major depressive disorder (Hung et al., 2019). Moreover, reduced levels of circulating miR-146a were reported in patients suffering from insufficient sleep

compared with control groups (Hijmans et al., 2019). These findings suggest that dysregulation and, more specifically, the insufficiency of the miR-146a may contribute to increased inflammatory conditions in the body, which may lead to allostatic overload in which biological processes involved in sleep regulation become mal-adaptive.

Among the many targets of miR-146a, nitric oxide synthase 1 (NOS1) – an enzyme responsible for nitric oxide (NO) production – is also one (Perske et al., 2010; Zhang, Huo, et al., 2018). NO is a signaling molecule produced by macrophages and other immune cells and governs a diversity of processes in the immune system involving differentiation, proliferation, and apoptosis of immune cells, for review see (Bogdan, 2001). In contrast to cytokines, which exert their effector functions through receptor binding, NO may also react with structures in the DNA, inorganic groups (e.g., oxygen) or prosthetic groups (e.g., heme) and thereby exert a broad range of effects, for review see (Bogdan, 2001). Also in the CNS NO may under physiological levels be neuroprotective, i.e., promote neuronal proliferation, survival, and differentiation (Carreira et al., 2015; Sülz et al., 2009), while excessive levels of NO may be neurotoxic (Nakaizumi et al., 2012), indicating its importance in neuropsychiatry, for review see (Calabrese et al., 2007; Chen et al., 2015). Accordingly, the miR-146a has a significant regulatory role during inflammation that may affect both the central and peripheral immune systems. Since the regulatory effects of miR-146a may become disrupted following chronic exposure to stressors, the fine-tuning of the innate immune response may be impaired. The absence of the anti-inflammatory mechanisms exerted by miR-146a may result in low-grade systemic inflammation. Neuroinflammation, due to increased levels of pro-inflammatory cytokines and excess levels of NO in the brain, following persistent exposure to stressors may cause dysregulation of neurocircuits and neurodegeneration that may affect mental health and behavior (D. W. Lee et al., 2016; Miller et al., 2013; Zhang et al., 2019).

Chronic exposure to psychological stressors is associated with prolonged activation of the SNS and the HPA axis (Lowrance et al., 2016; Raone et al., 2007; Ulrich-Lai et al., 2006; Zhou et al., 2018). The stress response becomes continuously active, resulting in a hyperarousal state, which may affect sleep regulation (Fernández-Mendoza et al., 2010; Jansson & Linton, 2007; Lorton et al., 2006). The chronic stress condition may burden the physiological and psychological processes in the body, i.e., allostatic overload, leading to mal-adaptation (McEwen, 2000). While these mal-adaptations may occur irrespective of genetics and personal coping strategies (Nielsen et al., 2017), genetic variation may explain why some individuals may tolerate more than others. The findings in this paper demonstrated that individuals with the miR-146a GG genotype have a strengthened association between exposure to workplace bullying and insomnia through distress compared to individuals with miR-146a GC/CC genotype. Overall, this paper emphasizes the importance of acquiring knowledge about genetic variations, which may also be essential to understand the underlying biological aspect of the outcomes of bullying.

5.1.2. Resident intruder paradigm (paper II)

The animal study in the present thesis intended to improve our knowledge about causal relationships between exposure to workplace bullying and associated health-related variables. The animal model of repeated social defeat incorporates the main features of the bullying definition, i.e., the negative behaviors are repeated and persistent over a long period, and there is a power imbalance between the two parties involved (Einarsen et al., 2011), which is parallel to what is seen in targets of systematic and long-term bullying (Einarsen, 2020; Hamre et al., 2020). As such, the resident-intruder paradigm served as a suitable model to resemble the bullying situation in humans. Moreover, the time scale of normal biological processes is different in humans and rats (one rat day is around 27 human days) wherein rats live shorter and accelerated lives (Agoston, 2017). This allows for a more rapid observation of the physiological and psychological consequences of workplace

bullying, which takes weeks and months in humans. Hence, the different time scales need to be considered during the translation of experimental findings to humans.

The resident-intruder paradigm conducted in this study demonstrated stress-induced physiological and behavioral changes in the form of increased defeat behavior throughout the stress-conditioning week (for each cycle of social defeat), which suggests that the implemented paradigm was successful. It may also indicate that this animal model of repeated social defeat had some resemblance to an on-going bullying situation where one's ability to defend is gradually reduced, in which the inability to defend is one of the main criteria in the definition of workplace bullying (Einarsen, 2020). Reduced weight gain and changes to the stress response system, i.e., reduced pro-opiomelanocortin (POMC) and increased Nr3c1 (glucocorticoid receptor) expression in the pituitary, were furthermore observed in stress-exposed rats. The isolated myeloid cells from the spleen showed reduced ADRB2 and ARRB2 as well as an increased IL-6 expression, demonstrating a pro-inflammatory profile of the isolated myeloid cells.

Earlier findings in murine models show that stress-induced physiological and behavioral changes may be cycle-dependent, i.e., it increases for each stress episode (Wohleb et al., 2011). While increased neuronal activity has been reported in the PFC, hippocampus, and amygdala after one cycle of social defeat, altered glucocorticoid sensitivity in peripheral macrophages, increased microglial activity, and anxiety-like behavior has been demonstrated between cycle three and six of social defeat in rats (Avitsur et al., 2002; Kinsey et al., 2007; Wohleb et al., 2011). Although the understanding of the mechanisms underlying our observation of increased social defeat behavior is out of scope for this thesis, it is theoretically plausible that the reduced tendency to fight back may involve learned helplessness behavior (Landgraf et al., 2015) and enhanced punishment avoidance (Paulus et al., 2003), again something that may resemble what is seen in targets of systematic and long-term bullying (Einarsen, 2020; Hamre et al., 2020).

Supported by our findings, evidence suggests that exposure to repeated social defeat is associated with attenuated body weight gain (Flak et al., 2014; Zelena et al., 1999). This may be explained by the reduced release of growth hormones (Sjörs Dahlman et al., 2019) or altered metabolism following exposure to persistent stressors. Earlier studies demonstrate an increased sucrose preference (Iniguez et al., 2014), increased glucose absorption in the intestine (Toyoda et al., 2015), and altered lipid metabolism (Chuang et al., 2010) following exposure to persistent stressors. Besides being central in the stress response regulation, the hypothalamus is also prominent for feeding behavior, for review see (Elmquist et al., 2005). Since prolonged exposure to stressors may dysregulate hypothalamic activity, it is plausible that the regulation of feeding behavior may be affected as well. These findings imply that the association between exposure to repeated social defeat and bodyweight may be multifactorial.

To study the impact of persistent exposure to social stressors on behavior the Crawley's sociability test – investigating anxiety-like behavior concerning social interaction – was conducted (Iniguez et al., 2014; Kaidanovich-Beilin et al., 2011). Due to methodological challenges, discussed later, a proper assessment of the social behavior was not achievable. However, a significant difference in locomotion between the stress-exposed group and the control group was observed. It is reasonable to believe that the observed increase in locomotor activity may be explained by the structural changes reported to occur in the brain following exposure to prolonged stressors (Liu et al., 2020; Patel et al., 2018; Zhang et al., 2019). Dendritic hypotrophy and synaptic loss in the PFC and hypertrophy of the amygdala following exposure to chronic stressors may support the reported dominating role of the amygdala and lack of the cognitive functions of the PFC, for review see (McEwen et al., 2016). The abnormal functions of the brain may explain the impulsive and hyperactive behavior and the observed increase in locomotor activity among the stress-exposed rats.

The functions of glucocorticoids are diverse and involve the regulation of energetic metabolism, immune suppression, neuronal regulation and behavioral, memory, and emotional adaptation to stressors (Achuthan et al., 2018; Roozendaal et al., 2006; van Donkelaar et al., 2014; Xie et al., 2019), for review see (Vyas et al., 2016). However, persistent exposure to stressors has earlier been shown to disrupt the normal functions of glucocorticoids (Quan et al., 2001), thus weakening its negative feedback function on the HPA axis and its anti-inflammatory effects on the immune system, which may promote low-grade systemic inflammatory conditions (Cohen et al., 2012; Silverman & Sternberg, 2012). The resilience towards exposure to chronic stressors, i.e., coping style, has shown to be reliant on how the neuroendocrine system is activated (Han et al., 2017). Mineralocorticoid receptors (MR) – mainly expressed in the hippocampus – and glucocorticoid receptors (GR) – expressed throughout the brain with higher expression in the hippocampus and the paraventricular nucleus (PVN) – bind to glucocorticoids with different affinities (MRs bind to glucocorticoids with a tenfold higher affinity than GRs) (Brinks et al., 2007) and may as such affect emotion, learning, and memory. The coordinated activation of these receptors and the balance of the MR/GR system seems to be crucial for the emotional and cognitive functioning (Brinks et al., 2007; Calfa et al., 2006; Donley et al., 2005). While MR activation with additional moderate GR activation shows low anxiety and high motivation, MR activation with substantial GR activation may lead to high anxiety, increased arousal, and impaired cognition (Brinks et al., 2007). As exemplified, the physiological effects of glucocorticoids are manifold and play a crucial role in the magnitude of HPA axis activity and the functioning of neurocircuits in critical brain regions, e.g., PFC and amygdala, when exposed to stressors. The dysregulation of glucocorticoids following exposure to chronic stressors may, therefore, cause wear and tear of the body and lead to pathophysiology, e.g., low-grade systemic inflammation, impaired cognition and memory, and mental health disorders.

Our results further show increased Nr3c1 expression (glucocorticoid receptor) in the pituitary gland following one week of exposure to social defeat in rats. This finding may be indicative of an adaptive response in which the glucocorticoids attempt to downregulate key mediators of the HPA axis, such as the POMC (the precursor for ACTH), to reduce the peripheral load of glucocorticoids (Bilodeau et al., 2006). Hence, many of the physiological and behavioral changes observed following exposure to repeated social defeat in rats seem to be related to the mal-adapted regulation of glucocorticoids. Accordingly, further investigation of the role of glucocorticoids in chronic social stress may be valuable.

As described in the introduction, exposure to stressors activate the SNS, which transmits signals from the CNS by utilizing its primary post-synaptic neurotransmitter, NE, to affect immune cell development, inflammatory phenotype and migrational capacity (Bierhaus et al., 2003). Empirical studies show that the binding of NE to adrenergic receptors may induce anti-inflammatory signal transduction[2] through a PKA- and cAMP-dependent pathway, which may suppress NF-κB signaling (Chen & Rothenberg, 1994; Neumann et al., 1995; Sternberg, 2006). The NE binding to its receptor may also, through an ERK 1/2 and MAPK-dependent mechanism, induce the expression of pro-inflammatory cytokines such as IL-6 and TNF-α (Powell et al., 2009). Signal transduction through the ADBR2 may be dependent on the concentration and duration of the NE signaling, for review see (Lorton & Bellinger, 2015). In our study, we observed decreased expression of ADRB2 and ARRB2 – a cytoplasmic adaptor molecule that interacts with ADRB2 but also stabilizes the inhibitor of NF-κB, thus, preventing NF-κB activation – accompanied by increased IL-6 mRNA levels in isolated myeloid cells from the spleen. Persistent NE exposure has been associated with increased desensitization of ADRB2 through decreased expression (Kizaki et al.,

[2] **Signal transduction** – also referred to as cell signaling, is the process by which molecular signals from the cell's exterior is transmitted to the cell's interior to generate cellular responses such as changes in enzyme activity, gene expression or ion-channel activity.

2008) and/or increased internalization[3] (Hadcock & Malbon, 1988). Reduced levels of ARRB2 may further lead to increased NF-κB translocation to the cell nucleus and increased transcriptional activity of NF-κB, which could explain the observed increase in IL-6 expression. These findings suggest that long-term NE signaling, as a result of exposure to repeated social defeat in rats, disrupt normal ADRB2 functioning. Fewer ADRB2 at the cell membrane, thus, less anti-inflammatory effects of ADRB2 following prolonged SNS activation may lead to a pro-inflammatory profile of the immune cells. This may eventually lead to a chronic inflammatory condition in the body.

5.1.3. β2 – adrenergic receptor genotype (paper III)

The findings in paper III demonstrated a stress-induced decrease in ADRB2 gene expression in isolated rat splenic myeloid cells. We observed a dose-dependent effect where short-latency animals (rats showing defeat behavior less than 75 sec after being introduced to the resident rat) presented the highest reduction in ADRB2 gene expression compared with control animals. Likewise, the cell culture experiments showed that the NE+DEX treatment – a stimulus resembling the SNS and HPA axis activation – decreased the ADRB2 gene expression and increased the release of MCP-1 from the treated EL-1 cells. Finally, the regression analysis of the human data demonstrated a moderating effect of the ADRB2 genotype rs1042714 on the relationship between workplace bullying and anxiety in which carriers of the C allele had a strengthened association on the bullying-anxiety relationship compared with carriers of the G allele.

The bidirectional communication between the central nervous system (CNS) and the immune system is well recognized (Lorton et al., 2006; Niraula et al., 2018; Wohleb et al., 2014; Yin et al., 2019), for review see (Reader et al., 2015; Wohleb et al., 2015). Both NE

[3] **Receptor internalization** – A process that results in the movement of receptor from the plasma membrane to the inside of the cell.

and glucocorticoids released from the CNS stimulate immune cells and trigger activation of inflammatory processes (Cohen et al., 2012; Miller et al., 2008; Powell et al., 2013; R. Yang et al., 2014). Since NE exerts its effects through binding to adrenergic receptors, it was of interest to understand the mechanisms of the ADRB2 as they are abundantly expressed on immune cells.

Earlier studies have demonstrated that long-term NE exposure induces receptor desensitization to reduce the cellular response, thus, impeding overactivation of the immune response (Green et al., 1994; Hadcock & Malbon, 1988), for review see (Lorton & Bellinger, 2015). Therefore, it was reasonable to believe that lack of anti-inflammatory signaling due to less membrane-bound ADRB2 may be associated with anxiety (Wohleb et al., 2011). Supportive of the earlier findings, our animal and cell culture experiments demonstrated NE-induced decrease of the ADRB2 receptor expression. Moreover, analyses of the human data showed that the ADRB2 genotype rs1042714 affecting the levels of membrane-bound ADRB2 had a moderating effect on the bullying-anxiety relationship. Moreover, individuals with the rs1042714 C allele had a significantly stronger association on the bullying-anxiety relationship as compared with G allele carriers. Again, information about genetic variation demonstrates how some individuals might be more resilient than others when exposed to psychological stressors. Also, such studies may provide some insight into the mechanism of how the receptor operates during chronic stress conditions.

5.1.4. Summary of the discussion of results

Taken together, exposure to persistent psychological stressors in the form of workplace bullying in humans or repeated social defeat in rats induces a state of inflammation. Insufficient anti-inflammatory signaling due to the missing “breaks” of the SNS and HPA axis, i.e., parasympathetic activity and negative feedback functions of glucocorticoids, may be a consequence of chronic exposure to stressors that causes overload on the adaptive

mechanisms of the body. Failure of the adaptive mechanisms to reinstate homeostasis may then again lead to mal-adaptation and pathophysiology.

All three papers in the present thesis present findings that link exposure to persistent psychological stressors to inflammation. Chronic inflammation, also known as low-grade systemic inflammation, is generally found to be associated with negative health outcomes (Jacobsen et al., 2019; Jacobsen et al., 2018; Liu et al., 2020; Miller et al., 2019; Tang et al., 2018). As described, inflammatory cytokines may interfere with neurocircuits and affect mental health (Geng et al., 2018; Niraula et al., 2018; Tang et al., 2018). Chronic inflammation has also been reported to be associated with increased pain sensitivity (Crettaz et al., 2013; Jacobsen et al., 2019; Sawicki et al., 2019) for review see (Walker et al., 2013). The condition of low-grade systemic inflammation seems to initiate a vicious circle that tears down both mental and physical health. Therefore, more effort should be invested in examining the underlying biological mechanisms of workplace bullying in humans. Though the aim of most bullying researchers is to understand how and when workplace bullying is related to other variables such as health, it is equally important to understand the biology and pathobiology of bullying exposure to understand how targets suffer as they do and to provide efficient treatments to the targets of bullying.

In that respect, the present thesis provides results that may be supportive of earlier findings indicating low-grade systemic inflammation as a link between exposure to chronic stressors and health (Miller et al., 2019; Niraula et al., 2018). Investigating the bullying-health relationship from a biological perspective revealed stress-induced physiological and behavioral changes. Moreover, the pro-inflammatory profile of the isolated myeloid cells, i.e., diminished anti-inflammatory effects of the ADRB2 and increased IL-6 expression, was suggestive of the possible stress-induced mal-adaptations of the stress response systems. Overall, the presented studies suggest that exposure to chronic psychological stressors, in the case of workplace bullying, leads to mal-adaptation of the stress response

systems, causing a chronic inflammatory condition, which may eventually progress to cause detrimental mental and physical health effects.

5.2. Methodological considerations and discussion

5.2.1. Sampling, generalizability and internal validity – human cohort

Both studies (paper I and III) used data collected from the Norwegian workforce. Among the 5000 questionnaires sent out by mail, 1608 persons returned their questionnaires (32 % response rate), and of these, 1204 individuals returned their saliva samples (24 %).

The response rate is of importance as it may be used as an indicator for the validity of the results in which a high response rate is associated with larger data samples, high statistical power, and smaller confidence intervals around sample statistics (Baruch & Holtom, 2008). Instead, if the response rate is low, the respondents may have a greater influence on the data and may affect the representativeness of the population. This type of bias may generate inaccurate conclusions and may prevent generalizing the results (Draugalis & Plaza, 2009).

Although a high response rate is important, the method used to obtain the sample may be equally important. As described in the method section, the collected sample was based on randomly selected subjects from the Norwegian working population between the ages of 18 to 65. Probability sampling gives each subject an equal chance of being selected (Shorten & Moorley, 2014). However, since the response rate was only 30 %, we cannot be certain if the collected sample is representative of the general working population in Norway. Also, the generalizability of the results may be threatened by nonresponse bias since the responses may not adequately reflect the population as a whole. However, since the nonresponse rate

has a limited impact on internal validity (Schalm & Kelloway, 2001), it should not be a problem concerning our findings.

All the main instruments used in the present thesis had a Cronbach's alpha value above the recommended 0.7 value, indicating strong internal stability of all scales (Cronbach, 1951). Even though this measure of internal consistency and scale reliability is within the acceptable range, issues related to construct validity can emerge. The NAQ-R inventory used in this thesis, to measure bullying, does not include one key element of the bullying definition – the power imbalance between the target and perpetrator. As such, the instrument does only ask the respondents for the frequency and duration of potential bullying behaviors in the workplace. Hence, we do not know if the respondents perceive the negative behavior as bullying or not.

Common method variance, i.e., variance that is attributable to the measurement method rather than to the constructs, represent a general problem in cross-sectional surveys, for review see (Podsakoff et al., 2003). In such surveys, the data on both stressors and potential outcomes are collected at the same time from the same respondent, which may threaten the validity of the conclusions made about the observed relationship. For instance, towards the end of a long questionnaire, the respondent may feel exhausted and be less thorough and less willing to provide accurate responses, for review see (Podsakoff et al., 2012). Although this may be a weakness also in the present study regarding the human data, the strength of our studies (paper I and III) is the inclusion of objective genetic variables, i.e., genotypes. These variables are determined using the DNA extracted from the respondents' saliva, which is then not a source of such a bias, and which should reduce somewhat the problems of common method variance inherited in the employed cross-sectional survey data.

5.2.2. The resident intruder paradigm

In the present thesis, the resident intruder paradigm was conducted to study the effects of exposure to psychological stressors in the form of repeated social defeat in rats. As previously explained, it was believed that the paradigm had some resemblance to ongoing bullying in humans and is a frequently used model to address the effects of psychological stressors by inducing social defeat in the intruder rats (Finnell et al., 2017; Koolhaas et al., 2013; Wohleb et al., 2011). A benefit of using rats, in this context, is their clearly defined hierarchy system (Lozano-Montes et al., 2019; Raab et al., 1986), which enables them to successfully induce a situation of a power imbalance between the resident and intruder rat. Also, the use of animals that can be sacrificed facilitates tissue harvesting, which is crucial when examining neuroendocrine and immunological changes following exposure to persistent psychological stressors.

The resident bully rats were selected based on aggressivity and superior body weight to assure the establishment of the power imbalance in the stress-conditioning week. Long Evans rats met both conditions. The most aggressive resident rats were screened prior to the stress-conditioning week based on latency to attack and endurance (Koolhaas et al., 2013). The Long Evans rats were housed in a 0.56 m^2 along with the female companion, to assure a more protective scene, to increase territoriality. Cleaning of the resident cages was also avoided since territoriality is strongly related to the presence of olfactory cues (Koolhaas et al., 2013). Seven weeks old Sprague Dawley rats – lower in body weight compared to Long Evans rats – were used as intruder rats. Group housing has shown to blunt the effects of social defeat in male rats due to positive interactions (Ruis et al., 1999) and for review, see (Beery & Kaufer, 2015). However, since isolation is a known stressor to rats and was not the intention of the present study, all animals were housed in pairs (Koolhaas et al., 2013). Moreover, since rats are nocturnal animals, the stress-conditioning was conducted in the dark phase when their activity is at the peak.

Handling of the rats induces stress but is necessary when cleaning cages and during transportation. Similarly, skin injuries due to biting may also affect the integrity of repeated social defeat as the only causative factor (Engler et al., 2004; Kollack-Walker et al., 1997). Therefore, only two caretakers performed all handling and husbandry routines throughout the entire study to avoid unnecessary exposure to stressors. Also, the interplay between the resident and intruder rat was closely monitored, and the rats were separated from the resident rats upon social defeat, as defined earlier, or after 10 minutes of interaction to prevent injuries (Merlot et al., 2003).

5.2.3. Social interaction test

A modified version of Crawley's sociability test (Nadler et al., 2004) was conducted one day after the last defeat exposure to investigate the effects of repeated social defeat on social interaction behavior (Kaidanovich-Beilin et al., 2011). To avoid disturbing their light-dark cycle and because increased illumination may decrease social interaction (File & Hyde, 1978), the test was performed in their night phase with minimal lighting conditions (15 lux) that was still sufficient for the camera recording. Also, since the unfamiliarity of the test box has shown to decrease the social interaction time of the rats (File & Hyde, 1978), four minutes were given for habituation before allowing the rat to explore the rest of the box.

The size of the sociability chamber used in the present study was relatively small, 0.56 m^2, which may have caused less sensitive measures. One way of overcoming this issue would have been to study social vigilance – a state in which exploratory behavior is substituted with scanning behavior (Abrams et al., 2005). Exposure to social stressors may increase social vigilance behavior in which the animal orients to an unfamiliar individual without approaching (Duque-Wilckens et al., 2018; Williams et al., 2020), which may be associated with anxiety-like behavior. Such scoring would perhaps give an insight that signifies social

withdrawal (Cryan & Holmes, 2005), commonly observed following social defeat, and is a common symptom observed in depressed individuals (Derntl et al., 2011).

Opposed to our observations, the mainstream of studies report that social defeat suppresses locomotor activity (Mul et al., 2018; Ota et al., 2018). The increase of locomotor activity, as observed in our data, may, however, be argued by structural changes in the brain in which the slow and attentive PFC regulation is dominated by the reflexive controlling of the amygdala (Giustino et al., 2020; Liu et al., 2020; Patel et al., 2018; Zhang et al., 2019). Also, the absence of exploratory behavior may result in a more continuous movement compared with control rats that may have fragmentary movements due to their exploratory behavior. The inter-individual differences may also influence the result and should, therefore, be considered in future studies. Also, due to contradictory findings, further investigations should be performed.

5.2.4. Anesthesia

The animals were anesthetized by isoflurane – a stable gas for inhalation-induced general anesthesia. It gives sedation, muscle relaxation, and may also affect nociceptive processes (Hung et al., 2011). Although isoflurane enabled rapid adjustment of anesthetic depth, the rats were exposed to a stressful event when exposed to the anesthesia induction chamber. Despite being short-lasting, this exposure could mask differences in circulating NE levels, which may partly explain why we did not observe any group differences when measuring NE concentrations in the circulation. Moreover, though the induction time of 1-2 minutes should not be sufficient to mask differences in circulatory glucocorticoids (Thrivikraman et al., 2000), the circadian and ultradian fluctuations of glucocorticoids made it challenging to hit right on time to measure potential group differences.

5.3. Ethical considerations

5.3.1. Human study

Performing research on humans includes retaining person sensitive data in which ethical considerations are highly important. Participation should be voluntary, and the anonymization of the respondents is compulsory, as is the case in the present study (World Medical, 2001). The respondents should be offered the ability to withdraw their consent at any time point in the study, without any explanation (World Medical, 2001). In the present thesis, the respondents were asked to return their saliva samples in addition to the questionnaires. As described in the method section 1204 out of 1608 responders returned their saliva samples. Although the respondents were assured that the details would be anonymized and undisclosed, it may be intimidating to send biological samples that contain genetic material, which may explain the drop in the number of respondents.

When examining genetic variation as an explanation for the various outcomes of exposure to workplace bullying, one should tread carefully to avoid being accused of "blaming the victim" (Zapf & Einarsen, 2003). "Blaming the victim" involves making arguments that the personalities, actions, and inactions of the target are partly the reason for the wrongdoing of the predator (Cortina et al., 2017). This also involves approving that it is the target who is responsible for the misconduct of another.

Although genetics play an important role in most human characteristics (Polderman et al., 2015), e.g., personality, behavior, and coping strategies, the present study did not examine the probability of certain genetic traits as a risk factor for exposure to workplace bullying. Rather, the present study investigated the direct and moderating effect of genetics on the outcome, i.e., insomnia and anxiety, when exposed to bullying behaviors. For example, exposure to workplace bullying is associated with insomnia. However, the association

between the predictor and outcome was shown to be stronger among individuals with the miR-146a GG genotype compared with individuals with the GC/CC genotype. Assigning certain genetic traits as being more sensitive or vulnerable to negative behaviors may be problematic ethically. It may be misused to "blame the victim," to take the focus away from perpetrators and situational and organizational risk factors, and may allow for genetic discrimination. However, this issue may be overcome by examining genetic variations as a health factor rather than a causal factor, as done in the present thesis. Despite the ethical challenges of studying genetics, knowledge, and information about genes and genetic variation may be of importance to understand the differences in health problems and, in the end, to provide better and more personalized treatments to the individual.

5.3.2. Animal study

Ethical considerations in animal research are also essential. The ethical guidelines followed in the present study are the three R's of Replacement, Reduction, and Refinement (Russell & Burch, 1959). Replacement is the substitution of living animals with other methods such as in vitro biological systems or computerized models. It is important to weigh the use of animals up against the benefits. The use of animals in experiments has benefited humans, but it is important to recognize that the life of animals is also valuable. As such, the use of animals should be substituted as often as possible. Currently, there are no other methods in which exposure to repeated social defeat and the following physiological effects can be assessed. Although cell culture experiments can substitute animal experiments to some degree, the biological systems and the dynamic interactions occurring in the body are impossible to study in cell culture experiments where you have single cells on a plastic cell plate. Hence, a replacement of the animal model – to study behavioral and physiological effects following exposure to persistent stressors – was not possible in the present study.

Reduction refers to the use of a minimal number of animals required to obtain reliable data. In the present study, 15 male and 15 female Long Evans rats were initially purchased for the purpose of this study to select the ten most dominant and aggressive resident rats. Since only ten male and ten female Long Evans rats were used in the animal study, in the end, it may seem unnecessary with the additional rats. However, even though the Long Evans rat strain is aggressive, there may be individual variations (Blanchard et al., 1984). Since the dominant and aggressive behavior of the resident rat is essential in the paradigm, the screening procedure was considered as unavoidable. Also, eight Sprague Dawley rats were used only for the purpose of the screening procedure. With this in mind, the minimal number of animals were used for the purpose of this study.

Refinement is to minimize the overall impact on the animals used. That is to choose less invasive methods. In our study, the rats were not exposed to any invasive procedures before the day of euthanasia. Also, bits and wounds during the resident-intruder paradigm were avoided by closely monitoring the interaction between the resident and intruder rat and by separating the rats after defeat or after ten minutes of interaction. However, during the stress-conditioning week, the experimenters (during handling) observed muscle fatigue and exhaustion in intruder rats (those exposed to a resident bully rat) compared with control rats. Also, throughout the stress-conditioning week, the intruder rats showed defeat behavior much earlier than the previous days of the week, indicating a reduced tendency to fight back (Landgraf et al., 2015). These observations may indicate – although invasive procedures and bits and wounds were avoided – that the repeated social defeat model imposed a strong sociopsychological stressor with a strong impact on the intruder rats. These observations might raise the question of whether conducting such experiments is ethically appropriate, even if the guidelines of the three R's were followed.

5.4. Implications

The results in this thesis show that targets of bullying develop health problems such as insomnia and anxiety, which may be explained by the low-grade systemic inflammatory state of the body following exposure to persistent stressors. Similarly, the animal study demonstrated physiological changes in the stress response system and a pro-inflammatory shift of the immune system following exposure to repeated social defeat. These findings are supportive of the allostatic model. Even though the adaptive mechanisms following acute stress exposure were not examined in the present thesis, the findings following exposure to persistent stressors are indicative of disturbances and mal-adaptation of mechanisms of the stress response system and the immune system.

Examinations of genes important in the stress response system and inflammation, e.g., the ADRB2, may improve our knowledge of how targets of bullying may react to stressful situations and that there are individual health-related differences in vulnerability, resilience and coping strategies when exposed to such stressors. Although individual variations and personal coping strategies do not seem to matter in high bullying intensity cases (Hamre et al., 2020; Nielsen et al., 2017; Reknes et al., 2016), such knowledge may help us understand how adaptive mechanisms shift to becoming mal-adaptive, leading to pathophysiology and severe health problems.

The findings of the present study emphasize the importance of investigating underlying biological mechanisms that are affected when exposed to persistent social stressors such as workplace bullying in humans. Investigating the bullying phenomenon from a biological perspective has given insight into how such strong psychological stressors leads to adverse health problems. Although genetic predispositions and personal coping strategies do not matter during high-intensity bullying, the understanding of genetic variations may be important in the understanding of why individuals respond differently to treatments.

Genetics is the basis for how biological components, e.g., proteins, interact with each other, and orchestrate cellular activities. At the organismal level, these genetic variations may affect how the physiological and psychological processes function during normal conditions and how they become mal-adapted during chronic exposure to stressors. Thus, the understanding of genetics and the underlying biological mechanisms of the bullying-health relationship may improve our knowledge about the bullying phenomenon and its associations with other variables. Also, these findings may be of value when developing treatment strategies for targets of bullying in which genetics should be taken into consideration. The present study, thus, emphasizes the importance of investigating the bullying phenomenon, at least the health-related part of the problem, from a biopsychosocial perspective. In the future, similar studies should be performed to improve our knowledge about the bullying phenomenon further, as biology is a central part of human experiences and may provide valuable information and understanding of the underlying mechanisms on the bullying-health relationship.

6. Future perspectives

6.1. Human study

The human arm of the project was based on a probability sample of the Norwegian working population. Replication in a different cohort should be conducted in order to validate the current findings on other cultures. While our sample should be quite relatable to the general working population in Europe, the detrimental effects of bullying may be less protruding in our sample due to the low prevalence of bullying in Norway (Jacobson et al., 2013; Nielsen et al., 2009). The hierarchical system in Norwegian organizations is relatively low compared to other European countries (Jacobson et al., 2013). As such, there is a chance that the biological effects may be diluted. It may, therefore, be reasonable to choose a cohort with a higher incidence of bullying and perhaps higher power distance when assessing the underlying biological systems that are affected, e.g., organizations with known high bullying rates. Studying such a cohort, which is more homogenous, may be valuable and help improve our knowledge about the underlying biological mechanisms that are affected by persistent exposure to stressors.

The results of paper I and III highlighted the importance of genetic variations and their effect on the studied outcome. Examinations of the moderating effects of miR-146a and ADRB2, central in the stress response system and inflammation, was performed. However, other genes in these systems may be more important and may play an even more crucial role in the vulnerability of developing adverse health effects (needle in a haystack problem). One way to conquer the problem may, therefore, be to perform screening analyses on the biological material collected from persons that are exposed to and not exposed to a psychological stressor, as previously done by Jacobsen et al. (2019) of which stress-induced changes in circulating miRNAs in rats were screened for and further analyzed. Examining

the differences between the two groups may identify genes that become significantly altered. The selected genes should then be prioritized based on their importance in stress response-related biological pathways or the immune system that are of interest.

6.2. Animal study

Studies have demonstrated the presence of gender differences in depression, anxiety disorders, and subjective pain (Glambek et al., 2018; McLean et al., 2011). However, the majority of studies on repeated social defeat conducted so far, including the present thesis, have been conducted exclusively in male rats (Finnell et al., 2017; Henderson et al., 2017; Patel et al., 2018). The reason being that male rodents are often more territorial than female rats. Also, initiating an attack behavior in females is more challenging (Golden et al., 2011; Miczek et al., 2008; Takahashi et al., 2017). While male rats tend to react to the exposed stressor, female rats have been found to respond by avoiding the stressor (Takahashi et al., 2017). Thus, it has been undemanding to conduct animal studies using male rats. However, females are part of the working population and are equally vulnerable as men to be exposed to workplace bullying. As such, future experiments should consider using female rats to understand the physiological and psychological effects that may be different from the findings in male rats, which may explain any gender differences in subjective health complaints (Glambek et al., 2018). Also, the intruder rats used in the present study were young adolescence (seven-eight weeks) at the time of exposure to repeated social defeat. At this stage of life, the brain is under substantial development, particularly in the PFC and amygdala – important for cognition and emotion – and maturation of the HPA axis, for review see (Eiland & Romeo, 2013; McCormick & Mathews, 2010). This period may, therefore, increase the vulnerability of rats to stressor induced negative health-related outcomes. On should bear in mind these differences when translating the findings to humans. Also, studies using adult rats should be preferred in future research as we study the effects of bullying in a working population consisting of adults.

As previously discussed, the social interaction test to assess social avoidance behavior did not result in any clear findings. However, in future studies, behavioral assessments such as sucrose preference test to measure stress-induced anhedonia – the inability to experience pleasure – may be used (Willner et al., 1987). Reduction in the sucrose preference in stress-induced rats compared with control rats is often indicative of depression-like behaviors. The light/dark preference test is also a tool to measure behaviors that are characteristic of anxiety (Arrant et al., 2013). Even though physiological changes following exposure to repeated social defeat are examined, behavioral assessments – to examine depression- and anxiety-like behavior – are needed to validate the reliability of the repeated social defeat model. As such, conducting multiple evaluations of behavior may be convenient in future studies.

Examination of the isolated splenic myeloid cells from rats showed a reduced ADRB2 and ARRB2 gene expression and increased expression of IL-6. Myeloid cells are essential components of the innate immune system and perform crucial functions to trigger the adaptive immune response, e.g., antigen presentation. However, examination of every immune cell population would have given a broader overview, and an insight into the changes caused to the immune system following persistent exposure to stressors. The different percentages of the different cell populations may indicate the priorities of the immune system following chronic exposure to stressors. Also, it would have been possible to estimate the degree of egress of immune cells from the BM to the periphery following exposure to chronic psychological stressors.

Future studies should place more emphasis on stratifying susceptible and resilient individuals, which may be more informative concerning individual variations. Understanding the causative processes that may be different depending on resiliency may help researchers understand the depth of the harmful effects in the different individuals (Hamre et al., 2020). Such knowledge may be helpful in interventions and treatments of

targets of bullying. Due to the low number of rats in the present study (ten in each group), the sub-grouping of the stress-exposed rats was not statistically achievable. Hence, studies employing a larger number of rats should be conducted in the future.

The study of epigenetic mechanisms – changes in gene expression that do not involve changes to the DNA sequence – may be indicative of gene silencing or gene activity following exposure to chronic social stressors (Hollis et al., 2010; McEwen, Gray, et al., 2015). Our group has already initiated this study in which the methylation profile of pituitary DNA is analyzed. These modifications are chemical compounds that are added to the DNA strand, which alters DNA accessibility and subsequent transcription of the gene. Such whole-genome analysis may give cues to various pathways that may be dominating in the pituitary gland following persistent exposure to psychological stressors. Such data may provide an idea of the altered signaling pathways in pituitary cells when exposed to chronic psychological stressors. Such knowledge may improve our understanding of how the pituitary gland (at the cellular level) – an important component of the HPA axis – respond to chronic stressors. This understanding may further be applied to investigate the downstream pathways and to obtain a better idea of how the physiological alterations lead to negative health outcomes following exposure to chronic stressors.

7. Conclusion

The present thesis demonstrated that persistent psychological stressors (workplace bullying humans and repeated social defeat in rats) may induce behavioral, neuroendocrine, and immunological changes that may be important in order to understand the relationship between exposure to workplace bullying and the development of health problems.

- The findings in the first article showed that exposure to bullying is associated with insomnia through distress. This association was shown to be moderated by the miR-146a genotype rs2910164, which may suggest an inflammatory link between exposure to workplace bullying and the development of negative health problems.

- The findings in the second paper showed that exposure to repeated social defeat may induce negative health effects, including increased locomotion, reduced weight gain, hypothalamic-pituitary-adrenal (HPA) axis changes, and an increased inflammatory profile of the isolated myeloid cells. These data support the idea that persistent exposure to stressors may cause behavioral and physiological changes.

- The findings in the third paper showed that exposure to persistent psychological stressors also changes the expression of the β2-adrenergic receptor (ADRB2). A moderating effect of the ADRB2 genotype rs1042714 on the bullying-anxiety relationship was observed. The pro-inflammatory effects of exposure to social stressors were also emphasized by the subsequent in vitro experiments.

Hence, the present thesis supports the idea that exposure to persistent stressors in the form of workplace bullying may have severe biological consequences. Our data, therefore, support the hypothesis that the burden of exposure to chronic stressors leads to allostatic overload. This may also promote a state of low-grade systemic inflammation and mal-

adaptive processes, which involve changes in the bi-directional communication between the brain and the immune system. Thus, workplace bullying may alter the regulation of neurocircuits in the brain as well, which in turn may be linked to negative health effects such as anxiety and insomnia.

In addition, the findings of the present thesis show a clear link between exposure to persistent psychological stressors, genetic factors, and severe health problems seen in targets of bullying. Therefore, we conclude that chronic activation of the neuroimmune system arising following exposure to bullying behaviors may cause harmful physiological changes. How these physiological changes affect individual differences in resilience and coping strategies and the role of genetic factors concerning these aspects of the bullying phenomenon remains to be investigated.

References

Abrams, J. K., Johnson, P. L., Hay-Schmidt, A., Mikkelsen, J. D., Shekhar, A., & Lowry, C. A. (2005). Serotonergic systems associated with arousal and vigilance behaviors following administration of anxiogenic drugs. *Neuroscience, 133*(4), 983-997. doi:10.1016/j.neuroscience.2005.03.025

Achuthan, A., Aslam, A. S. M., Nguyen, Q., Lam, P.-Y., Fleetwood, A. J., Frye, A. T., et al. (2018). Glucocorticoids promote apoptosis of proinflammatory monocytes by inhibiting ERK activity. *Cell Death & Disease, 9*(3), 267. doi:10.1038/s41419-018-0332-4

Adhikari, A., Lerner, T. N., Finkelstein, J., Pak, S., Jennings, J. H., Davidson, T. J., et al. (2015). Basomedial amygdala mediates top-down control of anxiety and fear. *Nature, 527*(7577), 179-185. doi:10.1038/nature15698

Agoston, D. V. (2017). How to Translate Time? The Temporal Aspect of Human and Rodent Biology. *Frontiers in Neurology, 8*(92). doi:10.3389/fneur.2017.00092

Ågotnes, K. W., Einarsen, S. V., Hetland, J., & Skogstad, A. (2018). The moderating effect of laissez-faire leadership on the relationship between co-worker conflicts and new cases of workplace bullying: A true prospective design. *Human Resource Management Journal, 28*(4), 555-568. doi:10.1111/1748-8583.12200

Akerstedt, T. (2006). Psychosocial stress and impaired sleep. *Scandinavian Journal of Work Environment & Health, 32*(6), 493-501. doi:10.5271/sjweh.1054

Alexander, J. K., DeVries, A. C., Kigerl, K. A., Dahlman, J. M., & Popovich, P. G. (2009). Stress exacerbates neuropathic pain via glucocorticoid and NMDA receptor activation. *Brain Behav Immun, 23*(6), 851-860. doi:https://doi.org/10.1016/j.bbi.2009.04.001

Alhurani, A. S., Dekker, R., Ahmad, M., Miller, J., Yousef, K. M., Abdulqader, B., et al. (2018). Stress, cognitive appraisal, coping, and event free survival in patients with heart failure. *Heart Lung, 47*(3), 205-210. doi:10.1016/j.hrtlng.2018.03.008

Almeida-Suhett, C. P., Prager, E. M., Pidoplichko, V., Figueiredo, T. H., Marini, A. M., Li, Z., et al. (2014). Reduced GABAergic inhibition in the basolateral amygdala

and the development of anxiety-like behaviors after mild traumatic brain injury. *PLoS One, 9*(7), e102627. doi:10.1371/journal.pone.0102627

American Academy of Sleep Medicine. (2014). *International classification of sleep disorders* (3rd ed.). Darien, IL: American Academy of Sleep Medicine.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andolina, D., Di Segni, M., Bisicchia, E., D'Alessandro, F., Cestari, V., Ventura, A., et al. (2016). Effects of lack of microRNA-34 on the neural circuitry underlying the stress response and anxiety. *Neuropharmacology, 107*, 305-316. doi:10.1016/j.neuropharm.2016.03.044

Araujo, L. P., Maricato, J. T., Guereschi, M. G., Takenaka, M. C., Nascimento, V. M., de Melo, F. M., et al. (2019). The Sympathetic Nervous System Mitigates CNS Autoimmunity via β2-Adrenergic Receptor Signaling in Immune Cells. *Cell reports, 28*(12), 3120-3130.e3125. doi:10.1016/j.celrep.2019.08.042

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci, 10*(6), 410-422. doi:10.1038/nrn2648

Arnsten, A. F. T., Raskind, M. A., Taylor, F. B., & Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of Stress, 1*, 89-99. doi:https://doi.org/10.1016/j.ynstr.2014.10.002

Arrant, A. E., Schramm-Sapyta, N. L., & Kuhn, C. M. (2013). Use of the light/dark test for anxiety in adult and adolescent male rats. *Behavioural Brain Research, 256*, 119-127. doi:10.1016/j.bbr.2013.05.035

Arrigoni, E., Chen, M. C., & Fuller, P. M. (2016). The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. *J Physiol, 594*(19), 5391-5414. doi:10.1113/jp271324

Asarian, L., Gloy, V., & Geary, N. (2012). Homeostasis. In V. S. Ramachandran (Ed.), *Encyclopedia of Human Behavior (Second Edition)* (pp. 324-333). San Diego: Academic Press.

Attarwala, H. (2010). TGN1412: From Discovery to Disaster. *Journal of young pharmacists : JYP, 2*(3), 332-336. doi:10.4103/0975-1483.66810

Auffray, C., Fogg, D., Garfa, M., Elain, G., Join-Lambert, O., Kayal, S., et al. (2007). Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science, 317*(5838), 666-670. doi:10.1126/science.1142883

Auphan, N., DiDonato, J. A., Rosette, C., Helmberg, A., & Karin, M. (1995). Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science, 270*(5234), 286-290. doi:10.1126/science.270.5234.286

Avitsur, R., Stark, J. L., Dhabhar, F. S., Padgett, D. A., & Sheridan, J. F. (2002). Social disruption-induced glucocorticoid resistance: kinetics and site specificity. *J Neuroimmunol, 124*(1-2), 54-61. doi:10.1016/s0165-5728(02)00010-3

Bacon, K. L., Heeren, T., Keysor, J. J., Stuver, S. O., Cauley, J. A., & Fredman, L. (2015). Longitudinal and Reciprocal Relationships Between Depression and Disability in Older Women Caregivers and Noncaregivers. *The Gerontologist, 56*(4), 723-732. doi:10.1093/geront/gnu157

Baillien, E., Neyens, I., De Witte, H., & De Cuyper, N. (2009). A qualitative study on the development of workplace bullying: Towards a three way model. *Journal of Community & Applied Social Psychology, 19*(1), 1-16. doi:10.1002/casp.977

Balbo, M., Leproult, R., & Van Cauter, E. (2010a). Impact of Sleep and Its Disturbances on Hypothalamo-Pituitary-Adrenal Axis Activity. *Int J Endocrinol, 2010*, 759234. doi:10.1155/2010/759234

Balbo, M., Leproult, R., & Van Cauter, E. (2010b). Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. *Int J Endocrinol, 2010*, 759234. doi:10.1155/2010/759234

Barnett, S. A. (1958). An analysis of social behaviour in wild rats. *Proceedings of the Zoological Society of London, 130*(1), 107-152. doi:10.1111/j.1096-3642.1958.tb00565.x

Baruch, Y., & Holtom, B. C. (2008). Survey response rate levels and trends in organizational research. *Human Relations, 61*(8), 1139-1160. doi:10.1177/0018726708094863

Beery, A. K., & Kaufer, D. (2015). Stress, social behavior, and resilience: insights from rodents. *Neurobiology of Stress, 1*, 116-127. doi:10.1016/j.ynstr.2014.10.004

Bellver-Landete, V., Bretheau, F., Mailhot, B., Vallières, N., Lessard, M., Janelle, M., et al. (2019). Microglia are an essential component of the neuroprotective scar that forms after spinal cord injury. *Nature Communications, 10*(1), 518. doi:10.1038/s41467-019-08446-0

Bergh, M. S., Bogen, I. L., Andersen, J. M., Oiestad, A. M. L., & Berg, T. (2018). Determination of adrenaline, noradrenaline and corticosterone in rodent blood by ion pair reversed phase UHPLC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci, 1072*, 161-172. doi:10.1016/j.jchromb.2017.11.016

Berset, M., Elfering, A., Luthy, S., Luthi, S., & Semmer, N. K. (2011). Work stressors and impaired sleep: rumination as a mediator. *Stress Health, 27*(2), e71-82. doi:10.1002/smi.1337

Bialas, A. R., & Stevens, B. (2013). TGF-β signaling regulates neuronal C1q expression and developmental synaptic refinement. *Nature Neuroscience, 16*(12), 1773-1782. doi:10.1038/nn.3560

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P. M., Petrov, D., et al. (2003). A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A, 100*(4), 1920-1925. doi:10.1073/pnas.0438019100

Bilodeau, S., Vallette-Kasic, S., Gauthier, Y., Figarella-Branger, D., Brue, T., Berthelet, F., et al. (2006). Role of Brg1 and HDAC2 in GR trans-repression of the pituitary POMC gene and misexpression in Cushing disease. *Genes Dev, 20*(20), 2871-2886. doi:10.1101/gad.1444606

Björkqvist, K., Österman, K., & Hjelt-Bäck, M. (1994). Aggression among university employees. *Aggressive Behavior, 20*(3), 173-184. doi:10.1080/13594329608414855.

Blanchard, R. J., Flannelly, K. J., Layng, M., & Blanchard, D. C. (1984). The effects of age and strain on aggression in male rats. *Physiol Behav, 33*(6), 857-861. doi:https://doi.org/10.1016/0031-9384(84)90219-1

Bogdan, C. (2001). Nitric oxide and the immune response. *Nature Immunology, 2*(10), 907-916. doi:10.1038/ni1001-907

Bola, R. A., & Kiyatkin, E. A. (2018). Inflow of oxygen and glucose in brain tissue induced by intravenous norepinephrine: relationships with central metabolic and peripheral vascular responses. *J Neurophysiol, 119*(2), 499-508. doi:10.1152/jn.00692.2017

Borodovitsyna, O., Flamini, M. D., & Chandler, D. J. (2018). Acute Stress Persistently Alters Locus Coeruleus Function and Anxiety-like Behavior in Adolescent Rats. *Neuroscience, 373*, 7-19. doi:https://doi.org/10.1016/j.neuroscience.2018.01.020

Briançon-Marjollet, A., Weiszenstein, M., Henri, M., Thomas, A., Godin-Ribuot, D., & Polak, J. (2015). The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. *Diabetology & Metabolic Syndrome, 7*(1), 25. doi:10.1186/s13098-015-0018-3

Brinks, V., van der Mark, M. H., de Kloet, E. R., & Oitzl, M. S. (2007). Differential MR/GR activation in mice results in emotional states beneficial or impairing for cognition. *Neural plasticity, 2007*, 90163-90163. doi:10.1155/2007/90163

Brousse, G., Fontana, L., Ouchchane, L., Boisson, C., Gerbaud, L., Bourguet, D., et al. (2008). Psychopathological features of a patient population of targets of workplace bullying. *Occup Med (Lond), 58*(2), 122-128. doi:10.1093/occmed/kqm148

Bruce, M., Streifel, K. M., Boosalis, C. A., Heuer, L., González, E. A., Li, S., et al. (2019). Acute peripheral immune activation alters cytokine expression and glial activation in the early postnatal rat brain. *Journal of neuroinflammation, 16*(1), 200. doi:10.1186/s12974-019-1569-2

Calabrese, V., Mancuso, C., Calvani, M., Rizzarelli, E., Butterfield, D. A., & Stella, A. M. (2007). Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. *Nat Rev Neurosci, 8*(10), 766-775. doi:10.1038/nrn2214

Calfa, G., Volosin, M., & Molina, V. A. (2006). Glucocorticoid receptors in lateral septum are involved in the modulation of the emotional sequelae induced by social defeat. *Behavioural Brain Research, 172*(2), 324-332. doi:10.1016/j.bbr.2006.05.022

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry, 161*(4), 598-607. doi:10.1176/appi.ajp.161.4.598

Cannon, W. B. (1926). Physiological regulation of normal states: some tentative postulates concerning biological homeostatics

A. Pettit (Ed.), A Charles Richet: ses amis, ses collègues, ses élèves, Les Éditions Médicales (1926),, p. 91.

Cano, G., Sved, A. F., Rinaman, L., Rabin, B. S., & Card, J. P. (2001). Characterization of the central nervous system innervation of the rat spleen using viral transneuronal tracing. *J Comp Neurol, 439*(1), 1-18. doi:10.1002/cne.1331

Capuron, L., Schroecksnadel, S., Féart, C., Aubert, A., Higueret, D., Barberger-Gateau, P., et al. (2011). Chronic Low-Grade Inflammation in Elderly Persons Is Associated with Altered Tryptophan and Tyrosine Metabolism: Role in Neuropsychiatric Symptoms. *Biol Psychiatry, 70*(2), 175-182. doi:https://doi.org/10.1016/j.biopsych.2010.12.006

Carreira, B. P., Santos, D. F., Santos, A. I., Carvalho, C. M., & Araújo, I. M. (2015). Nitric Oxide Regulates Neurogenesis in the Hippocampus following Seizures. *Oxidative medicine and cellular longevity, 2015*, 451512-451512. doi:10.1155/2015/451512

Carrillo-de Sauvage, M. Á., Maatouk, L., Arnoux, I., Pasco, M., Sanz Diez, A., Delahaye, M., et al. (2013). Potent and multiple regulatory actions of microglial glucocorticoid receptors during CNS inflammation. *Cell death and differentiation, 20*(11), 1546-1557. doi:10.1038/cdd.2013.108

Cavallotti, C., Bruzzone, P., & Mancone, M. (2002). Catecholaminergic nerve fibers and beta-adrenergic receptors in the human heart and coronary vessels. *Heart Vessels, 17*(1), 30-35. doi:10.1007/s003800200039

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annu Rev Physiol, 67*, 259-284. doi:10.1146/annurev.physiol.67.040403.120816

Chen, C. M., Lee, I. C., Su, Y. Y., Mullan, J., & Chiu, H. C. (2017). The longitudinal relationship between mental health disorders and chronic disease for older adults: a population-based study. *Int J Geriatr Psychiatry, 32*(9), 1017-1026. doi:10.1002/gps.4561

Chen, D., & Rothenberg, E. V. (1994). Interleukin 2 transcription factors as molecular targets of cAMP inhibition: delayed inhibition kinetics and combinatorial transcription roles. *J Exp Med, 179*(3), 931-942. doi:10.1084/jem.179.3.931

Chen, H.-J. C., Spiers, J. G., Sernia, C., & Lavidis, N. A. (2015). Response of the nitrergic system to activation of the neuroendocrine stress axis. *Frontiers in Neuroscience, 9*, 3. doi:10.3389/fnins.2015.00003

Christensen, H., Jorm, A. F., Mackinnon, A. J., Korten, A. E., Jacomb, P. A., Henderson, A. S., et al. (1999). Age differences in depression and anxiety symptoms: a structural equation modelling analysis of data from a general population sample. *Psychological Medicine, 29*(2), 325-339. doi:10.1017/S0033291798008150

Christiansen, J. J., Djurhuus, C. B., Gravholt, C. H., Iversen, P., Christiansen, J. S., Schmitz, O., et al. (2007). Effects of Cortisol on Carbohydrate, Lipid, and Protein Metabolism: Studies of Acute Cortisol Withdrawal in Adrenocortical Failure. *The Journal of Clinical Endocrinology & Metabolism, 92*(9), 3553-3559. doi:10.1210/jc.2007-0445

Chuang, J.-C., Cui, H., Mason, B. L., Mahgoub, M., Bookout, A. L., Yu, H. G., et al. (2010). Chronic social defeat stress disrupts regulation of lipid synthesis. *Journal of lipid research, 51*(6), 1344-1353. doi:10.1194/jlr.M002196

Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., et al. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A, 109*(16), 5995-5999. doi:10.1073/pnas.1118355109

Cortina, L. M., Rabelo, V. C., & Holland, K. J. (2017). Beyond Blaming the Victim: Toward a More Progressive Understanding of Workplace Mistreatment. *Industrial and Organizational Psychology, 11*(1), 81-100. doi:10.1017/iop.2017.54

Cousijn, H., Rijpkema, M., Qin, S., van Marle, H. J., Franke, B., Hermans, E. J., et al. (2010). Acute stress modulates genotype effects on amygdala processing in humans. *Proc Natl Acad Sci U S A, 107*(21), 9867-9872. doi:10.1073/pnas.1003514107

Crettaz, B., Marziniak, M., Willeke, P., Young, P., Hellhammer, D., Stumpf, A., et al. (2013). Stress-induced allodynia--evidence of increased pain sensitivity in healthy humans and patients with chronic pain after experimentally induced psychosocial stress. *PLoS One, 8*(8), e69460-e69460. doi:10.1371/journal.pone.0069460

Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16*(3), 297-334. doi:10.1007/BF02310555

Cryan, J. F., & Holmes, A. (2005). The ascent of mouse: advances in modelling human depression and anxiety. *Nat Rev Drug Discov, 4*(9), 775-790. doi:10.1038/nrd1825

Cserép, C., Pósfai, B., Lénárt, N., Fekete, R., László, Z. I., Lele, Z., et al. (2020). Microglia monitor and protect neuronal function through specialized somatic purinergic junctions. *Science, 367*(6477), 528. doi:10.1126/science.aax6752

Cui, X. Y., Yang, G., Cui, S. Y., Cao, Q., Huang, Y. L., Ding, H., et al. (2018). Sleep patterns deteriorate over time in chronic corticosterone-treated rats. *Neurosci Lett, 682*, 74-78. doi:10.1016/j.neulet.2018.06.017

Cunningham, W. A., & Kirkland, T. (2013). The joyful, yet balanced, amygdala: moderated responses to positive but not negative stimuli in trait happiness. *Social Cognitive and Affective Neuroscience, 9*(6), 760-766. doi:10.1093/scan/nst045

D'Mello, C., Le, T., & Swain, M. G. (2009). Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *J Neurosci, 29*(7), 2089-2102. doi:10.1523/jneurosci.3567-08.2009

Davis, C. J., Clinton, J. M., & Krueger, J. M. (2012). MicroRNA 138, let-7b, and 125a inhibitors differentially alter sleep and EEG delta-wave activity in rats. *Journal of Applied Physiology, 113*(11), 1756-1762. doi:10.1152/japplphysiol.00940.2012

de Haas, A. H., Boddeke, H. W. G. M., & Biber, K. (2008). Region-specific expression of immunoregulatory proteins on microglia in the healthy CNS. *Glia, 56*(8), 888-894. doi:10.1002/glia.20663

De Lucia, C., Rinchon, A., Olmos-Alonso, A., Riecken, K., Fehse, B., Boche, D., et al. (2016). Microglia regulate hippocampal neurogenesis during chronic neurodegeneration. *Brain Behav Immun, 55*, 179-190. doi:10.1016/j.bbi.2015.11.001

Dehue, F., Bolman, C., Völlink, T., & Pouwelse, M. (2012). Coping with bullying at work and health related problems. *International Journal of Stress Management, 19*(3), 175-197. doi:10.1037/a0028969

Demirel, Y., & Yoldaş, M. A. (2008). The comparison of mobbing behavior at health institutions of Turkey and Kazakhstan. *Journal of Human Sciences, 5*(2).

Demsky, C. A., Fritz, C., Hammer, L. B., & Black, A. E. (2019). Workplace incivility and employee sleep: The role of rumination and recovery experiences. *J Occup Health Psychol, 24*(2), 228-240. doi:10.1037/ocp0000116

Deng, Q., Riquelme, D., Trinh, L., Low, M. J., Tomić, M., Stojilkovic, S., et al. (2015). Rapid Glucocorticoid Feedback Inhibition of ACTH Secretion Involves Ligand-Dependent Membrane Association of Glucocorticoid Receptors. *Endocrinology, 156*(9), 3215-3227. doi:10.1210/en.2015-1265

Derntl, B., Seidel, E.-M., Eickhoff, S. B., Kellermann, T., Gur, R. C., Schneider, F., et al. (2011). Neural correlates of social approach and withdrawal in patients with major depression. *Social neuroscience, 6*(5-6), 482-501. doi:10.1080/17470919.2011.579800

Dhabhar, F. S., Malarkey, W. B., Neri, E., & McEwen, B. S. (2012). Stress-induced redistribution of immune cells—From barracks to boulevards to battlefields: A tale of three hormones – Curt Richter Award Winner. *Psychoneuroendocrinology, 37*(9), 1345-1368. doi:https://doi.org/10.1016/j.psyneuen.2012.05.008

Ding, L., & Morrison, S. J. (2013). Haematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. *Nature, 495*(7440), 231-235. doi:10.1038/nature11885

Ding, X. F., Zhao, X. H., Tao, Y., Zhong, W. C., Fan, Q., Diao, J. X., et al. (2014). Xiao Yao San Improves Depressive-Like Behaviors in Rats with Chronic Immobilization Stress through Modulation of Locus Coeruleus-Norepinephrine System. *Evid Based Complement Alternat Med, 2014*, 605914. doi:10.1155/2014/605914

Dingfelder, S. F. (2006). Banishing bullying. *APA Monitor on Psychology, 37*(7).

Donley, M. P., Schulkin, J., & Rosen, J. B. (2005). Glucocorticoid receptor antagonism in the basolateral amygdala and ventral hippocampus interferes with long-term memory of contextual fear. *Behav Brain Res, 164*(2), 197-205. doi:10.1016/j.bbr.2005.06.020

Doorn, K. J., Brevé, J. J. P., Drukarch, B., Boddeke, H. W., Huitinga, I., Lucassen, P. J., et al. (2015). Brain region-specific gene expression profiles in freshly isolated rat

microglia. *Frontiers in Cellular Neuroscience, 9*(84). doi:10.3389/fncel.2015.00084

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., et al. (2010). A meta-analysis of cytokines in major depression. *Biol Psychiatry, 67*(5), 446-457. doi:10.1016/j.biopsych.2009.09.033

Draugalis, J. R., & Plaza, C. M. (2009). Best practices for survey research reports revisited: implications of target population, probability sampling, and response rate. *Am J Pharm Educ, 73*(8), 142. doi:10.5688/aj7308142

Dudek, K. A., Dion-Albert, L., Lebel, M., LeClair, K., Labrecque, S., Tuck, E., et al. (2020). Molecular adaptations of the blood–brain barrier promote stress resilience vs. depression. *Proceedings of the National Academy of Sciences, 117*(6), 3326-3336. doi:10.1073/pnas.1914655117

Duque-Wilckens, N., Steinman, M. Q., Busnelli, M., Chini, B., Yokoyama, S., Pham, M., et al. (2018). Oxytocin Receptors in the Anteromedial Bed Nucleus of the Stria Terminalis Promote Stress-Induced Social Avoidance in Female California Mice. *Biol Psychiatry, 83*(3), 203-213. doi:https://doi.org/10.1016/j.biopsych.2017.08.024

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain. *Neuroscience, 249*, 162-171. doi:https://doi.org/10.1016/j.neuroscience.2012.10.048

Einarsen, S., Hoel, H., D., Z., & Cooper, C. L. (2011). The concept of bullying and harassment at work: The European tradition. In S. Einarsen, H. Hoel, D. Zapf & C. L. Cooper (Eds.). *Bullying and Harassment in the Workplace. Developments in Theory, Research and Practice*, (2nd Ed., pp.3-39).

Einarsen, S., Hoel, H., Zapf, D., & Cooper, C. L. (2011). Bullying and harassment in the workplace. Developments in theory, research, and practice (2nd ed.). Boca Raton: CRC Press.

Einarsen, S., Raknes, B. I., & Matthiesen, S. B. (1994). Bullying and harassment at work and their relationships to work environment quality: An exploratory study. *European Work and Organizational Psychologist, 4*(4), 381-401. doi:10.1080/13594329408410497

Einarsen, S., Raknes, B. I., Matthiesen, S. B. & Hellesøy, O. H. . (1994). Mobbing og harde personkonflikter. Helsefarlig samspill på arbeidsplassen. *Bergen: Sigma Forlag*.

Einarsen, S. R., B. I. . (1991). Mobbing i arbeidslivet. En undersøkelse av forekomst og helsemessige konsekvenser av mobbing på norske arbeidsplasser. *Bergen: Institutt for samfunnspsykologi: Universitetet i Bergen.*

Einarsen, S. V. (1999). The nature and causes of bullying at work. *International Journal of Manpower, 20*(1/2), 16-27. doi:10.1108/01437729910268588

Einarsen, S. V., Hoel, H., & Notelaers, G. (2009). Measuring exposure to bullying and harassment at work: Validity, factor structure and psychometric properties of the Negative Acts Questionnaire-Revised. *Work & Stress, 23*(1), 24-44. doi:10.1080/02678370902815673

Einarsen, S. V., Hoel, H., Zapf, D., & Cooper, C. L. . (2020). The concept of bullying and harassment at work: the European tradition. In S. V. Einarsen, H. Hoel, D. Zapf, & C. L. Cooper (Eds.). *Bullying and harassment in the workplace: Theory, research, and practice*(3rd ed.), pp. 3-53. Boca Raton: CRC Press.

Einarsen, S. V., & Nielsen, M. B. (2015). Workplace bullying as an antecedent of mental health problems: a five-year prospective and representative study. *Int Arch Occup Environ Health, 88*(2), 131-142. doi:10.1007/s00420-014-0944-7

Einarsen, S. V., & Raknes, B. I. (1997). Harassment in the Workplace and the Victimization of Men. *Violence Vict*(3), 247-263. doi:10.1891/0886-6708.12.3.247

Einarsen, S. V., & Skogstad, A. (1996). Bullying at work: Epidemiological findings in public and private organizations. *European Journal of Work and Organizational Psychology, 5*(2), 185-201. doi:10.1080/13594329608414854

Eisenberger, N. I., Berkman, E. T., Inagaki, T. K., Rameson, L. T., Mashal, N. M., & Irwin, M. R. (2010). Inflammation-Induced Anhedonia: Endotoxin Reduces Ventral Striatum Responses to Reward. *Biol Psychiatry, 68*(8), 748-754. doi:https://doi.org/10.1016/j.biopsych.2010.06.010

El Gazzar, M., Church, A., Liu, T., & McCall, C. E. (2011). MicroRNA-146a regulates both transcription silencing and translation disruption of TNF-alpha during TLR4-induced gene reprogramming. *J Leukoc Biol, 90*(3), 509-519. doi:10.1189/jlb.0211074

Elmore, Monica R. P., Najafi, Allison R., Koike, Maya A., Dagher, Nabil N., Spangenberg, Elizabeth E., Rice, Rachel A., et al. (2014). Colony-Stimulating Factor 1 Receptor Signaling Is Necessary for Microglia Viability, Unmasking a Microglia Progenitor Cell in the Adult Brain. *Neuron, 82*(2), 380-397. doi:https://doi.org/10.1016/j.neuron.2014.02.040

Elmquist, J. K., Coppari, R., Balthasar, N., Ichinose, M., & Lowell, B. B. (2005). Identifying hypothalamic pathways controlling food intake, body weight, and glucose homeostasis. *J Comp Neurol, 493*(1), 63-71. doi:10.1002/cne.20786

Emrick, M. A., Sadilek, M., Konoki, K., & Catterall, W. A. (2010). Beta-adrenergic-regulated phosphorylation of the skeletal muscle Ca(V)1.1 channel in the fight-or-flight response. *Proc Natl Acad Sci U S A, 107*(43), 18712-18717. doi:10.1073/pnas.1012384107

Engler, H., Bailey, M. T., Engler, A., & Sheridan, J. F. (2004). Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. *Journal of Neuroimmunology, 148*(1-2), 106-115. doi:10.1016/j.jneuroim.2003.11.011

Escartín, J., Rodríguez-Carballeira, A., Zapf, D., Porrúa, C., & Martín-Peña, J. (2009). Perceived severity of various bullying behaviours at work and the relevance of exposure to bullying. *Work & Stress, 23*(3), 191-205. doi:10.1080/02678370903289639

Fareed, M., & Afzal, M. (2013). Single nucleotide polymorphism in genome-wide association of human population: A tool for broad spectrum service. *Egyptian Journal of Medical Human Genetics, 14*(2), 123-134. doi:https://doi.org/10.1016/j.ejmhg.2012.08.001

Felix-Ortiz, A. C., Burgos-Robles, A., Bhagat, N. D., Leppla, C. A., & Tye, K. M. (2016). Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. *Neuroscience, 321*, 197-209. doi:10.1016/j.neuroscience.2015.07.041

Felten, D. L., Felten, S. Y., Carlson, S. L., Olschowka, J. A., & Livnat, S. (1985). Noradrenergic and peptidergic innervation of lymphoid tissue. *J Immunol, 135*(2 Suppl), 755s-765s.

Fergusson, D. M., McLeod, G. F. H., Horwood, L. J., Swain, N. R., Chapple, S., & Poulton, R. (2015). Life satisfaction and mental health problems (18 to 35 years). *Psychological Medicine, 45*(11), 2427-2436. doi:10.1017/S0033291715000422

Fernández-Mendoza, J., Vela-Bueno, A., Vgontzas, A. N., Ramos-Platón, M. J., Olavarrieta-Bernardino, S., Bixler, E. O., et al. (2010). Cognitive-emotional hyperarousal as a premorbid characteristic of individuals vulnerable to insomnia. *Psychosom Med, 72*(4), 397-403. doi:10.1097/PSY.0b013e3181d75319

Ferrè, S., Hoenderop, J. G., & Bindels, R. J. (2012). Sensing mechanisms involved in Ca2+ and Mg2+ homeostasis. *Kidney Int, 82*(11), 1157-1166. doi:10.1038/ki.2012.179

File, S. E., & Hyde, J. R. (1978). Can social interaction be used to measure anxiety? *British journal of pharmacology, 62*(1), 19-24. doi:10.1111/j.1476-5381.1978.tb07001.x

Fink, G. (2009). Stress: Definition and History. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (pp. 549-555). Oxford: Academic Press.

Finne, L. B., Knardahl, S., & Lau, B. (2011). Workplace bullying and mental distress - a prospective study of Norwegian employees. *Scand J Work Environ Health, 37*(4), 276-287. doi:10.5271/sjweh.3156

Finnell, J. E., Lombard, C. M., Padi, A. R., Moffitt, C. M., Wilson, L. B., Wood, C. S., et al. (2017). Physical versus psychological social stress in male rats reveals distinct cardiovascular, inflammatory and behavioral consequences. *PLoS One, 12*(2), e0172868. doi:10.1371/journal.pone.0172868

Flak, J. N., Myers, B., Solomon, M. B., McKlveen, J. M., Krause, E. G., & Herman, J. P. (2014). Role of paraventricular nucleus-projecting norepinephrine/epinephrine neurons in acute and chronic stress. *Eur J Neurosci, 39*(11), 1903-1911. doi:10.1111/ejn.12587

Franco, L. M., Gadkari, M., Howe, K. N., Sun, J., Kardava, L., Kumar, P., et al. (2019). Immune regulation by glucocorticoids can be linked to cell type-dependent transcriptional responses. *J Exp Med, 216*(2), 384-406. doi:10.1084/jem.20180595

Frank, M. G., Baratta, M. V., Sprunger, D. B., Watkins, L. R., & Maier, S. F. (2007). Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS

pro-inflammatory cytokine responses. *Brain Behav Immun, 21*(1), 47-59. doi:10.1016/j.bbi.2006.03.005

Frazier, P. A., Tix, A. P., & Barron, K. E. (2004). Testing Moderator and Mediator Effects in Counseling Psychology Research. *Journal of Counseling Psychology, 51*(1), 115-134. doi:10.1037/0022-0167.51.1.115

Freiberg, A. S. (2020). Why We Sleep: A Hypothesis for an Ultimate or Evolutionary Origin for Sleep and Other Physiological Rhythms. *J Circadian Rhythms, 18*, 2. doi:10.5334/jcr.189

Fu, Y., Westenbroek, R. E., Scheuer, T., & Catterall, W. A. (2013). Phosphorylation sites required for regulation of cardiac calcium channels in the fight-or-flight response. *Proc Natl Acad Sci U S A, 110*(48), 19621-19626. doi:10.1073/pnas.1319421110

Fuller, P., Sherman, D., Pedersen, N. P., Saper, C. B., & Lu, J. (2011). Reassessment of the structural basis of the ascending arousal system. *Journal of Comparative Neurology, 519*(5), 933-956. doi:10.1002/cne.22559

Gao, M., Wang, X., Zhang, X., Ha, T., Ma, H., Liu, L., et al. (2015). Attenuation of Cardiac Dysfunction in Polymicrobial Sepsis by MicroRNA-146a Is Mediated via Targeting of IRAK1 and TRAF6 Expression. *J Immunol, 195*(2), 672-682. doi:10.4049/jimmunol.1403155

Gaus, S. E., Strecker, R. E., Tate, B. A., Parker, R. A., & Saper, C. B. (2002). Ventrolateral preoptic nucleus contains sleep-active, galaninergic neurons in multiple mammalian species. *Neuroscience, 115*(1), 285-294. doi:10.1016/s0306-4522(02)00308-1

Geng, J., Wang, L., Zhang, L., Qin, C., Song, Y., Ma, Y., et al. (2018). Blood-Brain Barrier Disruption Induced Cognitive Impairment Is Associated With Increase of Inflammatory Cytokine. *Frontiers in Aging Neuroscience, 10*(129). doi:10.3389/fnagi.2018.00129

Gibbons, C., Dempster, M., & Moutray, M. (2008). Stress and eustress in nursing students. *J Adv Nurs, 61*(3), 282-290. doi:10.1111/j.1365-2648.2007.04497.x

Gibbs, R. A., Weinstock, G. M., Metzker, M. L., Muzny, D. M., Sodergren, E. J., Scherer, S., et al. (2004). Genome sequence of the Brown Norway rat yields insights into mammalian evolution. *Nature, 428*(6982), 493-521. doi:10.1038/nature02426

Gidron, Y., De Zwaan, M., Quint, K., & Ocker, M. (2010). Influence of stress and health-behaviour on miRNA expression. *Mol Med Rep, 3*(3), 455-457. doi:10.3892/mmr_00000279

Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., et al. (2010). Fate Mapping Analysis Reveals That Adult Microglia Derive from Primitive Macrophages. *Science, 330*(6005), 841-845. doi:10.1126/science.1194637

Giorgi, G., Perminienė, M., Montani, F., Fiz-Perez, J., Mucci, N., & Arcangeli, G. (2016). Detrimental Effects of Workplace Bullying: Impediment of Self-Management Competence via Psychological Distress. *Frontiers in Psychology, 7*(60). doi:10.3389/fpsyg.2016.00060

Giustino, T. F., Ramanathan, K. R., Totty, M. S., Miles, O. W., & Maren, S. (2020). Locus Coeruleus Norepinephrine Drives Stress-Induced Increases in Basolateral Amygdala Firing and Impairs Extinction Learning. *J Neurosci, 40*(4), 907-916. doi:10.1523/jneurosci.1092-19.2019

Glambek, M., Nielsen, M. B., Gjerstad, J., & Einarsen, S. (2018). Gender differences in the relationship between workplace bullying and subjective back and neck pain: A two-wave study in a Norwegian probability sample. *J Psychosom Res, 106*, 73-75. doi:https://doi.org/10.1016/j.jpsychores.2018.01.010

Golden, S. A., Covington, H. E., 3rd, Berton, O., & Russo, S. J. (2011). A standardized protocol for repeated social defeat stress in mice. *Nat Protoc, 6*(8), 1183-1191. doi:10.1038/nprot.2011.361

Goncharova, N., Chigarova, O., Rudenko, N., & Oganyan, T. (2019). Glucocorticoid Negative Feedback in Regulation of the Hypothalamic-Pituitary-Adrenal Axis in Rhesus Monkeys With Various Types of Adaptive Behavior: Individual and Age-Related Differences. *Frontiers in Endocrinology, 10*(24). doi:10.3389/fendo.2019.00024

Goodwin, P. R., Meng, A., Moore, J., Hobin, M., Fulga, T. A., Van Vactor, D., et al. (2018). MicroRNAs Regulate Sleep and Sleep Homeostasis in Drosophila. *Cell reports, 23*(13), 3776-3786. doi:10.1016/j.celrep.2018.05.078

Gosselin, D., Link, V. M., Romanoski, C. E., Fonseca, G. J., Eichenfield, D. Z., Spann, N. J., et al. (2014). Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. *Cell, 159*(6), 1327-1340. doi:10.1016/j.cell.2014.11.023

Gougeon, P.-Y., Lourenssen, S., Han, T. Y., Nair, D. G., Ropeleski, M. J., & Blennerhassett, M. G. (2013). The Pro-Inflammatory Cytokines IL-1β and TNFα Are Neurotrophic for Enteric Neurons. *The Journal of Neuroscience, 33*(8), 3339-3351. doi:10.1523/jneurosci.3564-12.2013

Grabert, K., Michoel, T., Karavolos, M. H., Clohisey, S., Baillie, J. K., Stevens, M. P., et al. (2016). Microglial brain region−dependent diversity and selective regional sensitivities to aging. *Nature Neuroscience, 19*(3), 504-516. doi:10.1038/nn.4222

Green, S. A., Turki, J., Innis, M., & Liggett, S. B. (1994). Amino-Terminal Polymorphisms of the Human .beta.2-Adrenergic Receptor Impart Distinct Agonist-Promoted Regulatory Properties. *Biochemistry, 33*(32), 9414-9419. doi:10.1021/bi00198a006

Grisanti, L. A., Evanson, J., Marchus, E., Jorissen, H., Woster, A. P., DeKrey, W., et al. (2010). Pro-inflammatory responses in human monocytes are beta1-adrenergic receptor subtype dependent. *Mol Immunol, 47*(6), 1244-1254. doi:10.1016/j.molimm.2009.12.013

Hackam, D. G., & Redelmeier, D. A. (2006). Translation of research evidence from animals to humans. *Jama, 296*(14), 1731-1732. doi:10.1001/jama.296.14.1731

Hadcock, J. R., & Malbon, C. C. (1988). Down-regulation of beta-adrenergic receptors: agonist-induced reduction in receptor mRNA levels. *Proc Natl Acad Sci U S A, 85*(14), 5021-5025. doi:10.1073/pnas.85.14.5021

Hammond, S. M., Bernstein, E., Beach, D., & Hannon, G. J. (2000). An RNA-directed nuclease mediates post-transcriptional gene silencing in Drosophila cells. *Nature, 404*(6775), 293-296. doi:10.1038/35005107

Hamre, K. V., Einarsen, S. V., Hoprekstad Ø, L., Pallesen, S., Bjorvatn, B., Waage, S., et al. (2020). Accumulated Long-Term Exposure to Workplace Bullying Impairs Psychological Hardiness: A Five-Year Longitudinal Study among Nurses. *Int J Environ Res Public Health, 17*(7). doi:10.3390/ijerph17072587

Han, Q.-Q., Yang, L., Huang, H.-J., Wang, Y.-L., Yu, R., Wang, J., et al. (2017). Differential GR Expression and Translocation in the Hippocampus Mediates Susceptibility vs. Resilience to Chronic Social Defeat Stress. *Frontiers in Neuroscience, 11*(287). doi:10.3389/fnins.2017.00287

Hanke, M. L., Powell, N. D., Stiner, L. M., Bailey, M. T., & Sheridan, J. F. (2012). Beta adrenergic blockade decreases the immunomodulatory effects of social disruption stress. *Brain Behav Immun, 26*(7), 1150-1159. doi:10.1016/j.bbi.2012.07.011

Hannibal, K. E., & Bishop, M. D. (2014). Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther, 94*(12), 1816-1825. doi:10.2522/ptj.20130597

Hansen, A. M., Hogh, A., & Persson, R. (2011). Frequency of bullying at work, physiological response, and mental health. *J Psychosom Res, 70*(1), 19-27. doi:10.1016/j.jpsychores.2010.05.010

Hansen, A. M., Hogh, A., Persson, R., Karlson, B., Garde, A. H., & Orbaek, P. (2006). Bullying at work, health outcomes, and physiological stress response. *J Psychosom Res, 60*(1), 63-72. doi:10.1016/j.jpsychores.2005.06.078

Haramati, S., Navon, I., Issler, O., Ezra-Nevo, G., Gil, S., Zwang, R., et al. (2011). MicroRNA as repressors of stress-induced anxiety: the case of amygdalar miR-34. *J Neurosci, 31*(40), 14191-14203. doi:10.1523/jneurosci.1673-11.2011

Harb, A., Rayan, A., & Al Khashashneh, O. Z. (2019). The Relationship Between Workplace Bullying and Positive Mental Health Among Registered Nurses. *J Am Psychiatr Nurses Assoc*, 1078390319877223. doi:10.1177/1078390319877223

Harnprasopwat, R., Ha, D., Toyoshima, T., Lodish, H., Tojo, A., & Kotani, A. (2010). Alteration of processing induced by a single nucleotide polymorphism in pri-miR-126. *Biochem Biophys Res Commun, 399*(2), 117-122. doi:10.1016/j.bbrc.2010.07.009

Harvey, A., Nathens, A. B., Bandiera, G., & Leblanc, V. R. (2010). Threat and challenge: cognitive appraisal and stress responses in simulated trauma resuscitations. *Med Educ, 44*(6), 587-594. doi:10.1111/j.1365-2923.2010.03634.x

Harvey, M., Treadway, D. C., & Heames, J. T. (2007). The occurrence of bullying in global organizations: A model and issues associated with social/emotional contagion. *Journal of Applied Social Psychology, 37*(11), 2576-2599. doi:10.1111/j.1559-1816.2007.00271.x

Harvey, S., & Keashly, L. (2003). Predicting the risk for aggression in the workplace: Risk factors, self-esteem and time at work. *Social Behavior and Personality: An International Journal, 31*(8), 807-814. doi:10.2224/sbp.2003.31.8.807

Heames, J., & Harvey, M. (2006). Workplace bullying: a cross-level assessment. *Management Decision, 44*(9), 1214-1230. doi:10.1108/00251740610707695

Heidt, T., Sager, H. B., Courties, G., Dutta, P., Iwamoto, Y., Zaltsman, A., et al. (2014). Chronic variable stress activates hematopoietic stem cells. *Nat Med, 20*(7), 754-758. doi:10.1038/nm.3589

Heinemann, P. P. (1972). *Mobbning: Gruppvåld bland barn och vuxna*: Natur och kultur.

Henderson, F., Vialou, V., El Mestikawy, S., & Fabre, V. (2017). Effects of Social Defeat Stress on Sleep in Mice. *Frontiers in behavioral neuroscience, 11*, 227. doi:10.3389/fnbeh.2017.00227

Hering, D., Lachowska, K., & Schlaich, M. (2015). Role of the Sympathetic Nervous System in Stress-Mediated Cardiovascular Disease. *Current Hypertension Reports, 17*(10), 80. doi:10.1007/s11906-015-0594-5

Herman, J. P., McKlveen, J. M., Solomon, M. B., Carvalho-Netto, E., & Myers, B. (2012). Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas, 45*(4), 292-298. doi:10.1590/s0100-879x2012007500041

Hewett, R., Liefooghe, A., Visockaite, G., & Roongrerngsuke, S. (2018). Bullying at work: Cognitive appraisal of negative acts, coping, wellbeing, and performance. *J Occup Health Psychol, 23*(1), 71-84. doi:10.1037/ocp0000064

Hijmans, J. G., Levy, M. a., Garcia, V., Lincenberg, G. M., Diehl, K. J., Greiner, J. J., et al. (2019). Insufficient sleep is associated with a pro-atherogenic circulating microRNA signature. *Experimental physiology, 104*(6), 975-982. doi:10.1113/EP087469

Hodes, G. E., Kana, V., Menard, C., Merad, M., & Russo, S. J. (2015). Neuroimmune mechanisms of depression. *Nature Neuroscience, 18*(10), 1386-1393. doi:10.1038/nn.4113

Hoel, H., Rayner, C., & Cooper, C. L. (1999). Workplace bullying *International review of industrial and organizational psychology 1999, Vol. 14.* (pp. 195-230). New York, NY, US: John Wiley & Sons Ltd.

Hogh, A., Hansen, A. M., Mikkelsen, E. G., & Persson, R. (2012). Exposure to negative acts at work, psychological stress reactions and physiological stress response. *J Psychosom Res, 73*(1), 47-52. doi:10.1016/j.jpsychores.2012.04.004

Hollis, F., Wang, H., Dietz, D., Gunjan, A., & Kabbaj, M. (2010). The effects of repeated social defeat on long-term depressive-like behavior and short-term histone modifications in the hippocampus in male Sprague-Dawley rats. *Psychopharmacology, 211*(1), 69-77. doi:10.1007/s00213-010-1869-9

Hoprekstad, Ø. L., Hetland, J., Wold, B., Torp, H., & Valvatne Einarsen, S. (2020). Exposure to Bullying Behaviors at Work and Depressive Tendencies: The Moderating Role of Victimization From Bullying During Adolescence. *Journal of Interpersonal Violence*, 0886260519900272. doi:10.1177/0886260519900272

Hou, J., Wang, P., Lin, L., Liu, X., Ma, F., An, H., et al. (2009). MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. *J Immunol, 183*(3), 2150-2158. doi:10.4049/jimmunol.0900707

Hou, Y., Sun, Y., Shan, H., Li, X., Zhang, M., Zhou, X., et al. (2012). beta-adrenoceptor regulates miRNA expression in rat heart. *Med Sci Monit, 18*(8), Br309-314. doi:10.12659/msm.883263

Hubert, A. B., & van Veldhoven, M. (2001). Risk sectors for undesirable behaviour and mobbing. *European Journal of Work and Organizational Psychology, 10*(4), 415-424. doi:10.1080/13594320143000799

Hung, C. H., Chu, C. C., Chen, Y. C., Chen, Y. W., Hong, H. J., & Wang, J. J. (2011). Isoflurane for spinal anesthesia in the rat. *Neurosci Lett, 501*(3), 138-142. doi:10.1016/j.neulet.2011.07.002

Hung, Y.-Y., Wu, M.-K., Tsai, M.-C., Huang, Y.-L., & Kang, H.-Y. (2019). Aberrant Expression of Intracellular let-7e, miR-146a, and miR-155 Correlates with Severity of Depression in Patients with Major Depressive Disorder and Is Ameliorated after Antidepressant Treatment. *Cells, 8*(7), 647. doi:10.3390/cells8070647

Igaz, P., Salvi, R., Rey, J. P., Glauser, M., Pralong, F. P., & Gaillard, R. C. (2006). Effects of cytokines on gonadotropin-releasing hormone (GnRH) gene expression in primary hypothalamic neurons and in GnRH neurons immortalized conditionally. *Endocrinology, 147*(2), 1037-1043. doi:10.1210/en.2005-0729

Iniguez, S. D., Riggs, L. M., Nieto, S. J., Dayrit, G., Zamora, N. N., Shawhan, K. L., et al. (2014). Social defeat stress induces a depression-like phenotype in adolescent male c57BL/6 mice. *Stress, 17*(3), 247-255. doi:10.3109/10253890.2014.910650

Irwin, M. R., Olmstead, R., & Carroll, J. E. (2016). Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry, 80*(1), 40-52. doi:10.1016/j.biopsych.2015.05.014

Iwata, M., Ota, K. T., Li, X. Y., Sakaue, F., Li, N., Dutheil, S., et al. (2016). Psychological Stress Activates the Inflammasome via Release of Adenosine Triphosphate and Stimulation of the Purinergic Type 2X7 Receptor. *Biol Psychiatry, 80*(1), 12-22. doi:10.1016/j.biopsych.2015.11.026

Jacobsen, D. P., Eriksen, M. B., Rajalingam, D., Nymoen, I., Nielsen, M. B., Einarsen, S. V., et al. (2019). Exposure to workplace bullying, microRNAs and pain; evidence of a moderating effect of miR-30c rs928508 and miR-223 rs3848900. *Stress*, 1-10. doi:10.1080/10253890.2019.1642320

Jacobsen, D. P., Nielsen, M. B., Einarsen, S., & Gjerstad, J. (2018). Negative social acts and pain: evidence of a workplace bullying and 5-HTT genotype interaction. *Scand J Work Environ Health, 44*(3), 283-290. doi:10.5271/sjweh.3704

Jacobson, K. J. L., Hood, J. N., & Van Buren, H. J. (2013). Workplace bullying across cultures: A research agenda. *International Journal of Cross Cultural Management, 14*(1), 47-65. doi:10.1177/1470595813494192

Jakubzick, C., Gautier, E. L., Gibbings, S. L., Sojka, D. K., Schlitzer, A., Johnson, T. E., et al. (2013). Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. *Immunity, 39*(3), 599-610. doi:10.1016/j.immuni.2013.08.007

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature, 517*(7534), 284-292. doi:10.1038/nature14188

Jansson, M., & Linton, S. J. (2007). Psychological mechanisms in the maintenance of insomnia: arousal, distress, and sleep-related beliefs. *Behav Res Ther, 45*(3), 511-521. doi:10.1016/j.brat.2006.04.003

Jenne, Craig N., Wong, Connie H. Y., Zemp, Franz J., McDonald, B., Rahman, Masmudur M., Forsyth, Peter A., et al. (2013). Neutrophils Recruited to Sites of

Infection Protect from Virus Challenge by Releasing Neutrophil Extracellular Traps. *Cell Host & Microbe, 13*(2), 169-180. doi:https://doi.org/10.1016/j.chom.2013.01.005

Joëls, M., Karst, H., & Sarabdjitsingh, R. A. (2018). The stressed brain of humans and rodents. *Acta physiologica (Oxford, England), 223*(2), e13066-e13066. doi:10.1111/apha.13066

Joëls, M., Sarabdjitsingh, R. A., & Karst, H. (2012). Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. *Pharmacological reviews, 64*(4), 901-938. doi:10.1124/pr.112.005892

Johnson, J. D., Barnard, D. F., Kulp, A. C., & Mehta, D. M. (2019). Neuroendocrine Regulation of Brain Cytokines After Psychological Stress. *Journal of the Endocrine Society, 3*(7), 1302-1320. doi:10.1210/js.2019-00053

Kaidanovich-Beilin, O., Lipina, T., Vukobradovic, I., Roder, J., & Woodgett, J. R. (2011). Assessment of social interaction behaviors. *Journal of visualized experiments : JoVE*(48), 2473. doi:10.3791/2473

Kallestad, H., Jacobsen, H. B., Landrø, N. I., Borchgrevink, P. C., & Stiles, T. C. (2015). The role of insomnia in the treatment of chronic fatigue. *J Psychosom Res, 78*(5), 427-432. doi:10.1016/j.jpsychores.2014.11.022

Kawano, M., Takagi, R., Saika, K., Matsui, M., & Matsushita, S. (2018). Dopamine regulates cytokine secretion during innate and adaptive immune responses. *International Immunology, 30*(12), 591-606. doi:10.1093/intimm/dxy057

Keashly, L. (1997). Emotional Abuse in the Workplace. *Journal of Emotional Abuse, 1*(1), 85-117. doi:10.1300/J135v01n01_05

Kesse, W. K., Parker, T. L., & Coupland, R. E. (1988). The innervation of the adrenal gland. I. The source of pre- and postganglionic nerve fibres to the rat adrenal gland. *J Anat, 157*, 33-41.

Kinsey, S. G., Bailey, M. T., Sheridan, J. F., Padgett, D. A., & Avitsur, R. (2007). Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. *Brain Behav Immun, 21*(4), 458-466. doi:10.1016/j.bbi.2006.11.001

Kirchler, E., & Lang, M. (1998). Mobbingerfahrungen: Subjektive Beschreibung und Bewertung der Arbeitssituation. *German Journal of Human Resource Management, 12*(3), 352-362. doi:10.1177/239700229801200305

Kivimäki, M., Virtanen, M., Elovainio, M., Väänänen, A., Keltikangas-Järvinen, L., & Vahtera, J. (2006). Prevalent cardiovascular disease, risk factors and selection out of shift work. *Scandinavian Journal of Work, Environment & Health*(3), 204-208. doi:10.5271/sjweh.1000

Kizaki, T., Izawa, T., Sakurai, T., Haga, S., Taniguchi, N., Tajiri, H., et al. (2008). Beta2-adrenergic receptor regulates Toll-like receptor-4-induced nuclear factor-kappaB activation through beta-arrestin 2. *Immunology, 124*(3), 348-356. doi:10.1111/j.1365-2567.2007.02781.x

Kobayashi, S. (2015). Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load. *Temperature (Austin, Tex.), 2*(3), 346-351. doi:10.1080/23328940.2015.1039190

Kok, B. E., Coffey, K. A., Cohn, M. A., Catalino, L. I., Vacharkulksemsuk, T., Algoe, S. B., et al. (2013). How Positive Emotions Build Physical Health: Perceived Positive Social Connections Account for the Upward Spiral Between Positive Emotions and Vagal Tone. *Psychological Science, 24*(7), 1123-1132. doi:10.1177/0956797612470827

Kollack-Walker, S., Watson, S. J., & Akil, H. (1997). Social stress in hamsters: defeat activates specific neurocircuits within the brain. *J Neurosci, 17*(22), 8842-8855.

Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., et al. (2011). Stress revisited: A critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews, 35*(5), 1291-1301. doi:https://doi.org/10.1016/j.neubiorev.2011.02.003

Koolhaas, J. M., Coppens, C. M., de Boer, S. F., Buwalda, B., Meerlo, P., & Timmermans, P. J. (2013). The resident-intruder paradigm: a standardized test for aggression, violence and social stress. *Journal of visualized experiments : JoVE*(77), e4367. doi:10.3791/4367

Kotas, M. E., & Medzhitov, R. (2015). Homeostasis, inflammation, and disease susceptibility. *Cell, 160*(5), 816-827. doi:10.1016/j.cell.2015.02.010

La Perle, K. M. D., & Dintzis, S. M. (2018). 15 - Endocrine System. In P. M. Treuting, S. M. Dintzis, & K. S. Montine (Eds.), *Comparative Anatomy and Histology (Second Edition)* (pp. 251-273). San Diego: Academic Press.

Lakshminarasimhan, H., & Chattarji, S. (2012). Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. *PLoS One, 7*(1), e30481. doi:10.1371/journal.pone.0030481

Landgraf, D., Long, J., Der-Avakian, A., Streets, M., & Welsh, D. K. (2015). Dissociation of learned helplessness and fear conditioning in mice: a mouse model of depression. *PLoS One, 10*(4), e0125892. doi:10.1371/journal.pone.0125892

Lavin, Y., Winter, D., Blecher-Gonen, R., David, E., Keren-Shaul, H., Merad, M., et al. (2014). Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment. *Cell, 159*(6), 1312-1326. doi:10.1016/j.cell.2014.11.018

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. New York, UNITED STATES: Springer Publishing Company.

Lee, D. W., Chung, S., Yoo, H. J., Kim, S. J., Woo, C. W., Kim, S. T., et al. (2016). Neurochemical Changes Associated with Stress-Induced Sleep Disturbance in Rats: In Vivo and In Vitro Measurements. *PLoS One, 11*(4), e0153346. doi:10.1371/journal.pone.0153346

Lee, H. M., Kim, T. S., & Jo, E. K. (2016). MiR-146 and miR-125 in the regulation of innate immunity and inflammation. *BMB Rep, 49*(6), 311-318.

Leymann, H. (1990). Mobbing and psychological terror at workplaces. *Violence Vict, 5*(2), 119-126.

Leymann, H. (1996). The content and development of mobbing at work *European Journal of Work and Organizational Psychology, 5*(2), 165-184. doi:10.1080/13594329608414853

Li, K., Ching, D., Luk, F. S., & Raffai, R. L. (2015). Apolipoprotein E enhances microRNA-146a in monocytes and macrophages to suppress nuclear factor-κB-driven inflammation and atherosclerosis. *Circ Res, 117*(1), e1-e11. doi:10.1161/circresaha.117.305844

Li, Y., Zhou, D., Ren, Y., Zhang, Z., Guo, X., Ma, M., et al. (2019). Mir223 restrains autophagy and promotes CNS inflammation by targeting ATG16L1. *Autophagy, 15*(3), 478-492. doi:10.1080/15548627.2018.1522467

Linton, S. J., Kecklund, G., Franklin, K. A., Leissner, L. C., Sivertsen, B., Lindberg, E., et al. (2015). The effect of the work environment on future sleep disturbances: a systematic review. *Sleep Med Rev, 23*, 10-19. doi:10.1016/j.smrv.2014.10.010

Litwiller, B., Snyder, L. A., Taylor, W. D., & Steele, L. M. (2017). The relationship between sleep and work: A meta-analysis. *J Appl Psychol, 102*(4), 682-699. doi:10.1037/apl0000169

Liu, W. Z., Zhang, W. H., Zheng, Z. H., Zou, J. X., Liu, X. X., Huang, S. H., et al. (2020). Identification of a prefrontal cortex-to-amygdala pathway for chronic stress-induced anxiety. *Nat Commun, 11*(1), 2221. doi:10.1038/s41467-020-15920-7

Lopez, J. P., Lim, R., Cruceanu, C., Crapper, L., Fasano, C., Labonte, B., et al. (2014). miR-1202 is a primate-specific and brain-enriched microRNA involved in major depression and antidepressant treatment. *Nat Med, 20*(7), 764-768. doi:10.1038/nm.3582

Lorton, D., & Bellinger, D. L. (2015). Molecular mechanisms underlying β-adrenergic receptor-mediated cross-talk between sympathetic neurons and immune cells. *International journal of molecular sciences, 16*(3), 5635-5665. doi:10.3390/ijms16035635

Lorton, D., Lubahn, C. L., Estus, C., Millar, B. A., Carter, J. L., Wood, C. A., et al. (2006). Bidirectional Communication between the Brain and the Immune System: Implications for Physiological Sleep and Disorders with Disrupted Sleep. *Neuroimmunomodulation, 13*(5-6), 357-374. doi:10.1159/000104864

Löwenberg, M., Tuynman, J., Bilderbeek, J., Gaber, T., Buttgereit, F., van Deventer, S., et al. (2005). Rapid immunosuppressive effects of glucocorticoids mediated through Lck and Fyn. *Blood, 106*(5), 1703-1710. doi:10.1182/blood-2004-12-4790

Lowrance, S. A., Ionadi, A., McKay, E., Douglas, X., & Johnson, J. D. (2016). Sympathetic nervous system contributes to enhanced corticosterone levels following chronic stress. *Psychoneuroendocrinology, 68*, 163-170. doi:10.1016/j.psyneuen.2016.02.027

Lozano-Montes, L., Astori, S., Abad, S., Guillot de Suduiraut, I., Sandi, C., & Zalachoras, I. (2019). Latency to Reward Predicts Social Dominance in Rats: A Causal Role for the Dopaminergic Mesolimbic System. *Frontiers in behavioral neuroscience, 13*, 69-69. doi:10.3389/fnbeh.2019.00069

Lucassen, E. A., de Mutsert, R., le Cessie, S., Appelman-Dijkstra, N. M., Rosendaal, F. R., van Heemst, D., et al. (2017). Poor sleep quality and later sleep timing are risk factors for osteopenia and sarcopenia in middle-aged men and women: The NEO study. *PLoS One, 12*(5), e0176685. doi:10.1371/journal.pone.0176685

Luo, Y. J., Li, Y. D., Wang, L., Yang, S. R., Yuan, X. S., Wang, J., et al. (2018). Nucleus accumbens controls wakefulness by a subpopulation of neurons expressing dopamine D(1) receptors. *Nat Commun, 9*(1), 1576. doi:10.1038/s41467-018-03889-3

Mackiewicz, M., Shockley, K. R., Romer, M. A., Galante, R. J., Zimmerman, J. E., Naidoo, N., et al. (2007). Macromolecule biosynthesis: a key function of sleep. *Physiol Genomics, 31*(3), 441-457. doi:10.1152/physiolgenomics.00275.2006

Madry, C., Kyrargyri, V., Arancibia-Carcamo, I. L., Jolivet, R., Kohsaka, S., Bryan, R. M., et al. (2018). Microglial Ramification, Surveillance, and Interleukin-1beta Release Are Regulated by the Two-Pore Domain K(+) Channel THIK-1. *Neuron, 97*(2), 299-312.e296. doi:10.1016/j.neuron.2017.12.002

Magee, C., Gordon, R., Robinson, L., Reis, S., Caputi, P., & Oades, L. (2015). Distinct workplace bullying experiences and sleep quality: A person-centred approach. *Personality and Individual Differences, 87*, 200-205. doi:https://doi.org/10.1016/j.paid.2015.08.004

Malinauskiene, V., & Einarsen, S. (2014). Workplace bullying and post-traumatic stress symptoms among family physicians in Lithuania: an occupation and region specific approach. *Int J Occup Med Environ Health, 27*(6), 919-932. doi:10.2478/s13382-014-0328-y

Martin, E. I., Ressler, K. J., Binder, E., & Nemeroff, C. B. (2009). The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *The Psychiatric clinics of North America, 32*(3), 549-575. doi:10.1016/j.psc.2009.05.004

McCall, Jordan G., Al-Hasani, R., Siuda, Edward R., Hong, Daniel Y., Norris, Aaron J., Ford, Christopher P., et al. (2015). CRH Engagement of the Locus Coeruleus

Noradrenergic System Mediates Stress-Induced Anxiety. *Neuron, 87*(3), 605-620. doi:https://doi.org/10.1016/j.neuron.2015.07.002

McCormick, C. M., & Mathews, I. Z. (2010). Adolescent development, hypothalamic-pituitary-adrenal function, and programming of adult learning and memory. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34*(5), 756-765. doi:https://doi.org/10.1016/j.pnpbp.2009.09.019

McDevitt, R. A., Szot, P., Baratta, M. V., Bland, S. T., White, S. S., Maier, S. F., et al. (2009). Stress-induced activity in the locus coeruleus is not sensitive to stressor controllability. *Brain Res, 1285*, 109-118. doi:10.1016/j.brainres.2009.06.017

McEwen, B. S. (2000). Allostasis and Allostatic Load: Implications for Neuropsychopharmacology. *Neuropsychopharmacology, 22*(2), 108-124. doi:10.1016/S0893-133X(99)00129-3

McEwen, B. S. (2005). Stressed or stressed out: what is the difference? *J Psychiatry Neurosci, 30*(5), 315-318.

McEwen, B. S. (2007a). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev, 87*(3), 873-904. doi:10.1152/physrev.00041.2006

McEwen, B. S. (2007b). Stress, Definitions and Concepts of*. In G. Fink (Ed.), *Encyclopedia of Stress (Second Edition)* (pp. 653). New York: Academic Press.

McEwen, B. S. (2012a). Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci U S A, 109 Suppl 2*(Suppl 2), 17180-17185. doi:10.1073/pnas.1121254109

McEwen, B. S. (2012b). The ever-changing brain: cellular and molecular mechanisms for the effects of stressful experiences. *Dev Neurobiol, 72*(6), 878-890. doi:10.1002/dneu.20968

McEwen, B. S. (2017). Neurobiological and Systemic Effects of Chronic Stress. *Chronic stress (Thousand Oaks, Calif.), 1*, 2470547017692328. doi:10.1177/2470547017692328

McEwen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., et al. (2015). Mechanisms of stress in the brain. *Nat Neurosci, 18*(10), 1353-1363. doi:10.1038/nn.4086

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and allostasis-induced brain plasticity. *Annual review of medicine, 62*, 431-445. doi:10.1146/annurev-med-052209-100430

McEwen, B. S., Gray, J., & Nasca, C. (2015). Recognizing Resilience: Learning from the Effects of Stress on the Brain. *Neurobiol Stress, 1*, 1-11. doi:10.1016/j.ynstr.2014.09.001

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology, 41*(1), 3-23. doi:10.1038/npp.2015.171

McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Arch Intern Med, 153*(18), 2093-2101.

McKim, D. B., Yin, W., Wang, Y., Cole, S. W., Godbout, J. P., & Sheridan, J. F. (2018). Social Stress Mobilizes Hematopoietic Stem Cells to Establish Persistent Splenic Myelopoiesis. *Cell reports, 25*(9), 2552-2562.e2553. doi:10.1016/j.celrep.2018.10.102

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research, 45*(8), 1027-1035. doi:https://doi.org/10.1016/j.jpsychires.2011.03.006

McNamee, E. N., Griffin, E. W., Ryan, K. M., Ryan, K. J., Heffernan, S., Harkin, A., et al. (2010). Noradrenaline acting at beta-adrenoceptors induces expression of IL-1beta and its negative regulators IL-1ra and IL-1RII, and drives an overall anti-inflammatory phenotype in rat cortex. *Neuropharmacology, 59*(1-2), 37-48. doi:10.1016/j.neuropharm.2010.03.014

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature, 454*(7203), 428-435. doi:10.1038/nature07201

Meister, G., Landthaler, M., Patkaniowska, A., Dorsett, Y., Teng, G., & Tuschl, T. (2004). Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs. *Mol Cell, 15*(2), 185-197. doi:10.1016/j.molcel.2004.07.007

Menard, C., Pfau, M. L., Hodes, G. E., Kana, V., Wang, V. X., Bouchard, S., et al. (2017). Social stress induces neurovascular pathology promoting depression. *Nature Neuroscience, 20*(12), 1752-1760. doi:10.1038/s41593-017-0010-3

Merkulov, V. M., Merkulova, T. I., & Bondar, N. P. (2017). Mechanisms of Brain Glucocorticoid Resistance in Stress-Induced Psychopathologies. *Biochemistry (Mosc), 82*(3), 351-365. doi:10.1134/s0006297917030142

Merlot, E., Moze, E., Dantzer, R., & Neveu, P. J. (2003). Importance of fighting in the immune effects of social defeat. *Physiol Behav, 80*(2-3), 351-357. doi:10.1016/j.physbeh.2003.08.005

Meyers, L. (2006). Worrying for a living? *APA Monitor on Psychology, 37*(7).

Miczek, K. A. (1979). A new test for aggression in rats without aversive stimulation: Differential effects of d-amphetamine and cocaine. *Psychopharmacology, 60*(3), 253-259. doi:10.1007/bf00426664

Miczek, K. A., Yap, J. J., & Covington, H. E., 3rd. (2008). Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. *Pharmacol Ther, 120*(2), 102-128. doi:10.1016/j.pharmthera.2008.07.006

Mikkelsen, E. G. e., & Einarsen, S. (2002). Basic assumptions and symptoms of post-traumatic stress among victims of bullying at work. *European Journal of Work and Organizational Psychology, 11*(1), 87-111. doi:10.1080/13594320143000861

Miller, A. H., Haroon, E., Raison, C. L., & Felger, J. C. (2013). Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits. *Depression and Anxiety, 30*(4), 297-306. doi:10.1002/da.22084

Miller, E. S., Apple, C. G., Kannan, K. B., Funk, Z. M., Plazas, J. M., Efron, P. A., et al. (2019). Chronic stress induces persistent low-grade inflammation. *Am J Surg, 218*(4), 677-683. doi:10.1016/j.amjsurg.2019.07.006

Miller, G. E., Chen, E., Sze, J., Marin, T., Arevalo, J. M., Doll, R., et al. (2008). A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF-kappa B signaling. *Biol Psychiatry, 64*(4), 266-272. doi:10.1016/j.biopsych.2008.03.017

Moberg, G. P. (1987). Problems in defining stress and distress in animals. *J Am Vet Med Assoc, 191*(10), 1207-1211.

Motivala, S. J. (2011). Sleep and Inflammation: Psychoneuroimmunology in the Context of Cardiovascular Disease. *Annals of Behavioral Medicine, 42*(2), 141-152. doi:10.1007/s12160-011-9280-2

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biol Psychiatry, 77*(3), 276-284. doi:10.1016/j.biopsych.2014.02.014

Mul, J. D., Soto, M., Cahill, M. E., Ryan, R. E., Takahashi, H., So, K., et al. (2018). Voluntary wheel running promotes resilience to chronic social defeat stress in mice: a role for nucleus accumbens ΔFosB. *Neuropsychopharmacology, 43*(9), 1934-1942. doi:10.1038/s41386-018-0103-z

Munnangi, S., & Boktor, S. W. (2020). Epidemiology Of Study Design *StatPearls*. Treasure Island (FL): StatPearls Publishing

Nadler, J. J., Moy, S. S., Dold, G., Simmons, N., Perez, A., Young, N. B., et al. (2004). Automated apparatus for quantitation of social approach behaviors in mice. *Genes, Brain and Behavior, 3*(5), 303-314. doi:10.1111/j.1601-183X.2004.00071.x

Nakaizumi, A., Horie, T., Kida, T., Kurimoto, T., Sugiyama, T., Ikeda, T., et al. (2012). Nitric oxide potentiates TNF-α-induced neurotoxicity through suppression of NF-κB. *Cell Mol Neurobiol, 32*(1), 95-106. doi:10.1007/s10571-011-9739-5

Neall, A. M., & Tuckey, M. R. (2014). A methodological review of research on the antecedents and consequences of workplace harassment. *Journal of Occupational and Organizational Psychology, 87*(2), 225-257. doi:10.1111/joop.12059

Neumann, M., Grieshammer, T., Chuvpilo, S., Kneitz, B., Lohoff, M., Schimpl, A., et al. (1995). RelA/p65 is a molecular target for the immunosuppressive action of protein kinase A. *Embo j, 14*(9), 1991-2004.

Niedhammer, I., Malard, L., & Chastang, J. F. (2015). Occupational factors and subsequent major depressive and generalized anxiety disorders in the prospective French national SIP study. *BMC Public Health, 15*(1), 200. doi:10.1186/s12889-015-1559-y

Nielsen, M. B., Christensen, J. O., Finne, L. B., & Knardahl, S. (2020). Workplace bullying, mental distress, and sickness absence: the protective role of social

support. *Int Arch Occup Environ Health, 93*(1), 43-53. doi:10.1007/s00420-019-01463-y

Nielsen, M. B., & Einarsen, S. V. (2012). Outcomes of exposure to workplace bullying: A meta-analytic review. *Work & Stress, 26*(4), 309-332. doi:10.1080/02678373.2012.734709

Nielsen, M. B., & Einarsen, S. V. (2018). What we know, what we do not know, and what we should and could have known about workplace bullying: An overview of the literature and agenda for future research. *Aggression and Violent Behavior, 42*, 71-83. doi:https://doi.org/10.1016/j.avb.2018.06.007

Nielsen, M. B., Gjerstad, J., Jacobsen, D. P., & Einarsen, S. V. (2017). Does Ability to Defend Moderate the Association between Exposure to Bullying and Symptoms of Anxiety? *Front Psychol, 8*, 1953. doi:10.3389/fpsyg.2017.01953

Nielsen, M. B., Harris, A., Pallesen, S., & Einarsen, S. V. (2020). Workplace bullying and sleep – A systematic review and meta-analysis of the research literature. *Sleep Medicine Reviews, 51*, 101289. doi:https://doi.org/10.1016/j.smrv.2020.101289

Nielsen, M. B., Hetland, J., Matthiesen, S. B., & Einarsen, S. V. (2012). Longitudinal relationships between workplace bullying and psychological distress. *Scandinavian Journal of Work, Environment & Health, 38*(1), 38-46.

Nielsen, M. B., Mageroy, N., Gjerstad, J., & Einarsen, S. (2014). Workplace bullying and subsequent health problems. *The Journal of the Norwegian Medical Association, 134*(12-13), 1233-1238. doi:10.4045/tidsskr.13.0880

Nielsen, M. B., Matthiesen, S. B., & Einarsen, S. (2008). Sense of coherence as a protective mechanism among targets of workplace bullying. *J Occup Health Psychol, 13*(2), 128-136. doi:10.1037/1076-8998.13.2.128

Nielsen, M. B., Matthiesen, S. B., & Einarsen, S. V. (2010). The impact of methodological moderators on prevalence rates of workplace bullying. A meta-analysis. *Journal of Occupational and Organizational Psychology, 83*(4), 955-979. doi:10.1348/096317909X481256

Nielsen, M. B., Notelaers, G., & Einarsen, S. (2011). Measuring exposure to workplace bullying. In S. Einarsen, H. Hoel, D. Zapf, & C. L. Cooper (Eds.) *Bullying and harassment in the workplace* (2nd ed., pp. 149-174). Boca Raton: CRC Press

Nielsen, M. B., Notelaers, G., & Einarsen, S. (2020). Methodological issues in the measurement of workplace bullying

Nielsen, M. B., Pallesen, S., Harris, A., & Einarsen, S. V. (2018). Protocol for a systematic review and meta-analysis of research on the associations between workplace bullying and sleep. *Systematic Reviews, 7*(1), 232. doi:10.1186/s13643-018-0898-z

Nielsen, M. B., Skogstad, A., Matthiesen, S. B., Glasø, L., Aasland, M. S., Notelaers, G., et al. (2009). Prevalence of workplace bullying in Norway: Comparisons across time and estimation methods. *European Journal of Work and Organizational Psychology, 18*(1), 81-101. doi:10.1080/13594320801969707

Nielsen, M. B., Tvedt, S. D., & Matthiesen, S. B. (2013). Prevalence and occupational predictors of psychological distress in the offshore petroleum industry: a prospective study. *Int Arch Occup Environ Health, 86*(8), 875-885. doi:10.1007/s00420-012-0825-x

Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science, 308*(5726), 1314-1318. doi:10.1126/science.1110647

Niraula, A., Witcher, K. G., Sheridan, J. F., & Godbout, J. P. (2018). Interleukin-6 Induced by Social Stress Promotes a Unique Transcriptional Signature in the Monocytes That Facilitate Anxiety. *Biol Psychiatry*. doi:https://doi.org/10.1016/j.biopsych.2018.09.030

Notelaers, G., Van der Heijden, B., Guenter, H., Nielsen, M. B., & Einarsen, S. V. (2018). Do Interpersonal Conflict, Aggression and Bullying at the Workplace Overlap? A Latent Class Modeling Approach. *Frontiers in Psychology, 9*(1743). doi:10.3389/fpsyg.2018.01743

Olcese, U., Oude Lohuis, M. N., & Pennartz, C. M. A. (2018). Sensory Processing Across Conscious and Nonconscious Brain States: From Single Neurons to Distributed Networks for Inferential Representation. *Frontiers in systems neuroscience, 12*, 49-49. doi:10.3389/fnsys.2018.00049

Olini, N., Rothfuchs, I., Azzinnari, D., Pryce, C. R., Kurth, S., & Huber, R. (2017). Chronic social stress leads to altered sleep homeostasis in mice. *Behav Brain Res, 327*, 167-173. doi:10.1016/j.bbr.2017.03.022

Olweus, D. (1978). *Aggression in the schools: Bullies and whipping boys*. Oxford, England: Hemisphere.

Olweus, D. (1993). *Bullying at school: What we know and what we can do*. Malden: Blackwell Publishing.

Osterlund, C. D., Rodriguez-Santiago, M., Woodruff, E. R., Newsom, R. J., Chadayammuri, A. P., & Spencer, R. L. (2016). Glucocorticoid Fast Feedback Inhibition of Stress-Induced ACTH Secretion in the Male Rat: Rate Independence and Stress-State Resistance. *Endocrinology, 157*(7), 2785-2798. doi:10.1210/en.2016-1123

Ota, S. M., Suchecki, D., & Meerlo, P. (2018). Chronic social defeat stress suppresses locomotor activity but does not affect the free-running circadian period of the activity rhythm in mice. *Neurobiology of Sleep and Circadian Rhythms, 5*, 1-7. doi:https://doi.org/10.1016/j.nbscr.2018.03.002

Ouyang, M., Hellman, K., Abel, T., & Thomas, S. A. (2004). Adrenergic signaling plays a critical role in the maintenance of waking and in the regulation of REM sleep. *J Neurophysiol, 92*(4), 2071-2082. doi:10.1152/jn.00226.2004

Pais, T. F., Figueiredo, C., Peixoto, R., Braz, M. H., & Chatterjee, S. (2008). Necrotic neurons enhance microglial neurotoxicity through induction of glutaminase by a MyD88-dependent pathway. *Journal of neuroinflammation, 5*(1), 43. doi:10.1186/1742-2094-5-43

Patel, D., Anilkumar, S., Chattarji, S., & Buwalda, B. (2018). Repeated social stress leads to contrasting patterns of structural plasticity in the amygdala and hippocampus. *Behav Brain Res, 347*, 314-324. doi:10.1016/j.bbr.2018.03.034

Pauley, K. M., Satoh, M., Chan, A. L., Bubb, M. R., Reeves, W. H., & Chan, E. K. (2008). Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients. *Arthritis Res Ther, 10*(4), R101. doi:10.1186/ar2493

Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage, 19*(4), 1439-1448.

Perske, C., Lahat, N., Levin, S. S., Bitterman, H., Hemmerlein, B., & Rahat, M. A. (2010). Loss of Inducible Nitric Oxide Synthase Expression in the Mouse Renal

Cell Carcinoma Cell Line RENCA Is Mediated by MicroRNA miR-146a. *The American Journal of Pathology, 177*(4), 2046-2054. doi:https://doi.org/10.2353/ajpath.2010.091111

Podsakoff, P. M., MacKenzie, S. B., Lee, J.-Y., & Podsakoff, N. P. (2003). Common method biases in behavioral research: A critical review of the literature and recommended remedies. *Journal of Applied Psychology, 88*(5), 879-903. doi:10.1037/0021-9010.88.5.879

Podsakoff, P. M., MacKenzie, S. B., & Podsakoff, N. P. (2012). Sources of Method Bias in Social Science Research and Recommendations on How to Control It. *Annual Review of Psychology, 63*(1), 539-569. doi:10.1146/annurev-psych-120710-100452

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., et al. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics, 47*(7), 702-709. doi:10.1038/ng.3285

Powell, N. D., Bailey, M. T., Mays, J. W., Stiner-Jones, L. M., Hanke, M. L., Padgett, D. A., et al. (2009). Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. *Brain Behav Immun, 23*(2), 225-231. doi:10.1016/j.bbi.2008.09.010

Powell, N. D., Sloan, E. K., Bailey, M. T., Arevalo, J. M., Miller, G. E., Chen, E., et al. (2013). Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. *Proc Natl Acad Sci U S A, 110*(41), 16574-16579. doi:10.1073/pnas.1310655110

Prieto, G. A., Tong, L., Smith, E. D., & Cotman, C. W. (2019). TNFα and IL-1β but not IL-18 Suppresses Hippocampal Long-Term Potentiation Directly at the Synapse. *Neurochem Res, 44*(1), 49-60. doi:10.1007/s11064-018-2517-8

Purvis, E. M., Klein, A. K., & Ettenberg, A. (2018). Lateral habenular norepinephrine contributes to states of arousal and anxiety in male rats. *Behavioural Brain Research, 347*, 108-115. doi:https://doi.org/10.1016/j.bbr.2018.03.012

Puvill, T., Lindenberg, J., de Craen, A. J. M., Slaets, J. P. J., & Westendorp, R. G. J. (2016). Impact of physical and mental health on life satisfaction in old age: a population based observational study. *BMC Geriatrics, 16*(1), 194. doi:10.1186/s12877-016-0365-4

Qi, M., & Gao, H. (2020). Acute psychological stress promotes general alertness and attentional control processes: An ERP study. *Psychophysiology, 57*(4), e13521. doi:10.1111/psyp.13521

Qian, L., Wu, H.-m., Chen, S.-H., Zhang, D., Ali, S. F., Peterson, L., et al. (2011). β2-Adrenergic Receptor Activation Prevents Rodent Dopaminergic Neurotoxicity by Inhibiting Microglia via a Novel Signaling Pathway. *The Journal of Immunology, 186*(7), 4443. doi:10.4049/jimmunol.1002449

Quan, N., Avitsur, R., Stark, J. L., He, L., Shah, M., Caligiuri, M., et al. (2001). Social stress increases the susceptibility to endotoxic shock. *J Neuroimmunol, 115*(1-2), 36-45.

Quirk, G. J., Likhtik, E., Pelletier, J. G., & Paré, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J Neurosci, 23*(25), 8800-8807. doi:10.1523/jneurosci.23-25-08800.2003

Raab, A., Dantzer, R., Michaud, B., Mormede, P., Taghzouti, K., Simon, H., et al. (1986). Behavioural, physiological and immunological consequences of social status and aggression in chronically coexisting resident-intruder dyads of male rats. *Physiol Behav, 36*(2), 223-228. doi:10.1016/0031-9384(86)90007-7

Radley, J., Morilak, D., Viau, V., & Campeau, S. (2015). Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neuroscience & Biobehavioral Reviews, 58*, 79-91. doi:https://doi.org/10.1016/j.neubiorev.2015.06.018

Radley, J. J., Rocher, A. B., Rodriguez, A., Ehlenberger, D. B., Dammann, M., McEwen, B. S., et al. (2008). Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. *J Comp Neurol, 507*(1), 1141-1150. doi:10.1002/cne.21588

Rai, A., & Agarwal Upasna, A. (2018). A review of literature on mediators and moderators of workplace bullying: Agenda for future research. *Management Research Review, 41*(7), 822-859. doi:10.1108/MRR-05-2016-0111

Raone, A., Cassanelli, A., Scheggi, S., Rauggi, R., Danielli, B., & De Montis, M. G. (2007). Hypothalamus-pituitary-adrenal modifications consequent to chronic stress exposure in an experimental model of depression in rats. *Neuroscience, 146*(4), 1734-1742. doi:10.1016/j.neuroscience.2007.03.027

Reader, B. F., Jarrett, B. L., McKim, D. B., Wohleb, E. S., Godbout, J. P., & Sheridan, J. F. (2015). Peripheral and central effects of repeated social defeat stress: monocyte trafficking, microglial activation, and anxiety. *Neuroscience, 289*, 429-442. doi:10.1016/j.neuroscience.2015.01.001

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., et al. (2001). Cytokine-Associated Emotional and Cognitive Disturbances in Humans. *Archives of General Psychiatry, 58*(5), 445-452. doi:10.1001/archpsyc.58.5.445

Reknes, I., Einarsen, S., Pallesen, S., Bjorvatn, B., Moen, B. E., & MagerØY, N. (2016). Exposure to bullying behaviors at work and subsequent symptoms of anxiety: the moderating role of individual coping style. *Industrial Health, 54*(5), 421-432. doi:10.2486/indhealth.2015-0196

Réus, G. Z., Fries, G. R., Stertz, L., Badawy, M., Passos, I. C., Barichello, T., et al. (2015). The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience, 300*, 141-154. doi:https://doi.org/10.1016/j.neuroscience.2015.05.018

Rivera, A., Siracusa, M. C., Yap, G. S., & Gause, W. C. (2016). Innate cell communication kick-starts pathogen-specific immunity. *Nature Immunology, 17*(4), 356-363. doi:10.1038/ni.3375

Rodenbeck, A., Huether, G., Rüther, E., & Hajak, G. (2002). Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett, 324*(2), 159-163. doi:10.1016/s0304-3940(02)00192-1

Rodríguez-Carballeira, A., Escartín Solanelles, J., Visauta Vinacua, B., Porrúa García, C., & Martín-Peña, J. (2010). Categorization and hierarchy of workplace bullying strategies: a Delphi survey. *Span J Psychol, 13*(1), 297-308. doi:10.1017/s1138741600003875

Rodríguez-Muñoz, A., Moreno-Jiménez, B., Sanz Vergel, A. I., & Garrosa Hernández, E. (2010). Post-Traumatic Symptoms Among Victims of Workplace Bullying: Exploring Gender Differences and Shattered Assumptions. *Journal of Applied Social Psychology, 40*(10), 2616-2635. doi:10.1111/j.1559-1816.2010.00673.x

Roman, A. R., Alán, A., Tomas, H., & Tibor, H. (2017). Molecular diversity of corticotropin-releasing hormone mRNA-containing neurons in the hypothalamus. *Journal of Endocrinology, 232*(3), R161-R172. doi:10.1530/JOE-16-0256

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nat Rev Neurosci, 10*(6), 423-433. doi:10.1038/nrn2651

Roozendaal, B., Okuda, S., Van der Zee, E. A., & McGaugh, J. L. (2006). Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci U S A, 103*(17), 6741-6746. doi:10.1073/pnas.0601874103

Rosander, M., & Blomberg, S. (2019). Levels of workplace bullying and escalation – a new conceptual model based on cut-off scores, frequency and self-labelled victimization. *European Journal of Work and Organizational Psychology, 28*(6), 769-783. doi:10.1080/1359432X.2019.1642874

Rosenkranz, J. A., & Grace, A. A. (2001). Dopamine Attenuates Prefrontal Cortical Suppression of Sensory Inputs to the Basolateral Amygdala of Rats. *The Journal of Neuroscience, 21*(11), 4090-4103. doi:10.1523/jneurosci.21-11-04090.2001

Rosenkranz, J. A., Venheim, E. R., & Padival, M. (2010). Chronic stress causes amygdala hyperexcitability in rodents. *Biol Psychiatry, 67*(12), 1128-1136. doi:10.1016/j.biopsych.2010.02.008

Rudland, J. R., Golding, C., & Wilkinson, T. J. (2020). The stress paradox: how stress can be good for learning. *Med Educ, 54*(1), 40-45. doi:10.1111/medu.13830

Ruis, M. A., te Brake, J. H., Buwalda, B., De Boer, S. F., Meerlo, P., Korte, S. M., et al. (1999). Housing familiar male wildtype rats together reduces the long-term adverse behavioural and physiological effects of social defeat. *Psychoneuroendocrinology, 24*(3), 285-300. doi:10.1016/s0306-4530(98)00050-x

Russell, W. M. S., & Burch, R. L. (1959). The principles of humane experimental technique.

Saba, R., Sorensen, D. L., & Booth, S. A. (2014). MicroRNA-146a: a dominant, negative regulator of the innate immune response. *Frontiers in Immunology, 5*. doi:10.3389/fimmu.2014.00578

Saito, Y. C., Maejima, T., Nishitani, M., Hasegawa, E., Yanagawa, Y., Mieda, M., et al. (2018). Monoamines Inhibit GABAergic Neurons in Ventrolateral Preoptic Area That Make Direct Synaptic Connections to Hypothalamic Arousal Neurons. *J Neurosci, 38*(28), 6366-6378. doi:10.1523/jneurosci.2835-17.2018

Sanders, S. K., & Shekhar, A. (1995). Regulation of anxiety by GABAA receptors in the rat amygdala. *Pharmacol Biochem Behav, 52*(4), 701-706. doi:10.1016/0091-3057(95)00153-n

Saper, C. B., & Fuller, P. M. (2017). Wake-sleep circuitry: an overview. *Curr Opin Neurobiol, 44*, 186-192. doi:10.1016/j.conb.2017.03.021

Satoorian, T., Li, B., Tang, X., Xiao, J., Xing, W., Shi, W., et al. (2016). MicroRNA223 promotes pathogenic T-cell development and autoimmune inflammation in central nervous system in mice. *Immunology, 148*(4), 326-338. doi:10.1111/imm.12611

Savas, M., Vinkers, C. H., Rosmalen, J. G. M., Hartman, C. A., Wester, V. L., van den Akker, E. L. T., et al. (2020). Systemic and Local Corticosteroid Use Is Associated with Reduced Executive Cognition, and Mood and Anxiety Disorders. *Neuroendocrinology, 110*(3-4), 282-291. doi:10.1159/000501617

Sawicki, C. M., Kim, J. K., Weber, M. D., Faw, T. D., McKim, D. B., Madalena, K. M., et al. (2019). Microglia Promote Increased Pain Behavior through Enhanced Inflammation in the Spinal Cord during Repeated Social Defeat Stress. *The Journal of Neuroscience, 39*(7), 1139. doi:10.1523/JNEUROSCI.2785-18.2018

Saygin, D., Wanner, N., Rose, J. A., Naga Prasad, S. V., Tang, W. H. W., Erzurum, S., et al. (2018). Relative quantification of beta-adrenergic receptor in peripheral blood cells using flow cytometry. *Cytometry A, 93*(5), 563-570. doi:10.1002/cyto.a.23358

Schalm, R. L., & Kelloway, E. K. (2001). The relationship between response rate and effect size in occupational health psychology research. *J Occup Health Psychol, 6*(2), 160-163. doi:10.1037/1076-8998.6.2.160

Schutte, S., Chastang, J. F., Malard, L., Parent-Thirion, A., Vermeylen, G., & Niedhammer, I. (2014). Psychosocial working conditions and psychological well-being among employees in 34 European countries. *Int Arch Occup Environ Health, 87*(8), 897-907. doi:10.1007/s00420-014-0930-0

Schwartz, J. R. L., & Roth, T. (2008). Neurophysiology of sleep and wakefulness: basic science and clinical implications. *Current neuropharmacology, 6*(4), 367-378. doi:10.2174/157015908787386050

Selye, H. (1936). A Syndrome produced by Diverse Nocuous Agents. *Nature, 138*, 32. doi:10.1038/138032a0

Selye, H. (1950). Stress and the general adaptation syndrome. *British medical journal, 1*(4667), 1383-1392. doi:10.1136/bmj.1.4667.1383

Selye, H. (1975). Confusion and controversy in the stress field. *J Human Stress, 1*(2), 37-44. doi:10.1080/0097840x.1975.9940406

Shastry, B. S. (2002). SNP alleles in human disease and evolution. *J Hum Genet, 47*(11), 561-566. doi:10.1007/s100380200086

Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry, 50*(9), 651-658. doi:10.1016/s0006-3223(01)01263-x

Shorten, A., & Moorley, C. (2014). Selecting the sample. *Evidence Based Nursing, 17*(2), 32-33. doi:10.1136/eb-2014-101747

Shu, X., Mao, Y., Li, Z., Wang, W., Chang, Y., Liu, S., et al. (2019). MicroRNA-93 regulates angiogenesis in peripheral arterial disease by targeting CDKN1A. *Mol Med Rep, 19*(6), 5195-5202. doi:10.3892/mmr.2019.10196

Silverman, M. N., & Sternberg, E. M. (2012). Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Annals of the New York Academy of Sciences, 1261*, 55-63. doi:10.1111/j.1749-6632.2012.06633.x

Sjörs Dahlman, A., Blennow, K., Zetterberg, H., Glise, K., & Jonsdottir, I. H. (2019). Growth factors and neurotrophins in patients with stress-related exhaustion disorder. *Psychoneuroendocrinology, 109*, 104415. doi:https://doi.org/10.1016/j.psyneuen.2019.104415

Skogstad, A., Matthiesen Stig, B., & Einarsen, S. (2007). Organizational changes: A precursor of bullying at work? *International Journal of Organization Theory & Behavior, 10*(1), 58-94. doi:10.1108/IJOTB-10-01-2007-B003

Smalheiser, N. R., Lugli, G., Rizavi, H. S., Torvik, V. I., Turecki, G., & Dwivedi, Y. (2012). MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. *PLoS One, 7*(3), e33201. doi:10.1371/journal.pone.0033201

Smith, L. K., Shah, R. R., & Cidlowski, J. A. (2010). Glucocorticoids modulate microRNA expression and processing during lymphocyte apoptosis. *The Journal of biological chemistry, 285*(47), 36698-36708. doi:10.1074/jbc.M110.162123

Snyder, J. M., Hagan, C. E., Bolon, B., & Keene, C. D. (2018). 20 - Nervous System. In P. M. Treuting, S. M. Dintzis, & K. S. Montine (Eds.), *Comparative Anatomy and Histology (Second Edition)* (pp. 403-444). San Diego: Academic Press.

Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., et al. (2017). Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Research Reviews, 36*, 78-87. doi:https://doi.org/10.1016/j.arr.2017.03.005

Steffens, D. C., McQuoid, D. R., Welsh-Bohmer, K. A., & Krishnan, K. R. R. (2003). Left Orbital Frontal Cortex Volume and Performance on the Benton Visual Retention Test in Older Depressives and Controls. *Neuropsychopharmacology, 28*(12), 2179-2183. doi:10.1038/sj.npp.1300285

Sternberg, E. M. (2006). Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol, 6*(4), 318-328. doi:10.1038/nri1810

Strandmark, M., & Hallberg, L.-M. (2007). Being Rejected and Expelled from the Workplace: Experiences of Bullying in the Public Service Sector. *Qualitative Research in Psychology, 4*(1-2), 1-14. doi:10.1080/14780880701473359

Sugama, S., Takenouchi, T., Hashimoto, M., Ohata, H., Takenaka, Y., & Kakinuma, Y. (2019). Stress-induced microglial activation occurs through β-adrenergic receptor: noradrenaline as a key neurotransmitter in microglial activation. *Journal of neuroinflammation, 16*(1), 266-266. doi:10.1186/s12974-019-1632-z

Sülz, L., Astorga, G., Bellette, B., Iturriaga, R., Mackay-Sim, A., & Bacigalupo, J. (2009). Nitric oxide regulates neurogenesis in adult olfactory epithelium in vitro. *Nitric Oxide, 20*(4), 238-252. doi:10.1016/j.niox.2009.01.004

Sun, G., Yan, J., Noltner, K., Feng, J., Li, H., Sarkis, D. A., et al. (2009). SNPs in human miRNA genes affect biogenesis and function. *Rna, 15*(9), 1640-1651. doi:10.1261/rna.1560209

Takahashi, A., Chung, J.-R., Zhang, S., Zhang, H., Grossman, Y., Aleyasin, H., et al. (2017). Establishment of a repeated social defeat stress model in female mice. *Scientific Reports, 7*(1), 12838. doi:10.1038/s41598-017-12811-8

Tang, Z., Ye, G., Chen, X., Pan, M., Fu, J., Fu, T., et al. (2018). Peripheral proinflammatory cytokines in Chinese patients with generalised anxiety disorder. *J Affect Disord, 225*, 593-598. doi:10.1016/j.jad.2017.08.082

Taylor Tavares, J. V., Clark, L., Furey, M. L., Williams, G. B., Sahakian, B. J., & Drevets, W. C. (2008). Neural basis of abnormal response to negative feedback in unmedicated mood disorders. *Neuroimage, 42*(3), 1118-1126. doi:10.1016/j.neuroimage.2008.05.049

Thrivikraman, K. V., Nemeroff, C. B., & Plotsky, P. M. (2000). Sensitivity to glucocorticoid-mediated fast-feedback regulation of the hypothalamic-pituitary-adrenal axis is dependent upon stressor specific neurocircuitry. *Brain Res, 870*(1-2), 87-101. doi:10.1016/s0006-8993(00)02405-7

Tjosvold, D. (1991). *The Conflict-positive Organization: Stimulate Diversity and Create Unity*: Addison-Wesley Publishing Company.

Török, E., Hansen Å, M., Grynderup, M. B., Garde, A. H., Høgh, A., & Nabe-Nielsen, K. (2016). The association between workplace bullying and depressive symptoms: the role of the perpetrator. *BMC Public Health, 16*, 993. doi:10.1186/s12889-016-3657-x

Toyoda, A., Iio, W., Matsukawa, N., & Tsukahara, T. (2015). Influence of Chronic Social Defeat Stress on Digestive System Functioning in Rats. *J Nutr Sci Vitaminol (Tokyo), 61*(3), 280-284. doi:10.3177/jnsv.61.280

Trépanier, S.-G., Fernet, C., & Austin, S. (2013). Workplace bullying and psychological health at work: The mediating role of satisfaction of needs for autonomy, competence and relatedness. *Work & Stress, 27*(2), 123-140. doi:10.1080/02678373.2013.782158

Ulrich-Lai, Y. M., Figueiredo, H. F., Ostrander, M. M., Choi, D. C., Engeland, W. C., & Herman, J. P. (2006). Chronic stress induces adrenal hyperplasia and hypertrophy in a subregion-specific manner. *Am J Physiol Endocrinol Metab, 291*(5), E965-973. doi:10.1152/ajpendo.00070.2006

van Donkelaar, E. L., Vaessen, K. R. D., Pawluski, J. L., Sierksma, A. S., Blokland, A., Cañete, R., et al. (2014). Long-term corticosterone exposure decreases insulin sensitivity and induces depressive-like behaviour in the C57BL/6NCrl mouse. *PLoS One, 9*(10), e106960-e106960. doi:10.1371/journal.pone.0106960

van Olst, L., Bielefeld, P., Fitzsimons, C. P., de Vries, H. E., & Schouten, M. (2018). Glucocorticoid-mediated modulation of morphological changes associated with aging in microglia. *Aging Cell, 17*(4), e12790. doi:10.1111/acel.12790

Vartia, M. (1991). Bullying at workplaces. In S. Lehtinen, J. Rantanen, P. Juuti. A. Koskela, K. Lindström, P.Rehnström and J. Saari (eds.), *Towards the 21st century. Proceedings from the International Symposium on Future Trends in the Changing Working Life*. (pp. 131-135).

Vartia, M. (1996). The sources of bullying–psychological work environment and organizational climate *European Journal of Work and Organizational Psychology, 5*(2), 203-214. doi:10.1080/13594329608414855

Verkuil, B., Atasayi, S., & Molendijk, M. L. (2015). Workplace Bullying and Mental Health: A Meta-Analysis on Cross-Sectional and Longitudinal Data. *PLoS One, 10*(8), e0135225. doi:10.1371/journal.pone.0135225

Vie, T. L., Glaso, L., & Einarsen, S. (2011). Health outcomes and self-labeling as a victim of workplace bullying. *J Psychosom Res, 70*(1), 37-43. doi:10.1016/j.jpsychores.2010.06.007

Vie, T. L., Glasø, L., & Einarsen, S. (2012). How does it feel? Workplace bullying, emotions and musculoskeletal complaints. *Scand J Psychol, 53*(2), 165-173. doi:10.1111/j.1467-9450.2011.00932.x

Voorhees, J. L., Tarr, A. J., Wohleb, E. S., Godbout, J. P., Mo, X., Sheridan, J. F., et al. (2013). Prolonged restraint stress increases IL-6, reduces IL-10, and causes persistent depressive-like behavior that is reversed by recombinant IL-10. *PLoS One, 8*(3), e58488. doi:10.1371/journal.pone.0058488

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci, 22*(15), 6810-6818. doi:20026655

Vyas, S., Rodrigues, A. J., Silva, J. M., Tronche, F., Almeida, O. F. X., Sousa, N., et al. (2016). Chronic Stress and Glucocorticoids: From Neuronal Plasticity to Neurodegeneration. *Neural plasticity, 2016*, 6391686. doi:10.1155/2016/6391686

Walker, A. K., Kavelaars, A., Heijnen, C. J., & Dantzer, R. (2013). Neuroinflammation and comorbidity of pain and depression. *Pharmacological reviews, 66*(1), 80-101. doi:10.1124/pr.113.008144

Wamsteeker Cusulin, J. I., Fuzesi, T., Watts, A. G., & Bains, J. S. (2013). Characterization of corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus of Crh-IRES-Cre mutant mice. *PLoS One, 8*(5), e64943. doi:10.1371/journal.pone.0064943

Wang, Z.-J., Zhang, X.-Q., Cui, X.-Y., Cui, S.-Y., Yu, B., Sheng, Z.-F., et al. (2015). Glucocorticoid receptors in the locus coeruleus mediate sleep disorders caused by repeated corticosterone treatment. *Scientific Reports, 5*, 9442-9442. doi:10.1038/srep09442

Weber, M. D., Godbout, J. P., & Sheridan, J. F. (2017). Repeated Social Defeat, Neuroinflammation, and Behavior: Monocytes Carry the Signal. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 42*(1), 46-61. doi:10.1038/npp.2016.102

Welcome, M. O. (2020). Cellular mechanisms and molecular signaling pathways in stress-induced anxiety, depression, and blood–brain barrier inflammation and leakage. *Inflammopharmacology, 28*(3), 643-665. doi:10.1007/s10787-020-00712-8

Wiley, J. W., Higgins, G. A., & Athey, B. D. (2016). Stress and glucocorticoid receptor transcriptional programming in time and space: Implications for the brain-gut axis. *Neurogastroenterol Motil, 28*(1), 12-25. doi:10.1111/nmo.12706

Wilhelm, I., Born, J., Kudielka, B. M., Schlotz, W., & Wüst, S. (2007). Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology, 32*(4), 358-366. doi:https://doi.org/10.1016/j.psyneuen.2007.01.008

Williams, A. V., Duque-Wilckens, N., Ramos-Maciel, S., Campi, K. L., Bhela, S. K., Xu, C. K., et al. (2020). Social approach and social vigilance are differentially regulated by oxytocin receptors in the nucleus accumbens. *Neuropsychopharmacology*. doi:10.1038/s41386-020-0657-4

Willner, P., Towell, A., Sampson, D., Sophokleous, S., & Muscat, R. (1987). Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology (Berl), 93*(3), 358-364. doi:10.1007/bf00187257

Wohleb, E. S., Hanke, M. L., Corona, A. W., Powell, N. D., Stiner, L. M., Bailey, M. T., et al. (2011). beta-Adrenergic receptor antagonism prevents anxiety-like behavior

and microglial reactivity induced by repeated social defeat. *J Neurosci, 31*(17), 6277-6288. doi:10.1523/jneurosci.0450-11.2011

Wohleb, E. S., McKim, D. B., Shea, D. T., Powell, N. D., Tarr, A. J., Sheridan, J. F., et al. (2014). Re-establishment of Anxiety in Stress-Sensitized Mice Is Caused by Monocyte Trafficking from the Spleen to the Brain. *Biol Psychiatry, 75*(12), 970-981. doi:https://doi.org/10.1016/j.biopsych.2013.11.029

Wohleb, E. S., McKim, D. B., Sheridan, J. F., & Godbout, J. P. (2015). Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. *Frontiers in Neuroscience, 8*, 17. doi:10.3389/fnins.2014.00447

Wood, S. K., Wood, C. S., Lombard, C. M., Lee, C. S., Zhang, X.-Y., Finnell, J. E., et al. (2015). Inflammatory Factors Mediate Vulnerability to a Social Stress-Induced Depressive-like Phenotype in Passive Coping Rats. *Biol Psychiatry, 78*(1), 38-48. doi:https://doi.org/10.1016/j.biopsych.2014.10.026

World Health Organization. (2014). Retrieved from http://www.who.int/features/factfiles/mental_health/en/

World Medical, A. (2001). World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bulletin of the World Health Organization, 79*(4), 373-374.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377. doi:10.1126/science.1241224

Xie, Y., Tolmeijer, S., Oskam, J. M., Tonkens, T., Meijer, A. H., & Schaaf, M. J. M. (2019). Glucocorticoids inhibit macrophage differentiation towards a pro-inflammatory phenotype upon wounding without affecting their migration. *Dis Model Mech, 12*(5). doi:10.1242/dmm.037887

Yang, J., Zhang, L., Yu, C., Yang, X.-F., & Wang, H. (2014). Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. *Biomarker research, 2*(1), 1-1. doi:10.1186/2050-7771-2-1

Yang, R., Lin, Q., Gao, H. B., & Zhang, P. (2014). Stress-related hormone norepinephrine induces interleukin-6 expression in GES-1 cells. *Brazilian journal of medical and*

biological research = Revista brasileira de pesquisas medicas e biologicas, 47(2), 101-109. doi:10.1590/1414-431X20133346

Yang, Z., & Nielsen, R. (2000). Estimating Synonymous and Nonsynonymous Substitution Rates Under Realistic Evolutionary Models. *Molecular Biology and Evolution, 17*(1), 32-43. doi:10.1093/oxfordjournals.molbev.a026236

Yin, W., Gallagher, N. R., Sawicki, C. M., McKim, D. B., Godbout, J. P., & Sheridan, J. F. (2019). Repeated social defeat in female mice induces anxiety-like behavior associated with enhanced myelopoiesis and increased monocyte accumulation in the brain. *Brain Behav Immun, 78*, 131-142. doi:10.1016/j.bbi.2019.01.015

Yona, S., Kim, K. W., Wolf, Y., Mildner, A., Varol, D., Breker, M., et al. (2013). Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity, 38*(1), 79-91. doi:10.1016/j.immuni.2012.12.001

Yu, Q. N., Guo, Y. B., Li, X., Li, C. L., Tan, W. P., Fan, X. L., et al. (2018). ILC2 frequency and activity are inhibited by glucocorticoid treatment via STAT pathway in patients with asthma. *Allergy, 73*(9), 1860-1870. doi:10.1111/all.13438

Yuen, E. Y., Wei, J., Liu, W., Zhong, P., Li, X., & Yan, Z. (2012). Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. *Neuron, 73*(5), 962-977. doi:10.1016/j.neuron.2011.12.033

Zant, J. C., Leenaars, C. H., Kostin, A., Van Someren, E. J., & Porkka-Heiskanen, T. (2011). Increases in extracellular serotonin and dopamine metabolite levels in the basal forebrain during sleep deprivation. *Brain Res, 1399*, 40-48. doi:10.1016/j.brainres.2011.05.008

Zapf, D., & Einarsen, S. (2003). Individual antecedents of bullying. In S. Einarsen, H. Hoel, D. Zapf & C. L. Cooper (Eds.), *Bullying and emotional abuse in the workplace: International perspectives in research and practice* (pp. (pp. 165–184)): London: Taylor & Francis. .

Zapf, D., & Einarsen, S. (2005). Mobbing at Work: Escalated Conflicts in Organizations *Counterproductive work behavior: Investigations of actors and targets.* (pp. 237-270). Washington, DC, US: American Psychological Association.

Zapf, D., & Gross, C. (2001). Conflict escalation and coping with workplace bullying: A replication and extension. *European Journal of Work and Organizational Psychology, 10*(4), 497-522. doi:10.1080/13594320143000834

Zelena, D., Haller, J., Halasz, J., & Makara, G. B. (1999). Social stress of variable intensity: physiological and behavioral consequences. *Brain Res Bull, 48*(3), 297-302. doi:10.1016/s0361-9230(98)00176-2

Zhan, Y., Paolicelli, R. C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., et al. (2014). Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nature Neuroscience, 17*(3), 400-406. doi:10.1038/nn.3641

Zhang, J. Y., Liu, T. H., He, Y., Pan, H. Q., Zhang, W. H., Yin, X. P., et al. (2019). Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner. *Biol Psychiatry, 85*(3), 189-201. doi:10.1016/j.biopsych.2018.06.019

Zhang, X., Ge, T. T., Yin, G., Cui, R., Zhao, G., & Yang, W. (2018). Stress-Induced Functional Alterations in Amygdala: Implications for Neuropsychiatric Diseases. *Front Neurosci, 12*, 367. doi:10.3389/fnins.2018.00367

Zhang, X., Huo, Q., Sun, W., Zhang, C., Wu, Z., Xing, B., et al. (2018). Rs2910164 in microRNA146a confers an elevated risk of depression in patients with coronary artery disease by modulating the expression of NOS1. *Mol Med Rep, 18*(1), 603-609. doi:10.3892/mmr.2018.8929

Zhong, M., Wang, X., Xiao, J., Yi, J., Zhu, X., Liao, J., et al. (2011). Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biological Psychology, 88*(2), 233-242. doi:https://doi.org/10.1016/j.biopsycho.2011.08.007

Zhou, J. J., Gao, Y., Zhang, X., Kosten, T. A., & Li, D. P. (2018). Enhanced Hypothalamic NMDA Receptor Activity Contributes to Hyperactivity of HPA Axis in Chronic Stress in Male Rats. *Endocrinology, 159*(3), 1537-1546. doi:10.1210/en.2017-03176

I

frontiers in Psychology

ORIGINAL RESEARCH
published: 24 May 2019
doi: 10.3389/fpsyg.2019.01204

Exposure to Workplace Bullying, Distress, and Insomnia: The Moderating Role of the miR-146a Genotype

Dhaksshaginy Rajalingam[1], Daniel Pitz Jacobsen[2], Morten Birkeland Nielsen[1,2], Ståle Valvatne Einarsen[1] and Johannes Gjerstad[1,2]*

[1] Department of Psychosocial Science, University of Bergen, Bergen, Norway, [2] National Institute of Occupational Health, Oslo, Norway

Several lines of evidence show that systematic exposure to negative social acts at the workplace i.e., workplace bullying, results in symptoms of depression and anxiety among those targeted. However, little is known about the association between bullying, inflammatory genes and sleep problems. In the present study, we examined the indirect association between exposure to negative social acts and sleep through distress, as moderated by the miR-146a genotype. The study was based on a nationally representative survey of 1179 Norwegian employees drawn from the Norwegian Central Employee Register by Statistics Norway. Exposure to workplace bullying was measured with the 9-item version of Negative Acts Questionnaire – Revised (NAQ-R) inventory. Seventeen items from Hopkins Symptom Checklist (HSCL-25) was used to measure distress. Insomnia was assessed with three items reflecting problems with sleep onset, maintenance of sleep and early morning awakening. Genotyping with regard to miR-146a rs2910164, previously linked to inflammatory processes, was carried out using Taqman assay. The data revealed that individuals systematically exposed to negative social acts at the workplace reported higher levels of sleep problems than non-exposed individuals. Moreover, the relationship between distress induced by exposure to negative social acts and insomnia was significantly stronger for individuals with the miR-146a GG genotype. Thus, the miR-146a genotype moderated the association between distress and insomnia among individuals exposed to negative social acts. The present report support the hypothesis that inflammation could play a role in stress-induced insomnia among individuals exposed to workplace bullying.

Keywords: bullying, distress, insomnia, genotype, miR-146a, rs2910164

OPEN ACCESS

Edited by:
Gianluca Castelnuovo, Catholic University of the Sacred Heart, Italy

Reviewed by:
Kathryn Hall, Harvard University, United States
Daniel Boyce Mckim, University of Illinois at Urbana-Champaign, United States

****Correspondence:***
Dhaksshaginy Rajalingam
dhaksshaginy.rajalingam@uib.no

Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *04 December 2018*
Accepted: *07 May 2019*
Published: *24 May 2019*

Citation:
Rajalingam D, Jacobsen DP, Nielsen MB, Einarsen SV and Gjerstad J (2019) Exposure to Workplace Bullying, Distress, and Insomnia: The Moderating Role of the miR-146a Genotype. Front. Psychol. 10:1204. doi: 10.3389/fpsyg.2019.01204

INTRODUCTION

Exposure to bullying at the workplace, be it from one's peers or one's superiors, is a prevalent social stressor with severe consequences in those targeted (Nielsen and Einarsen, 2012). Representing a systematic form of exposure to workplace mistreatment, the term "bullying" refers to a situation in which a person repeatedly is subjected to negative social acts in a situation, where the target is

unable to defend him/herself (Einarsen and Skogstad, 1996; Gredler, 2003). Bullying is not an either or phenomenon, but rather a gradually escalating process ranging from single acts of incivility to systematic exposure to aggression and social exclusion at work. To this date, most research on outcomes of bullying has focused on mental distress and has established bullying as a significant predictor of depression and anxiety in targets (Hansen et al., 2011). The empirical evidence for an association between bullying and sleep is; however, more scarce. Yet, from a bio-physiological perspective, it is theoretically plausible that systematic exposure to bullying-related stress at work also affects sleep via elevated levels of distress. For example, exposure to negative social acts may induce mental distress caused by cognitive rumination and persistent central nervous system (CNS) activation – which in turn could be associated with sleep problems (Akerstedt, 2006; Fortunato and Harsh, 2006; Han et al., 2012).

Exposure to negative social acts is a strong stressor that may affect both the hypothalamus in the brain stem and the autonomous nervous system (ANS). Thus, an alternative explanation for an association between exposure to negative social acts and sleep is that the exposure may lead to a disturbed balance between the parasympathetic and sympathetic branch of the ANS, i.e., reduced acetylcholine (Ach) and more norepinephrine (NE) release close to the ANS target organs (Mineur et al., 2013; Won and Kim, 2016). Moreover, exposure to systematic negative social acts, through the sympatho-adreno-medullary connections, increase the release of circulating catecholamines. Exposure to negative social acts also activates the hypothalamic-pituitary-adrenal (HPA) axis, which promote release of corticotrophin releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol (Akerstedt, 2006).

Interestingly, reduced parasympathetic or increased sympathetic activity following exposure to negative social acts may promote inflammatory processes in circulating immune cells through the influence on the spleen and other lymphoid tissues. Such stress-induced autonomic influence on lymphoid tissues, may be associated with low-grade systemic inflammation, which in turn could be linked to sleep problems (Motivala, 2011). In addition, in the initial stage of sleep, the level of ACTH and cortisol is reduced. This suppresses the activity of HPA axis and induces sleep. In the later stage, before awakening, HPA axis activity increases. Accordingly, the rise of ACTH in the morning controls the end of sleep (Akerstedt, 2006). Therefore, increased HPA axis activity due to distress, will most likely also cause insomnia.

Stress-induced changes in the immune system involves many innate immune cells i.e., lymphoid and myeloid cells, which release circulating cytokines (Chrousos, 1995; Turnbull and Rivier, 1995). Over time this could be a threat to homeostasis of the immune system (Turnbull and Rivier, 1995) and is therefore, maladaptive (Wohleb et al., 2015). Thus, chronic stress, including exposure to bullying, may be associated with many negative physiological and immunological changes (Chrousos, 1995; Wohleb et al., 2015). Increasing evidence support the idea that microRNAs (miRs), RNA molecules of ∼ 22 nucleotides in length, play key roles in these immunological processes (McDonald and Ajit, 2015). The miRs bind to messenger RNA (mRNA) and inhibit translation of mRNA to proteins by binding to complementary sequences in the 3′ untranslated region of a specific mRNA target. Alternatively, miR-binding to the complementary sequence can result in degradation of the mRNA.

A crucial protein complex controlled by the ANS efferents to the spleen, which also influences systemic inflammatory processes, may be the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Interestingly, activation of the NF-κB pathway in circulating monocytes or other immune cells results in up-regulation of many inflammatory cytokines, but also miR-146a – which in turn targets upstream proteins and further modulate the inflammatory response (Saba et al., 2014). Therefore, the gene encoding miR-146a (Baltimore et al., 2008; Saba et al., 2014), has been implicated to play a central role in regulating the innate immune response (Saba et al., 2014; Lee et al., 2016). Given that low-grade systemic inflammation promotes insomnia (Motivala, 2011), the miR-146a rs2910164 G allele that supports inflammatory processes (Shen et al., 2008), may also affect sleep.

Several lines of evidence show that miR-146a may be a dominant, negative regulator of the innate immune response (Saba et al., 2014; Lee et al., 2016). For example, miR-146a can target mRNA of proteins in the NF-κB pathway, which in turn may regulate the expression of a cluster of cytokines including IL-1 and TNFα. Interestingly, it has been proposed that miR-146a may influence on Toll-like receptor and cytokine signaling in monocytes through a negative feedback loop involving down-regulation of IL-1 receptor-associated kinase 1 and TNF receptor-associated factor 6 protein levels (Taganov et al., 2006). Moreover, nitric oxide synthase 1 (NOS1), an important retrograde signaling molecule in the CNS that also affects peripheral inflammatory processes, is reported to be a target of miR-146a (Zhang et al., 2018). Therefore, based on the link between stress-induced inflammation and sleep – and the fact that miR-146a may control both IL-1, TNFα and NOS1 – we hypothesized that the relationship between distress and insomnia may be amplified by the miR-146a rs2910164 GG genotype. A graphical illustration of the proposed relationship investigated in the present study is shown in **Figure 1**.

MATERIALS AND METHODS

Design and Sample

This study is based on a probability survey of the Norwegian workforce. A random sample of 5000 employees was drawn from The Norwegian Central Employee Register by Statistics Norway. The Norwegian Central Employee Register is the official register of all Norwegian employees, as reported by employers. Sampling criteria were adults from 18 to 60 years of age employed in a Norwegian enterprise. Questionnaires were distributed through the Norwegian Postal Service during spring 2015. Altogether 1608 persons returned the questionnaire (32%) and all respondents provided usable responses. Subjects who gave consent were also sent saliva collection kits. Among these,

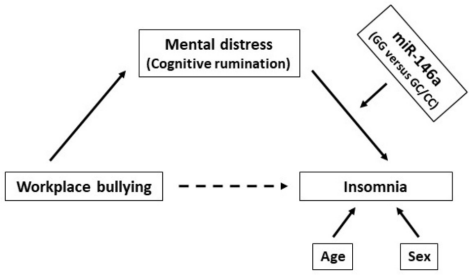

FIGURE 1 | A graphic illustration of the proposed relationship between workplace bullying, distress and insomnia moderated by the miR-146a genotype (adjusted for the covariates age and sex).

1204 returned the saliva sample kit. The analyses were; however, performed with 1179 subjects due to missing data. The survey was approved by the Regional Committee for Medical Research Ethics for Eastern Norway. Responses were treated anonymously, and informed consent was given by the respondents.

Mean age was 45.19 (SD = 10.04) years with a range from 21 to 61 years. The sample consisted of slightly more women (52.1%) than men (47.8%). In total, 54.9% were married, 24.5% were common-law partners, 13.8% were unmarried, and 6.8% were widowed, separated, or divorced. Altogether 8.4% had less than 11 years of education, 30.8% had between 11 and 13 years, 32.3% had between 14 and 17 years, and 28.5% had 18 or more years. A total of 89.6% were in a full-time employment, 6.6% were in part-time employment, 3.5% were on a sick leave or occupational rehabilitation, and 0.3% were disabled pensioners or retired. Moreover, 36% had a leadership position with personnel responsibilities. Comparisons of sample characteristics with available data from Statistics Norway suggested that the sample distribution was somewhat skewed compared to the overall working population with regard to gender (53% men in population), educational level (less than 11 years of education: 17%; between 11 and 13 years: 42%; more than 14 years: 41% in population), and age mean of 41.8 years in population.

Instruments

Exposure to negative social acts at the workplace was measured with the 9-item version of the Negative Acts Questionnaire – Revised (NAQ-R) inventory (Einarsen et al., 2009). NAQ-R describes negative and unwanted behaviors that may be perceived as bullying if occurring on a regular basis. All items are formulated in behavioral terms and hence, focus on the mere exposure to inappropriate behaviors while at work with no references to the term bullying (Einarsen and Nielsen, 2015). The NAQ-R contains items referring to both direct (e.g., openly attacking the victim) and indirect (e.g., social isolation, slander) behaviors (Einarsen et al., 2009). The items do also distinguish between personal and work related forms of bullying (Einarsen et al., 2009). Example items are "Being ignored or excluded," "Repeated reminders of your errors or mistakes," and "Someone withholding information which affects your performance." The respondents were asked to indicate how often they had been exposed to each specific item in questionnaire at their present worksite during the last 6 months. Response categories ranged from 1 to 5 ('never,' 'now and then,' 'monthly,' 'weekly,' and 'daily'). This nine item version of the NAQ-R had a Cronbach's alpha of 0.86 in this study.

Seventeen items from Hopkins Symptom Checklist (HSCL-25) reflecting typical symptoms of anxiety and depression measured *symptoms of psychological distress* during the last week. The HSCL is a valid and reliable (Rickels et al., 1976) self-administered instrument measuring mental distress (anxiety, depression, and psychosomatic complaints) in population surveys (Derogatis et al., 1974). Earlier comparisons show that shorter versions perform as well as the more extensive versions of the inventory (Strand et al., 2003). Responses were given on a four-point scale, ranging from "1 = not at all" to "4 = extremely." Example items are "Feeling no interest in things" and "Feeling hopeless about the future." Cronbach's alpha for this scale was 0.87 in the current study.

Insomnia was assessed with three items reflecting problems with sleep onset, maintenance of sleep and early morning awakening. Response categories ranged from 1 to 4 ('not bothered,' 'a little bothered,' 'considerably bothered,' 'seriously bothered'). These symptoms are core nocturnal characteristics of insomnia, in line with modern nosology (American Psychiatric Association, 2013; American Academy of Sleep Medicine, 2014). A composite insomnia score was calculated by adding the score of the three items and dividing the sum by three. The Cronbach alpha for the insomnia scale was 0.81 in the present study.

Genotyping

As previously described (Jacobsen et al., 2018), genomic DNA was extracted from saliva using an OrageneRNA sample collection kit (DNA Genotech Inc., Kanata, Ontario, Canada). Single nucleotide polymorphism (SNP) genotyping was carried out using predesigned TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, United States). Approximately 10 ng genomic DNA was amplified in a 5 μl reaction mixture in a 384-well plate containing 1x TaqMan genotyping master mix (Applied Biosystems) and 1x assay mix, the latter containing the respective primers and probes. The probes were labeled with the reporter dye FAM or VIC to distinguish between the two alleles. After initial denaturation and enzyme activation at 95°C for 10 min, the reaction mixture was subjected to 40 cycles of 95°C for 15 s and 60°C for 1 min on an ABI 7900HT sequence detection system. Negative controls were included in every run. Genotypes were determined using the SDS 2.2 software (Applied Biosystems, Foster City, CA, United States). Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

Statistical Analysis

Exposure to negative social acts was calculated using the mean-score of the 9 items in the NAQ-R inventory. Since we in our sample had 759 GG subjects, 401 GC subjects, but only 45 CC subjects, the miR-146a genotype was included as a dichotomous variable, GG versus GC/CC. To investigate the

hypotheses about main and moderating effects, we conducted a moderated mediation regression analysis using a modeling tool, SPSS; PROCESS v3.1, to test for linear associations between exposure to negative social acts and insomnia, as well as the interactive effects of negative social acts and miR-146a genotype (GG versus GC/CC) with regard to insomnia. Deviation from the Hardy–Weinberg equilibrium was tested by the Chi-squared test ($Chi^2 = 0.7936$).

As discussed in the introduction of this manuscript, there are theoretical reasons for expecting that the impact of workplace bullying on insomnia is mediated by psychological distress, and that the magnitude of this relationship is conditioned by miR-146a rs2910164 genotype. Specifically, we hypothesized that bullying is expected to increase levels of distress and the increased levels of distress is further expected to lead to insomnia among employees with the GG genotype. To empirically test this theoretical relationship we analyzed a moderated mediation model.

A mediation model is one that seeks to identify and explain the mechanism or process that underlies an observed relationship between an independent variable and a dependent variable via the inclusion of a third variable (i.e., mediator variable), in our case between bullying and insomnia. According to Baron and Kenny (1986), there is evidence that a variable mediates the relationship between a predictor variable and an outcome variable when each of the following conditions have been met: (a) there is a significant relationship between a predictor (e.g., exposure to workplace bullying) and an outcome (e.g., insomnia), (b) there is a significant relationship between a predictor and a proposed mediator variable (e.g., psychological distress), (c) there is a significant relationship between a proposed mediator and an outcome (with the predictor controlled), and (d) the strength of the relationship between a predictor and an outcome decreases significantly when a proposed mediator is controlled (Frazier et al., 2004). A full mediation is supported when a predictor variable is no longer significantly associated with the outcome after adjusting for the mediating variable. A moderated mediation model is supported if the magnitude of the indirect association between the predictor and outcome variable through the mediator is conditionally dependent upon the values of the moderator variable (e.g., in our case, miR-146a rs2910164).

The hypothesized moderated mediation model was tested in full by means of the PROCESS macro (model 14) developed for SPSS. PROCESS uses an ordinary least squares (OLS) or logistic regression-based path analytical framework for estimating indirect effects in both un-moderated and moderated mediation models with a single or multiple mediators and moderators (Hayes, 2013). Bootstrap methods are implemented in PROCESS for inference about indirect effects in both unmoderated as well as moderated mediation models. Bootstrapping is a statistical procedure that allows for the calculations of effect sizes even when you do not know the underlying distribution. The analysis was adjusted for age and sex, as covariates. A significant interaction term and a significant increase in explained variance (R^2) were considered as indicative of an interaction effect.

As the scores on the NAQ-R (skewness: 4.18, kurtosis: 26.85) were non-normally distributed, all analyses were conducted using bootstrapping (5000 resamples). The bootstrap method has the advantage that it does not need to meet the assumptions of normality, equal variances and homoscedasticity that are required in ordinary regression analyses. Multicollinearity was not an issue in the current study (VIF = 1.01). The level of significance was set to $p < 0.05$.

RESULTS

The present data showed that 55% of the individuals included in our probability sample reported exposure to at least one negative act; NAQ > 1 at the workplace during the last 6 months. Mean negative acts scores were similar for men and women; NAQ = 1.18. The mean insomnia scores for men and women were 1.64 and 1.72, respectively. ANOVA analyses with age and gender as covariates showed no significant differences between genotypes with regard to scores on NAQ, insomnia, and distress.

The characteristics of the subjects are presented in **Table 1**. As expected, genotyping demonstrated that the majority, i.e., 63%, of the subjects had the ordinary variant GG, whereas the rest, i.e., 37%, carried the rare variant GC/CC. No deviation from the Hardy–Weinberg equilibrium was observed.

The data from the moderated mediation analysis is presented in **Table 2**. Analyses of direct associations between the predictor and outcome variables in the hypothesized model showed that, after adjusting for age and gender, exposure to negative acts, i.e., elevated NAQ score, was associated with insomnia ($b = 0.55$; $p < 0.001$). Negative acts and the control variables explained eight percent of the variance in insomnia. Exposure to negative acts was also significantly associated with distress ($b = 0.37$; $p < 0.001$), and explained 13.9% of the variance in distress. When including the mediator (distress) and the moderator (miR-146a GG versus GC/CC) variables in the analyses of the association between exposure to negative acts and insomnia, the findings showed that exposure to negative acts had an indirect (mediated) association with insomnia through distress for both genotypes (see **Table 2**). However, a significant interaction term showed that this indirect effect was stronger among individuals with the GG genotype ($B = 0.31$; 95% CI: 0.23–0.41) than among individuals with the GC/CC genotype ($B = 0.16$; 95% CI: 0.08–0.23). Hence, the present data revealed that there was an indirect relationship between exposure to negative acts and insomnia through distress and that the magnitude of this indirect relationship was stronger for individuals with GG than for individuals with GC/CC (**Figure 2** and **Supplementary Figure S1**). When including the mediator and the interaction term in the model, the variables explained 19% of the variance in insomnia.

DISCUSSION

In the present study, we demonstrated that individuals systematically exposed to negative social acts at the workplace report higher levels of sleep problems than non-exposed individuals. Our data also demonstrated that this association may be strengthened among individuals having the miR-146a rs2910164 GG genotype. Since previous observations

TABLE 1 | Characteristics of the subjects grouped by the miR-146a genotype rs2910164; GG versus GC/CC.

	Range	GG				GC/CC				Sum	*T*-test
		N	%	Mean	SEM	N	%	Mean	SEM		
Subjects		758	62.9			446	37			1204	
Insomnia	1 to 4			1.71	0.027			1.64	0.315		1.50
NAQ	1 to 5			1.18	0.011			1.21	0.017		−1.77
Distress	1 to 4			1.36	0.013			1.37	0.018		−0.51
Age				46	0.813			44.5	0.465		
Male		378	49.8			200	44.8				
Female		380	50.1			246	55.2				
Education											
Secondary school or less		20	2.6			6	1.3				
High school		277	36.5			169	37.9				
University ≤ 4 years		237	31.3			149	33.4				
University ≥ 4 years		222	29.3			119	26.7				

NAQ, Negative Acts Questionnaire; SEM, Standard error of the mean.

TABLE 2 | Regression analysis SPSS PROCESS model 14 with the miR-146a genotype rs2910164; GG versus GC/CC (bootstrapping with 5000 samples).

	B	SE	*P*-value	95% CI
Distress				
NAQ	0.3668	0.287	0.0000	0. 3104 to 0.4232
Age	−0.0006	0.0005	0.2425	−0. 0016 to 0.0004
Sex	0.0954	0.0194	0.0000	0. 0573 to 0.1335
Insomnia				
NAQ	0.3188	0.0600	0.0000	0. 2011 to 0.4366
Age	0.0043	0.0010	0.0000	0. 0023 to 0.0063
Sex	0.0182	0.0384	0.6356	−0.0571 to 0.0935
Distress	0.6752	0.0571	0.0000	0. 5632 to 0.7872
miR-146a GG* vs. GC/CC	−0.0813	0.0394	0.0391	−0.1585 to -0.0041
Distress x miR146a GG* vs. GC/CC	−0.4337	0.1080	0.0001	−0.6457 to -0.2218

**reference group. The analysis were adjusted for the covariates age and sex. SE, standard error; CI, confidence interval.*

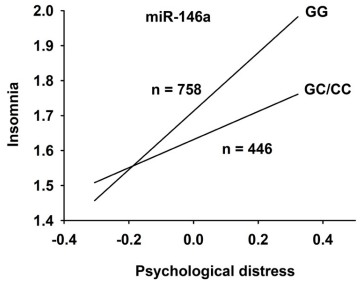

FIGURE 2 | The relationship between psychological distress and insomnia after correction for age and sex. Subjects were divided into groups based on miR-146a genotype rs2910164; GG versus GC/CC.

show that miR-146a may be upregulated in, but also is a regulator of inflammatory processes, the present data suggest that inflammation could play a role in stress-induced insomnia among individuals exposed to negative social acts.

Over the last 20 years, there has been an evolving understanding of the bidirectional communication between the CNS and the immune system (Krueger and Majde, 2003), which also provides the network for sleep regulatory circuits in the brain (Davis and Krueger, 2012). The important roles of cytokines as signaling molecules in this communication and their ability to bypass the blood-brain-barrier has also been recognized. Several lines of evidence show that cytokines, i.e., IL-1 and TNFα through their influence on neuronal signaling regulates sleep and enhance non-rapid eye movements (Krueger and Majde, 2003; Del Gallo et al., 2014). Studies also show that variation in plasma levels of IL-1 and TNFα are associated with sleep quality in patients with chronic inflammation (Krueger et al., 2011). The correlation between cytokine levels, sleep and pathology support the hypothesis that a low-grade systemic inflammation induced by chronic stress, in our case social stress, could cause changes in circulating cytokine levels, which influence on sleep circuits in the brain (Olini et al., 2017).

Previous data show that miR-146a targets mRNA of proteins in the NF-κB pathway in circulating monocytes and that miR-146a therefore may attenuate the innate immune response (Saba et al., 2014). A study performed by Shen and colleagues

(Shen et al., 2008) shows that the rs2910164 G allele results in reduced levels of expression of the anti-inflammatory miR-146a in MCF-7 cells, a breast cancer cell-line. This shows that the G allele could promote low-grade systemic inflammation and sleep problems. However, other studies suggest that the G allele also may have the opposite effect due to the stability of the pre-miR (Jazdzewski et al., 2008; Xu et al., 2008). Apparently, the miR-146a G > C polymorphism may have different effects in different tissues (Park et al., 2016).

Recently, the nitric oxide synthase 1 (NOS1) has been reported to be a direct target of miR-146a (Zhang et al., 2018), meaning that the NOS1 expression would be affected by the miR-146a G > C polymorphism (Luan et al., 2016). NOS1 is an enzyme, responsible for the production of nitric oxide (NO) – an important pro-inflammatory molecule and a retrograde signaling messenger in the CNS. Previous data show that NOS1 and the nitric oxide pathway is directly linked to the HPA axis and the regulation of glucocorticoids (Chen et al., 2015). In addition, NOS1 may be involved in psychological distress (Luciano et al., 2012), suggesting that miR-146a polymorphism could have an effect on depression and anxiety. It is tempting to speculate that miR-146a could influence on the neuronal processes underlying psychological distress, which in turn affect immunity and sleep. This demonstrates the capability of miRs in regulating neural circuits important for stress-induced insomnia and other health complaints.

Being based on cross-sectional data, however, the present study has its limitations. Moreover, the study design causes problems explaining causal relationships. In addition, as the measurement instruments for negative social acts and insomnia were self-report measures, the study could be influenced by bias such as set tendencies and social desirability. Also, the overall response rate for the questionnaire survey was only 32%, and <20% of the invited participants returned their saliva samples. Thus, we cannot be certain that the final sample is representative for the overall population. Nevertheless, as response rate and representatively seems to have limited impact on the internal validity (Schalm and Kelloway, 2001), the response rate may not really be a problem with regard to our findings.

In summary, the present data suggest that exposure to bullying-related negative social acts at the workplace may lead to increased risk of sleep problems through elevated levels of mental distress. Moreover, our data show that the link between distress and insomnia may be moderated by the miR-146a genotype, i.e., the rs2910164 G > C polymorphism within the precursor sequence of miR-146a. Hence, the present study indicate that the effect of systematic exposure to negative social acts at work on insomnia among those that are targeted is strengthened in individuals with the miR-146a genotype GG. Thus, it is important that such biological factors are taken into account when future intervention studies are designed. In particular, the interaction between exposure to negative social acts, genetics and insomnia should be acknowledged. Such knowledge could be of vital importance when treating and rehabilitating patients who have suffered mental health problems after exposure to workplace bullying and other forms of social stress and mistreatment while at work. We conclude that the association between distress and insomnia among individuals exposed to negative social acts is moderated by genetic variability in the gene encoding miR-146a.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Regional Committee for Medical Research Ethics for Eastern Norway" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was also approved by the "Regional Committee for Medical Research Ethics for Eastern Norway."

AUTHOR CONTRIBUTIONS

DR, DJ, MN, SE, and JG designed the research. DR, DJ, and JG performed the research. DR and MN analyzed the data. DR and JG wrote the manuscript. All authors have commented on, read and approved the final manuscript.

FUNDING

The study is part of a larger research project entitled "Workplace bullying: From mechanisms and moderators to problem treatment" funded by the Norwegian Research Council and the University of Bergen (Grant Nos. 250127 and 237777).

ACKNOWLEDGMENTS

We thank Anne-Mari Gjestvang Moe, Tiril Schjølberg, and Aqsa Mahmood for their excellent technical support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.01204/full#supplementary-material

FIGURE S1 | The effect of miR-146a genotype on insomnia in low, median, and high distress individuals.

REFERENCES

Akerstedt, T. (2006). Psychosocial stress and impaired sleep. *Scand. J. Work Environ. Health* 32, 493–501. doi: 10.5271/sjweh.1054

American Academy of Sleep Medicine (2014). *International Classification of Sleep Disorders*. Darien, IL: American Academy of Sleep Medicine.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Publishing.

Baltimore, D., Boldin, M. P., O'Connell, R. M., Rao, D. S., and Taganov, K. D. (2008). MicroRNAs: new regulators of immune cell development and function. *Nat. Immunol.* 9, 839–845. doi: 10.1038/ni.f.209

Baron, R. M., and Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* 51, 1173–1182.

Chen, H.-J. C., Spiers, J. G., Sernia, C., and Lavidis, N. A. (2015). Response of the nitrergic system to activation of the neuroendocrine stress axis. *Front. Neurosci.* 9:3. doi: 10.3389/fnins.2015.00003

Chrousos, G. P. (1995). The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N. Engl. J. Med.* 332, 1351–1362. doi: 10.1056/nejm199505183322008

Davis, C. J., and Krueger, J. M. (2012). Sleep and cytokines. *Sleep Med. Clin.* 7, 517–527.

Del Gallo, F., Opp, M. R., and Imeri, L. (2014). The reciprocal link between sleep and immune responses. *Arch. Ital. Biol.* 152, 93–102. doi: 10.12871/000298292014234

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., and Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): a self report symptom inventory. *Behav. Sci.* 19, 1–15.

Einarsen, S., Hoel, H., and Notelaers, G. (2009). Measuring exposure to bullying and harassment at work: validity, factor structure and psychometric properties of the negative acts questionnaire-revised. *Work Stress* 23, 24–44. doi: 10.1080/02678370902815673

Einarsen, S., and Nielsen, M. B. (2015). Workplace bullying as an antecedent of mental health problems: a five-year prospective and representative study. *Int. Arch. Occup. Environ. Health* 88, 131–142. doi: 10.1007/s00420-014-0944-7

Einarsen, S., and Skogstad, A. (1996). Bullying at work: epidemiological findings in public and private organizations. *Eur. J. Work Organ. Psychol.* 5, 185–201. doi: 10.1080/13594329608414854

Fortunato, V. J., and Harsh, J. (2006). Stress and sleep quality: the moderating role of negative affectivity. *Pers. Individ. Diff.* 41, 825–836. doi: 10.1016/j.paid.2006.03.024

Frazier, P. A., Tix, A. P., and Barron, K. E. (2004). Testing moderator and mediator effects in counseling psychology research. *J. Counsel. Psychol.* 51, 115–134.

Gredler, G. R. (2003). Olweus, D. (1993). Bullying at school: what we know and what we can do. Malden, MA: Blackwell Publishing, 140 pp. *Psychol. Sch.* 40, 699–700. doi: 10.1002/pits.10114

Han, K. S., Kim, L., and Shim, I. (2012). Stress and sleep disorder. *Exp. Neurobiol.* 21, 141–150. doi: 10.5607/en.2012.21.4.141

Hansen, A. M., Hogh, A., and Persson, R. (2011). Frequency of bullying at work, physiological response, and mental health. *J. Psychosom. Res.* 70, 19–27. doi: 10.1016/j.jpsychores.2010.05.010

Hayes, A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY: Guilford Press.

Jacobsen, D. P., Nielsen, M. B., Einarsen, S., and Gjerstad, J. (2018). Negative social acts and pain: evidence of a workplace bullying and 5-HTT genotype interaction. *Scand. J. Work Environ. Health* 44, 283–290. doi: 10.5271/sjweh.3704

Jazdzewski, K., Murray, E. L., Franssila, K., Jarzab, B., Schoenberg, D. R., and de la Chapelle, A. (2008). Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. *Proc. Natl. Acad. Sci. U.S.A.* 105, 7269–7274. doi: 10.1073/pnas.0802682105

Krueger, J. M., Clinton, J. M., Winters, B. D., Zielinski, M. R., Taishi, P., Jewett, K. A., et al. (2011). Involvement of cytokines in slow wave sleep. *Prog. Brain Res.* 193, 39–47. doi: 10.1016/B978-0-444-53839-0.00003-X

Krueger, J. M., and Majde, J. A. (2003). Humoral Links between Sleep and the Immune System. *Ann. N. Y. Acad. Sci.* 992, 9–20. doi: 10.1111/j.1749-6632.2003.tb03133.x

Lee, H. M., Kim, T. S., and Jo, E. K. (2016). MiR-146 and miR-125 in the regulation of innate immunity and inflammation. *BMB Rep.* 49, 311–318.

Luan, Y., Li, D., Gao, L., Xie, S., and Pei, L. (2016). A single nucleotide polymorphism in hsamiR146a is responsible for the development of bronchial hyperresponsiveness in response to intubation during general anesthesia. *Mol. Med. Rep.* 14, 2297–2304. doi: 10.3892/mmr.2016.5499

Luciano, M., Huffman, J. E., Arias-Vasquez, A., Vinkhuyzen, A. A., Middeldorp, C. M., Giegling, I., et al. (2012). Genome-wide association uncovers shared genetic effects among personality traits and mood states. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159b, 684–695. doi: 10.1002/ajmg.b.32072

McDonald, M. K., and Ajit, S. K. (2015). "MicroRNA Biology and Pain," in *Molecular and Cell Biology of Pain*, eds T. J. Price and G. Dussor (San Diego, CA: Elsevier Academic Press Inc.), 215–249.

Mineur, Y. S., Obayemi, A., Wigestrand, M. B., Fote, G. M., Calarco, C. A., Li, A. M., et al. (2013). Cholinergic signaling in the hippocampus regulates social stress resilience and anxiety- and depression-like behavior. *Proc. Natl. Acad. Sci. U.S.A.* 110, 3573–3578. doi: 10.1073/pnas.1219731110

Motivala, S. J. (2011). Sleep and inflammation: psychoneuroimmunology in the context of cardiovascular disease. *Ann. Behav. Med.* 42, 141–152. doi: 10.1007/s12160-011-9280-2

Nielsen, M. B., and Einarsen, S. (2012). Outcomes of exposure to workplace bullying: a meta-analytic review. *Work Stress* 26, 309–332. doi: 10.1080/02678373.2012.734709

Olini, N., Rothfuchs, I., Azzinnari, D., Pryce, C. R., Kurth, S., and Huber, R. (2017). Chronic social stress leads to altered sleep homeostasis in mice. *Behav. Brain Res.* 327, 167–173. doi: 10.1016/j.bbr.2017.03.022

Park, R., Lee, W. J., and Ji, J. D. (2016). Association between the three functional miR-146a single-nucleotide polymorphisms, rs2910164, rs57095329, and rs2431697, and autoimmune disease susceptibility: a meta-analysis. *Autoimmunity* 49, 451–458. doi: 10.3109/08916934.2016.1171854

Rickels, K., Garcia, C. R., Lipman, R. S., Derogatis, L. R., and Fisher, E. L. (1976). The hopkins symptom checklist. assessing emotional distress in obstetric-gynecologic practice. *Prim Care* 3, 751–764.

Saba, R., Sorensen, D. L., and Booth, S. A. (2014). MicroRNA-146a: a dominant, negative regulator of the innate immune response. *Front. Immunol.* 5:578. doi: 10.3389/fimmu.2014.00578

Schalm, R. L., and Kelloway, E. K. (2001). The relationship between response rate and effect size in occupational health psychology research. *J. Occup. Health Psychol.* 6, 160–163. doi: 10.1037/1076-8998.6.2.160

Shen, J., Ambrosone, C. B., DiCioccio, R. A., Odunsi, K., Lele, S. B., and Zhao, H. (2008). A functional polymorphism in the miR-146a gene and age of familial breast/ovarian cancer diagnosis. *Carcinogenesis* 29, 1963–1966. doi: 10.1093/carcin/bgn172

Strand, B. H., Dalgard, O. S., Tambs, K., and Rognerud, M. (2003). Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord. J. Psychiatry* 57, 113–118. doi: 10.1080/08039480310000932

Taganov, K. D., Boldin, M. P., Chang, K.-J., and Baltimore, D. (2006). NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A.* 103, 12481–12486. doi: 10.1073/pnas.0605298103

Turnbull, A. V., and Rivier, C. (1995). Regulation of the HPA Axis by Cytokines. *Brain Behav. Immun.* 9, 253–275. doi: 10.1006/brbi.1995.1026

Wohleb, E. S., McKim, D. B., Sheridan, J. F., and Godbout, J. P. (2015). Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. *Front. Neurosci.* 8:17. doi: 10.3389/fnins.2014.00447

Won, E., and Kim, Y.-K. (2016). Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. *Curr. Neuropharmacol.* 14, 665–673. doi: 10.2174/1570159X14666151208113006

Xu, T., Zhu, Y., Wei, Q. K., Yuan, Y., Zhou, F., Ge, Y. Y., et al. (2008). A functional polymorphism in the miR-146a gene is associated with the risk for hepatocellular carcinoma. *Carcinogenesis* 29, 2126–2131. doi: 10.1093/carcin/bgn195

Zhang, X., Huo, Q., Sun, W., Zhang, C., Wu, Z., Xing, B., et al. (2018). Rs2910164 in microRNA146a confers an elevated risk of depression in patients with coronary artery disease by modulating the expression of NOS1. *Mol. Med. Rep.* 18, 603–609. doi: 10.3892/mmr.2018.8929

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

II

BMC Neuroscience

RESEARCH ARTICLE

Open Access

Repeated social defeat promotes persistent inflammatory changes in splenic myeloid cells; decreased expression of β-arrestin-2 (ARRB2) and increased expression of interleukin-6 (IL-6)

Dhaksshaginy Rajalingam[1*†], Ingeborg Nymoen[2†], Daniel Pitz Jacobsen[2], Mina Baarnes Eriksen[2], Erik Dissen[3], Morten Birkeland Nielsen[1,2], Ståle Valvatne Einarsen[1] and Johannes Gjerstad[1,2]

Abstract

Background: Previous studies suggest that persistent exposure to social stress in mammals may be associated with multiple physiological effects. Here, we examine the effects of social stress in rats, i.e. repeated social defeat, on behavior, hypothalamic–pituitary–adrenal (HPA)-axis and immune system.

Methods: A resident-intruder paradigm, where an intruder rat was exposed to social stress by a dominant resident rat for 1 hour each day for 7 consecutive days was used. The day after the last stress exposure in the paradigm the data were analyzed. Variation in social interaction was observed manually, whereas locomotion was analyzed off-line by a purpose-made software. Gene expression in the pituitary gland, adrenal gland and myeloid cells isolated from the spleen was measured by qPCR.

Results: The exposure to social stress induced decreased weight gain and increased locomotion. An increased nuclear receptor subfamily group C number 1 (NR3C1) expression in the pituitary gland was also shown. In myeloid cells harvested from the spleen, we observed decreased expression of the β_2-adrenergic receptor (ADRB2) and β-arrestin-2 (ARRB2), but increased expression of interleukin-6 (IL-6). Subsequent analyses in the same cells showed that ARRB2 was negatively correlated with IL-6 following the stress exposure.

Conclusion: Our results show that that the experience of social stress in the form of repeated social defeat in rats is a potent stressor that in myeloid cells in the spleen promotes persistent inflammatory changes. Future research is needed to examine whether similar inflammatory changes also can explain the impact of social stress, such as bullying and harassment, among humans.

Keywords: Social stressors, Repeated social defeat, Bullying, ADRB2, ARRB2, IL-6

Background

Previous studies show that environmental stressors in mammals induce increased activity of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA)-axis [1–3]. Activation of these systems may be associated with altered behavior [4], hormonal signaling [5] as well as changes in the immune system, for review see [6]. Environmental stressors may promote myelopoiesis in the bone marrow [7], glucocorticoid

*Correspondence: Dhaksshaginy.Rajalingam@uib.no
†Dhaksshaginy Rajalingam and Ingeborg Nymoen contributed equally to this work
[1] Department of Psychosocial Science, University of Bergen, Bergen, Norway
Full list of author information is available at the end of the article

(GC) resistance in the brain and the spleen [8], increased circulatory levels of cytokines [9] and altered inflammatory profile in the brain [10].

Recent data demonstrate that exposure to repeated social defeat—through the resident-intruder paradigm in rats or bullying in humans—is a strong environmental stressor [11]. Previous observations show that environmental stressors may induce neuronal activation of the reticular formation in the brain stem including locus coeruleus (LC) [1], which in turn affects efferent sympathetic nerve fibers that innervate the adrenal gland and spleen [12, 13]. In the adrenal medulla, this innervation results in epinephrine (E) release from chromaffin cells into the circulation [14, 15]. In addition, exposure to environmental stressors leads to activation of the paraventricular nucleus (PVN) of the hypothalamus [1]. This stimulates the HPA-axis through corticotropin releasing hormone (CRH) [16] that promotes secretion of corticosteroids (CORTs) from the adrenal cortex [17].

Regarding the autonomic influence on the thymus, spleen, lymph nodes and bone marrow, norepinephrine (NE) signaling by efferent sympathetic nerve fibers plays a crucial role [18]. Stimulation of adrenergic receptors on immune cells causes changes in differentiation, inflammatory profile and migration capacity [19, 20]. For instance, increased sympathetic signaling may facilitate the induction of genes involved in myeloid lineage effector functions, signal transduction and transcription control [7]. Earlier observations suggest that stress-induced inflammation and myelopoiesis may be linked to increased activity of transcription factors such as nuclear factor kappa B (NF-κB) [7, 9].

Evidence exists that activation of the SNS and HPA-axis may be involved in the regulation of leukocyte trafficking [21, 22]. Leukocyte counts have also revealed increased cell numbers in bone marrow, peripheral blood and spleen following repeated social defeat in mice [23]. These observations are consistent with stress-induced changes in splenic neutrophil and macrophage numbers. Moreover, stress may cause leukocyte recruitment from the bone marrow to the spleen [23]. Increased levels of granulocyte-monocyte colony-stimulating factor (GM-CSF) in circulating monocytes may be a part of the underlying mechanism [7]. Further observations suggest that repeated social defeat may lead to increased release of monocyte chemoattractant protein-1 (MCP-1) from microglia cells [24], which induces monocyte recruitment from the spleen to the capillaries in the brain [10].

It has been proposed that environmental stressors, through activation of β2-adrenergic receptors (ADRB2s), may lead to inflammatory changes of splenic immune cells [7, 25, 26]. In addition, earlier observations suggest that persistent activation of ADRB2s in murine macrophages increases mRNA and protein levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1β (IL-1β) [27]. Moreover, evidence exists that β2-adrenergic signaling also involves β-arrestin 2 (ARRB2), a protein known to inhibit NF-κB nuclear translocation by stabilizing cytoplasmic IκBα activity through ADRB2 activation [28, 29]. However, whether or not ADRB2 and ARRB2 may be associated with the expression of cytokines such as IL-6 during social stress has not been clarified. The aim of the present study was to examine the effect of social defeat on the neuroimmune interface.

Methods

Animals

As described below, a resident-intruder paradigm, where Sprague–Dawley intruder rats were exposed to social stress by dominant Long Evans resident rats; 1 h each day (between 09:00 and 13:00) for 7 consecutive days, was used to study stress-induced changes in the HPA-axis and the immune system. Each of the ten male Long Evans rats (500–550 g) was housed with a female Long Evans rat (200–250 g) in a 0.56 m^2 cage. The ten male Sprague–Dawley rats (300–400 g) used as intruders were housed in pairs, as were the ten male Sprague–Dawley rats (300–400 g) used as controls. The different strains–Long Evans rats from Envigo; USA and Sprague–Dawley rats from Janvier Labs; France–were kept in separate rooms. All rats were acclimatized to a 12:12 h light:dark cycle, ventilation rate of 15 × air per hour, 21–22 °C and 45–55% humidity. At all times, the rats had ad libitum access to food and water. Bedding was changed once a week. All animal procedures were approved by the Norwegian Food Safety Authority and performed in conformity with laws and regulations controlling experiments and procedures on live animals in Norway.

Screening

To ensure dominant behavior of Long Evan males i.e., the resident rats in the paradigm, a screening was performed prior to the stress-conditioning week. Top ten aggressive rats were chosen based on the highest incidences of attacks over a period of 10 min.

Resident-intruder paradigm

First, the female rat was temporarily removed from the resident cage 1 hour before the stress conditioning. Next, the stress conditioning was performed by introducing the intruder animal into the resident cage. The male resident and intruder rat were separated upon three episodes of social defeat (submissive supine posture, freeze or flight), or after 10 min of interaction by a perforated plastic wall, allowing the intruder rat to still see, smell and hear the

resident rat. Finally, after 60 min in the resident cage, the intruder rat was returned to its home cage, and the female rat was returned to the resident cage. The conditioning procedure described above was repeated for 7 days. To prevent habituation to the dominance establishment with the resident rat, the intruder animals were introduced to a new resident animal every day. The animals randomized to control followed the same procedure except that they visited a foreign cage without a resident rat.

Social interaction test

A modified version of the social interaction test was used to assess the social interaction behavior of the Sprague–Dawley rats (i.e., the test rats) following 1week of stress or control conditioning [30]. More specifically, the social interaction test was conducted 1 day after the last episode of defeat. The test arena was a purpose made box (0.56 m^2) divided into three compartments by two gated plastic walls and a small wire-like container in each flanking compartment. The test rats were allowed to habituate in the center compartment for 4 minutes (Additional file 1: Fig. S1a) before a novel rat of the same strain was placed into one of the small wire-like containers (Additional file 1: Fig. S1b). The subsequent opening of the gates allowed the test rat to move freely between the compartments for 6 minutes (Additional file 1: Fig. S1c). Movement and behavior of the test animals were recorded by a camera placed in a rack above the box. Thus, changes in behavior were examined after the experiments, including the time spent in each chamber and the time spent in direct social interaction with the novel rat. The novel rats were habituated to the wire-like container prior to the social interaction test, but did not take part in the resident-intruder paradigm.

Video analysis

Recorded videotapes of rats moving in the three-chamber box were analyzed using a purpose-made software program, which was programmed and developed in C. The time spent in each of the three chambers and locomotion of rats (10 s intervals) were scored by the software.

Anesthesia and blood sampling

Following the social interaction test and one hour rest in their home cage, on day 8, the intruder Sprague–Dawley and control rats were sedated with 5% isoflurane in air in a gas box prior to being moved to a 3% isoflurane anesthetic gas mask. Absence of withdrawal reflexes was considered sufficient anesthesia for surgery.

The animal was fixated in a dorsal recumbence position and a v-cut through the skin and abdominal wall was made. The heart was exposed by opening the thoracic cage, cutting through the diaphragm. A 10 mL syringe with a 1.2 mm cannula coated with 1.8 mg/mL EDTA (Sigma Life Science; Switzerland), was inserted into the left ventricle (cardiac puncture). Blood samples of 2 ml were drawn from the exposed and control Sprague–Dawley rats. In accordance with the procedure previously described, 500 µL of the blood was immediately placed on liquid nitrogen for NE and CORT concentration measurements performed (Additional file 1: Fig. S2) [31].

Tissue harvesting

All Sprague–Dawley rats were euthanized by dislocation of the neck under isoflurane anesthesia. The pituitary gland and adrenal glands were harvested, frozen on liquid nitrogen and later stored in a −80 °C freezer.

Enrichment of splenic myeloid cells

The spleen was mechanically disrupted with scissors, and pieces of spleen tissue were passed multiple times through a 10 mL syringe and filtered through a 70 µM cell strainer in order to get a single cell suspension. Mononuclear cells were retrieved by density centrifugation. The suspension was diluted with PBS (GE Healthcare Lifesciences; USA), loaded on top of a 15 mL Lymphoprep^{TM} medium (STEMCELL technologies; Norway) and centrifugated (400x*g* for 30 min at 4 °C). The layer of mononuclear cells was carefully aspirated, diluted in PBS supplemented with 2% FBS, washed by centrifugation (300x*g*, 10 min, 4 °C) and resuspended in PBS (2% FBS). Myeloid cells were purified from the spleen mononuclear fraction by immunomagnetic bead separation. To avoid unspecific monoclonal antibody (mAb) binding, the Fc receptors were pre-blocked by incubating the cells in PBS with 10% rat serum for 15 min at 4 °C. Subsequently, cells were incubated with a biotinylated mouse mAb (OX41) specific for rat CD172a (SIRP-α, expressed on the surface of all myeloid cells) at 2 µg/mL in PBS (10% rat serum) for 15 min at 4 °C and washed three times in PBS (2% FBS, 10 mM NaN_3) before incubation with streptavidine-coated magnetic microbeads (MACS, Miltenyi Biotec; Germany) resuspended in PBS supplemented with 2 mM EDTA and 0.5% BSA for 30 min at 4 °C, using 40 µL of beads per 4 x 10^7 cells. The cells were then run through MACS LS columns in the magnetic field of a quadroMACS^{TM} separator (Miltenyi Biotec; Germany) to separate bead-captured cells from unstained, non-myeloid cells according to manufacturer instructions.

Flow cytometry

Flow cytometry was used to verify the enrichment of CD172 positive cells and the nature of contaminating non-myeloid cells. Two separate mixes of fluorochrome-conjugated mAbs for test and isotype controls were used,

diluted in PBS (2% FBS, 10 mM NaN_3) (Additional file 1: Table S1). Staining with isotype control antibodies was included to evaluate unspecific mAb binding capacity to splenic cell subsets.

A small fraction of the cell sample i.e., 3 x 10 ^{5}, was used for flow cytometry analysis and incubated with 50 µL mAb test or isotype mix (2 µg/mL) in PBS (2% FBS, 10 mM NaN_3) for 30 min on ice. After staining with primary antibody mixes, the cells were washed three times by centrifugation (300x*g*, 2 min, 4 °C), resuspended in PBS (2% FBS, 10 mM NaN_3) and incubated with Streptavidin-Alexa Fluor 647 conjugated for detection of OX41-biotin or IgG1-biotin binding, respectively. Cells were washed and analyzed on a CytoFlex flow cytometry (Beckman Coulter Life Sciences, USA) using CytExpert software.

RNA isolation and cDNA synthesis

The allprep DNA/RNA/miRNA Universal Kit (Qiagen; Germany) was used to isolate total RNA from the frozen pituitary, adrenal and enriched myeloid cells. Total RNA was extracted by homogenizing the frozen tissue with magnetic beads in a bead beater. The lysate was then used for RNA isolation following the manufacturer's protocol. Synthesis of cDNA from these tissues was carried out using the qSCript cDNA synthesis kit (Quanta Biosciences Inc.; USA).

Gene expression analyses

RNA quantification of the different genes was achieved by a two-step real-time reverse transcription qPCR (RT-qPCR). Primer sequences (fwd,rev) were from Sigma Life Sciences, Switzerland: POMC (5′AACGCCATCAAG AAC3′ and 5′AAGGTTTTATTTCCTAACTACAC3′); NR3C1 (5′CAGAGAATGTCTCTACCCTG3′ and 5′CTT AGGAACTGAGGAGAGAAG3′); MC2R (5′AGAAAC TGGATCCTTCCG3′ and 5′TGGTGTGTTCATACG AATTG3′); β-actin (5′CTAAGGCCAACCGTGAAA AGA3′ and 5′ACAACACAGCCTGGATGGCAT3′); IL-6 (5′TGCCCTTCAGGAACA3′ and 5′AAGGCAGTG GCTGTC3′); ADRB2 (5′AAAGAGAGAGAGAGAGAC T3′ and 5′ACAACACTTCAGACAGAAAC3′); HPRT (5′ACTGGTAAAACAATGCAGGAC3′ and 5′CCTGAA GTGCTCATTATAGTC3′); PtPrc (5′GCTATAAAAAGA CCCCTTCAG3′ and 5′CATAGGCAAATAGAGACA CTG3′); ARRB2 (5′GCAGCCAGGACCAGAGGACA3′ and 5′CCACGCTTCTCTCGGTTGTC3′). PCR was run on Quantstudio 5 (Thermofisher Scientific; Norway) and analyzed using Quantstudio™ Design and Analysis Software.

Statistics

The data were shown by representative examples and mean ± standard error of the mean. Statistical analyses were conducted with Sigmaplot 14.0 and the level of significance was set to $p < 0.05$. Shapiro–Wilk test was run to assess normality. Differences in body weight, social interaction, locomotion, gene expression levels and differences in percentage of myeloid cells between exposed group and control group were analyzed using Student's *t* test.

Results

Behavior

The resident-intruder paradigm changed the behavior of the intruder rats in the residential cage (Fig. 1). For each day passing, the number of rats showing subordinate defeat behavior increased. After 6 days of stress conditioning all intruder rats showed a clear social defeat within the 10-min frame (Fig. 2a).

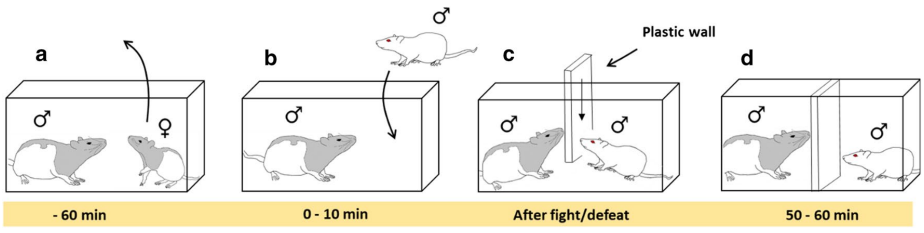

Fig. 1 Resident-intruder paradigm. The set-up used to induce defeat stress in the intruder Sprague–Dawley rats (white) in the cage of the resident male Long Evans rat (black-hooded). **a** The Long Evans female was removed 60 min prior to the experiment. **b** An intruder Sprague–Dawley rat was placed in the home cage of a resident male Long Evans rat. **c** Upon three episodes of social defeat (submissive supine posture, freeze or flight), or after 10 min of interaction, a plexiglas wall was used to separate the resident and intruder rats. **d** Sensory interaction in the divided cage was allowed for the remaining time of the hour. Both the male Sprague–Dawley and female Long Evans rats were returned to their home cage after the conditioning. (Illustrated by Nymoen, I.)

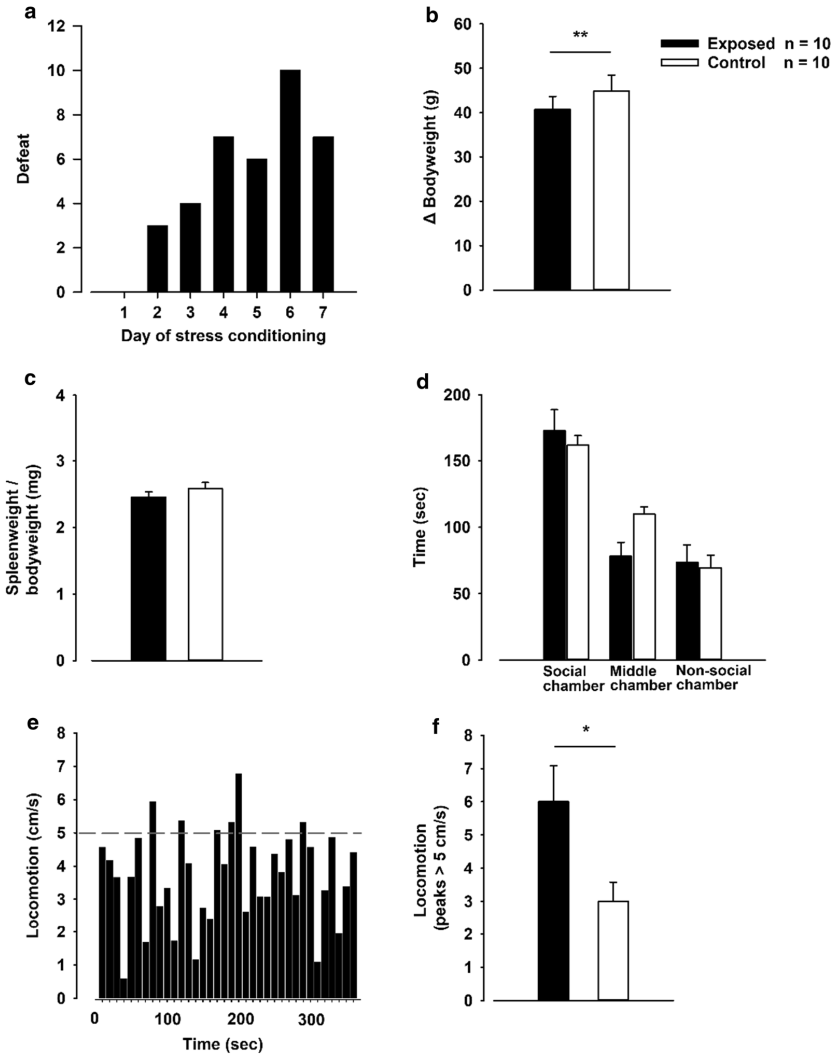

Fig. 2 Behavior, weight gain and locomotion. **a** Number of defeated stress-exposed rats (intruder rats) during conditioning at day 1–7. **b** Bodyweight at day seven in stress-exposed rats versus control rats (relative to baseline), $p = 0.007$. **c** Organ-to-bodyweight ratio of the spleen in stress-exposed rats versus control rats. **d** Social interaction test; time spent in the three different chambers, stress-exposed rats versus control rats. **e** Example of locomotion in the three different chambers (10 s intervals). **f** Peak locomotion > (5 cm/s) stress-exposed rats versus control rats, $p = 0.029$. *$p < 0.05$, **$p < 0.01$, Students t-test

The exposed rats gained less weight during the conditioning week, compared to controls (Fig. 2b). However, we did not observe any increase of spleen weight-to-bodyweight ratio (Fig. 2c), and thus there was no evidence of splenomegaly following stress exposure.

Following the conditioning week, all exposed and control animals went through a social interaction test. No difference was observed between the two groups, evaluated by time spent in the three different chambers (Fig. 2d). Locomotion (cm/s) of the rats in 10 s intervals

was measured by a computer. The stress exposed rats had significantly higher locomotion compared to control rats (Fig. 2e, f).

HPA-axis gene expression and NE/CORT in plasma

The stress exposure did not result in any clear changes of pro-opiomelanocortin (POMC) (Fig. 3a), but showed a significant increase in the expression of NR3C1 in the pituitary gland (Fig. 3b). The exposure did not alter adrenal gland expression of MC2R (ACTH receptor) or NR3C1 (Fig. 3c, d) nor the NE or CORT levels in plasma (Additional file 1: Fig. S2a, b).

Enrichment of splenic myeloid cells

Flow cytometry analysis of the final cell suspension from the enrichment procedure was performed to elucidate the amount of myeloid cells compared to the amount of contaminating cells (Fig. 4a–f, Additional file 1: Fig.S3). The estimated SIRP-α positive fraction was 81.9% ± 1.73 in the exposed group and 86.6% ± 1.12 in the control group. The predominant contaminating cell type was CD45RABC positive cells (most likely B cells). We observed 12.1% ± 1.28 CD45RABC positive cells in the exposed group and 8.82% ± 0.77 CD45RABC positive cells in the control group (Fig. 4g).

Gene expression in splenic myeloid cells

The ADRB2 and ARRB2 were both significantly down-regulated following 1 week of stress exposure (Fig. 5a, b). In addition, our results showed an increased expression of IL-6 in exposed animals compared to controls and that the IL-6 levels were associated with ARRB2 levels in myeloid cells (Fig. 5c, d). The NR3C1 expression levels revealed no difference in the cell population studied (Additional file 1: Fig. S4).

Discussion

In the present study, we addressed stress-induced changes in behavior, HPA-axis and immune system. In addition to increased locomotion and reduced weight

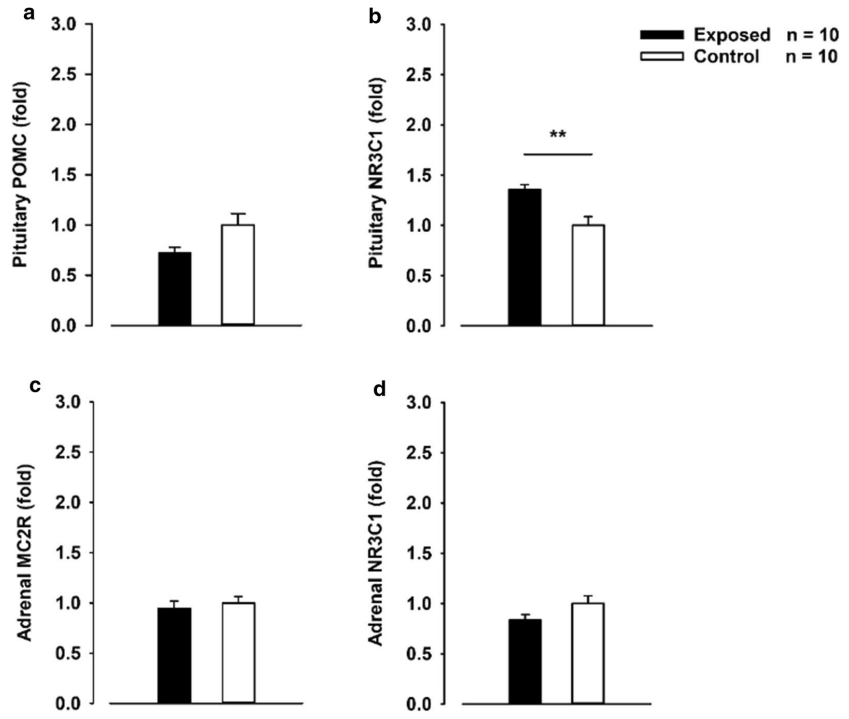

Fig. 3 The pituitary- and adrenal- gland. **a**, **b** Fold expression of adrenocorticotropic hormone (ACTH) precursor POMC, and glucocorticoid receptor (Nr3C1) in the pituitary gland of stress-exposed rats versus control rats, p = 0.003. **c, d** Fold expression of melanocortin type-2 receptor (MC2R) and Nr3C1 in the left adrenal gland of stress-exposed rats versus control rats. The data were normalized to β-actin and then to baseline. *p < 0.05, **p < 0.01, Students t-test

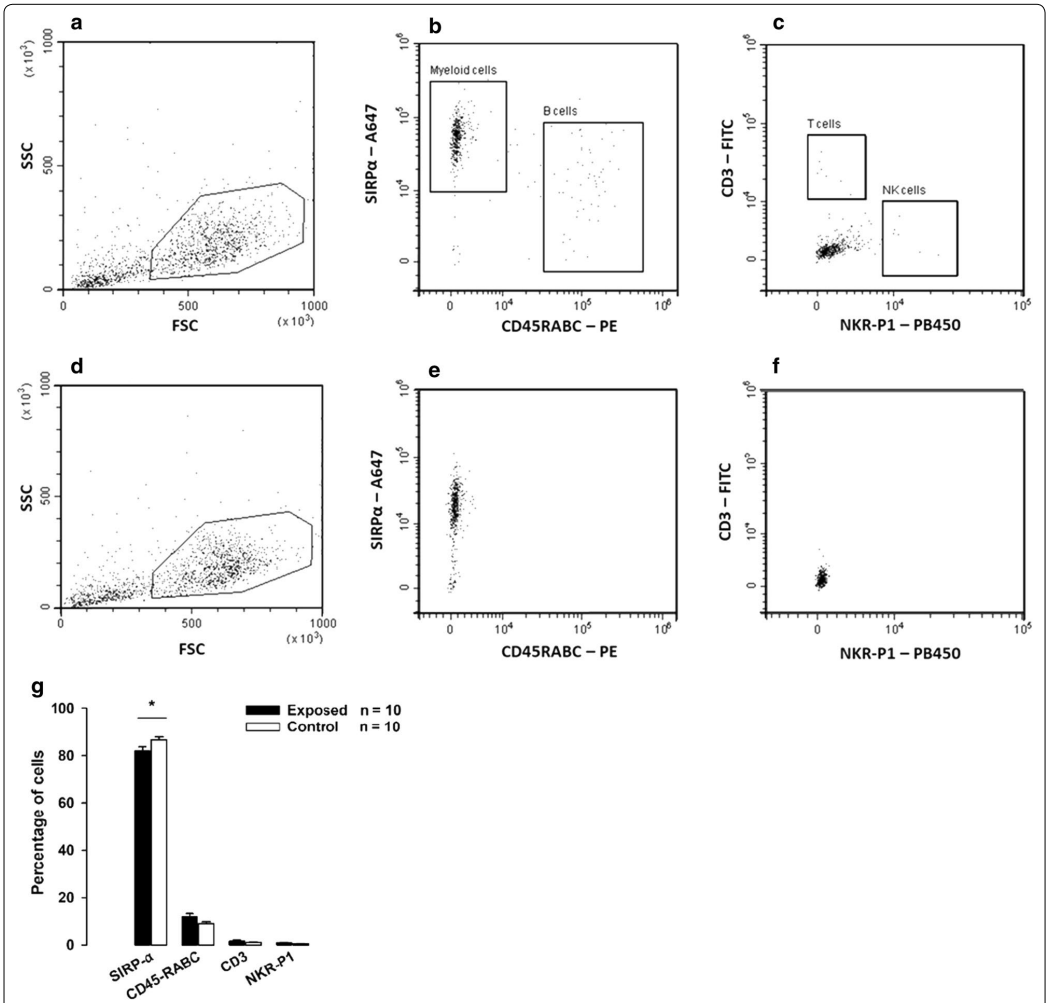

Fig. 4 Enrichment of myeloid cells from the spleen. **a** Living cells were included in a polygon gate, whereas the remaining cells (mostly dead and apoptotic cells) were excluded (SSC v FSC). Gated cells (exclusion of the negative population, see Additional file 1: Fig. S3) were visualized with the (**b**) SIRP α–A647 v CD45RABC–PE channels and the (**c**) CD3–FITC v NKR-P1–PB450 channels. **d–f** Scatter plots for isotype controls. **g** Following the enrichment procedure, all samples were analyzed by flow cytometry to characterize the final cell suspension. The mean CD3–percentage of SIRP-α positive cells were 81.9% ± 1.73 and 86.6% ± 1.12 for exposed and control, respectively, $p = 0.04$. The fraction of contaminating cells made up 12.1% ± 1.28 and 8.8% ± 0.77 CD45RABC positive cells, 1.6% ± 0.51 and 1.1% ± 0.14 CD3 positive cells and 0.9% ± 0.14 and 0.5% ± 0.07 NKR-P1 positive cells in the final isolated cell pellet from exposed and control animals, respectively. *$p < 0.05$, Students t-test

gain, we observed an increased NR3C1 expression in the pituitary gland after 1 week with social stress. The most robust effects of the stress exposure were, however, seen on isolated splenic immune cells. In these myeloid cells, we observed decreased expression of the ADRB2 and ARRB2, but increased expression of IL-6, the day after the last stress exposure in the paradigm. Moreover, stress exposure induced a downregulation of ARRB2 that was negatively correlated with IL-6. Hence, the present data support the idea that reduced expression of ARRB2 may enhance the translocation of the NF-κB to the nucleus and activate the transcription of IL-6.

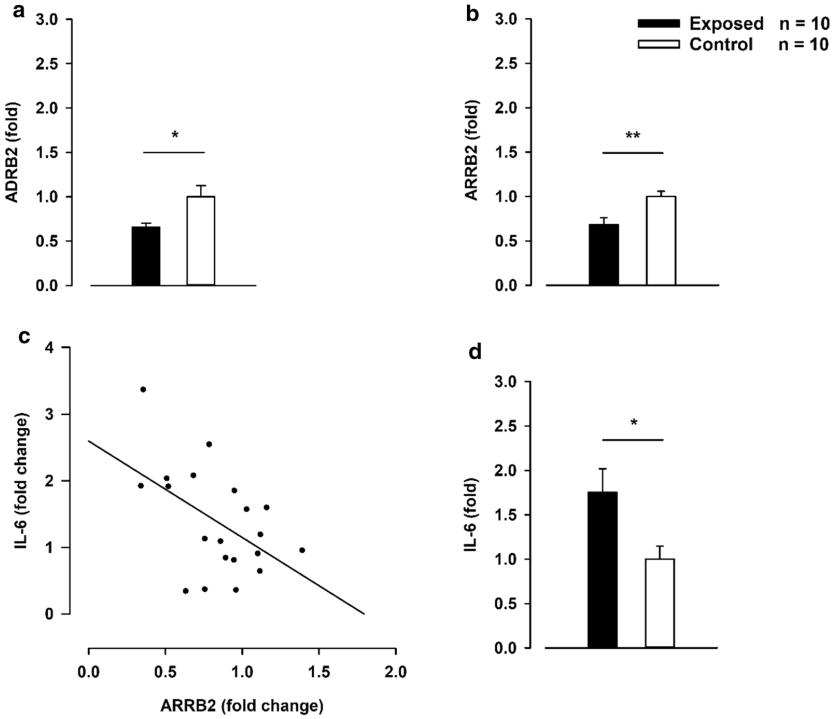

Fig. 5 Myeloid cells from the spleen. **a** Fold expression of β2-adrenergic receptor (ADRB2) in the stress-exposed rats versus control rats, p = 0.02. **b** Fold expression of β-arrestin 2 (ARRB2) in stress-exposed rats versus control rats, p = 0.007. **c** The relationship between IL-6 and ARRB2 expression levels, r = 0.509, p = 0.022. **d** Fold expression of interleukin 6 (IL-6) in the stress-exposed rats versus control rats, p = 0.02. All data were normalized to the mean of hypoxanthine phosphoribosyltransferase (HPRT) and protein tyrosine phosphatase receptor type C (PTPRC) and then to the baseline. *p < 0.05, **p < 0.01, Students t-test

Earlier findings in murine models indicate that stress-induced physiological changes, including reduced CORT sensitivity in peripheral macrophages, central microglia activation and anxiety-like behavior during stress exposure, may be cycle-dependent, i.e., increases for each stress episode. Previous data also show a stress-induced reduced preference towards sucrose [32] and IL-6 driven energy expenditure affecting gain of body weight [33]. It is therefore tempting to speculate that the observed submissive behavior may involve depression and lack of appetite, but also learned helplessness behavior [34] and enhanced punishment avoidance [35, 36]. In accordance with earlier observations [1, 4, 37], we demonstrated a clear stress-induced decrease in weight gain.

Several studies suggest that the resident-intruder paradigm in mice may cause leukocyte egress from the bone marrow, enhanced recruitment of myeloid cells to the spleen, which in turn may be associated with splenomegaly, i.e., increased spleen weight [21–23, 38]. However, since the enhanced recruitment of myeloid cells to the spleen have been reported to be more pronounced in wounded animals than in those without any injuries [23], the earlier reported stress-induced splenomegaly could be a result of the immunological changes caused by infections etc. Thus, splenomegaly may be a result of physical injuries (wounds) rather than social stress.

In the present study we used rats, not mice. Therefore, it was possible to avoid bites and wounds. The intruder animals in our study were therefore only exposed to social stress, not confounding factors such as physical injuries that could lead to immunological changes caused by infections. Interestingly, the present resident-intruder paradigm in our study, where we used rats, did not change the spleen volume/weight. Therefore, the present study supports the idea that splenomegaly induced by the resident-intruder paradigm may be explained by infections rather than social stress.

Exposure to chronic stress may impair neurogenesis in the prefrontal cortex (PFC) and hippocampus, but have the opposite effect in amygdala [39–41]. Moreover, stress may induce amygdala hyperactivity, increase synaptic connectivity in amygdala [42], and stimulate amygdala-dependent fear learning [43]. Thus, when the exposure to stress persists, the brain seems to switch from slow, attentive PFC regulation to more reflexive responses predominantly controlled by the amygdala and related subcortical structures [44, 45]. Social stress, which involves PFC dysregulation and amygdala hyperactivity, could therefore also promote behavioral changes such as rapid movements observed in the present study.

Previous studies suggest a link between stress-induced migration of leukocytes from the bone marrow and splenomegaly [21–23, 38]. Moreover, the egress of cells from the bone marrow in this process may be controlled by NE/E [22] and CORTs [21]. However, previous data also show that enhanced myeloid recruitment to the spleen could be caused by minor infections following wounds [23]. Thus, whether or not social stress alone is enough to induce splenomegaly may be debated. Our data did not support any clear stress-induced change in spleen weight.

Stress-induced mononuclear cell migration, pro-inflammatory activation, and anxiety-like behavior seem to be catecholamine-dependent [25]. Thus, stress may involve activation of the G protein-coupled adrenergic receptors on leukocytes [46]. Furthermore, earlier findings suggest that NE and/or E activation of ADRB2s may induce the expression of pro-inflammatory cytokines through ERK1/2 and MAPK-dependent mechanisms [27]. In addition to G proteins, cytoplasmic adaptor molecules such as ARRB2 may interact with the ADRB2, conveying signals of anti-inflammatory origin by inhibiting NF-κB nuclear translocation [29]. However, PKA- and cAMP-dependent suppression of NF-κB can also be induced by ADRB2 signaling.

Interestingly, our data demonstrated reduced ADRB2 and ARRB2 mRNA levels accompanied by increased mRNA levels of IL-6 in the isolated splenic myeloid cells of the stress-exposed rats. It seems plausible that repeated or persistent NE exposure may cause ADRB2 desensitization [47], which is associated with downregulation of ARRB2 [48]. Reduced levels of ARRB2 may result in increased nuclear translocation and transcriptional activity of NF-κB. Since NF-κB may bind to the IL-6 promoter [49] for review see [50], it seems reasonable to believe that the expression of IL-6 is controlled by the transcription factor NF-κB through a promoter binding mechanism [51, 52]. It is tempting to speculate that stress-induced upregulation of IL-6 is a result of reduced ARRB2.

The functional diversity of IL-6 may be reflected through its activation of glycoprotein 130 (gp130) and STAT [53] signal transduction. The ubiquitous expression of gp130 allows for a wide range of actions for the cytokines that utilize this pathway [54]. Signal transduction via gp130 has the capacity to suppress innate immune responses [55] and promote adaptive immunity by lymphocyte trafficking [56]. IL-6 is a key mediator in T cell infiltration of tissue and in the neutrophil to mononuclear cell switch in leukocyte recruitment pattern [57, 58]. Moreover, previous data show that this cytokine is essential for differentiation of naïve T cells and B cells into effector cells [59–61]. In addition, IL-6 production and secretion from splenic myeloid cells may act in an autocrine fashion [53]. Thus, stress-induced splenic upregulation of IL-6 and IL-6 downstream processes may be important for the transition from the acute to persistent immune activation.

Conclusion

Taken together, our results suggest that the experience of 1 week of repeated social defeat in rats is a potent stressor that triggers prolonged myeloid inflammatory changes in lymphoid tissues such as the spleen. We believe our results demonstrate neuroendocrine and immunological changes caused by social stress only, not confounding factors such as physical injuries and infections often seen in mice. This shows that the inflammatory effect of such social stress may be stronger than previously assumed. The role of this mechanism following exposure to social stress in humans remains to be investigated.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12868-020-00574-4.

Additional file 1: Figure S1. The test used to assess behavior. **Figure S2.** Plasma**. Figure S3.** Gating strategy to assess purity of enriched myeloid cell population from rat spleen. **Figure S4.** Myeloid cells from the spleen. **Table S1.** Two separate mixes of fluorochrome-conjugated monoclonal antibodies for test and control. The two mixes were separately added to a small fraction of the final cell suspension.

Abbreviations

ADRB2: β2-adrenergic receptor; ARRB2: β-arrestin-2; CORT: Corticosterone; CRH: Corticotropin-releasing hormone; E: Epinephrine; ERK: Extracellular signal-regulated kinases; GC: Glucocorticoid; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HPA: Hypothalamic–pituitary–adrenal; IL-6: Interleukin 6; IL-1β: Interleukin 1 β; LC: Locus coreleus; MAPK: Mitogen activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; NE: Noradrenaline; NFKB: Nuclear factor kappa-lit-chain-enhancer of activated B cells; NR3C1: Nuclear receptor subfamily 3, group c, member 1; PFC: Prefrontal cortex; POMC: Pro-opiomelanocortin; PVN: Paraventricular nucleus; SNS: Sympathetic nervous system; STAT: Signal transducer and activator of transcription.

Acknowledgements

We thank Anne-Mari Gjestvang Moe, Tiril Schjølberg, Fang-Chin Lin, Oda Helgesen Ramberg and Rune Asgeir Madsen for their excellent technical

support. We also thank Marianne Bergh and Jannike Mørch Andersen at the Norwegian Institute of Public Health (NIPH) for the NE and CORT concentration measurements.

Authors' contributions
There are no sources in the current document. DR, IN, DJ, ME, ED, MN, SE, and JG designed the research; DR, IN, DJ and JG performed the research; DR, IN, and JG analyzed the data; DR, IN and JG wrote the paper. All authors read and approved the final manuscript.

Funding
The study is part of two larger research projects entitled "Workplace bullying: From mechanisms and moderators to problem treatment" funded by The Norwegian Research Council and the University of Bergen/"Psychosocial work factors, persistent back pain and sickness absenteeism–the role of mental distress and epigenetic changes" funded by The Norwegian Research Council and National Institute of Occupational Health. Grant numbers: 250127/237777. The funder was not a participant in any research experiments or data analysis.

Availability of data and materials
The datasets supporting the conclusions of this article are included within the article and its additional files.

Ethics approval and consent to participate
All procedures were approved by the Norwegian Food Safety Authority (application ID: 11671) and performed in conformity with laws and regulations controlling experiments and procedures on live animals in Norway [62, 63].

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

Author details
[1] Department of Psychosocial Science, University of Bergen, Bergen, Norway. [2] National Institute of Occupational Health, Oslo, Norway. [3] Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway.

Received: 10 February 2020 Accepted: 20 May 2020
Published online: 29 May 2020

References

1. Flak JN, Myers B, Solomon MB, McKlveen JM, Krause EG, Herman JP. Role of paraventricular nucleus-projecting norepinephrine/epinephrine neurons in acute and chronic stress. European J Neurosci. 2014;39(11):1903–11.
2. Raone A, Cassanelli A, Scheggi S, Rauggi R, Danielli B, De Montis MG. Hypothalamus-pituitary-adrenal modifications consequent to chronic stress exposure in an experimental model of depression in rats. Neuroscience. 2007;146(4):1734–42.
3. Zhou JJ, Gao Y, Zhang X, Kosten TA, Li DP. Enhanced hypothalamic NMDA receptor activity contributes to hyperactivity of HPA axis in chronic stress in male rats. Endocrinology. 2018;159(3):1537–46.
4. Zelena D, Haller J, Halasz J, Makara GB. Social stress of variable intensity: physiological and behavioral consequences. Brain Res Bull. 1999;48(3):297–302.
5. Lowrance SA, Ionadi A, McKay E, Douglas X, Johnson JD. Sympathetic nervous system contributes to enhanced corticosterone levels following chronic stress. Psychoneuroendocrinology. 2016;68:163–70.
6. Glaser R, Kiecolt-Glaser JK. Science and society - Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005;5(3):243–51.
7. Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. Proc Natl Acad Sci USA. 2013;110(41):16574–9.
8. Quan N, Avitsur R, Stark JL, He L, Shah M, Caligiuri M, Padgett DA, Marucha PT, Sheridan JF. Social stress increases the susceptibility to endotoxic shock. J Neuroimmunol. 2001;115(1–2):36–45.
9. Miller GE, Chen E, Sze J, Marin T, Arevalo JM, Doll R, Ma R, Cole SW. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappa B signaling. Biol Psychiat. 2008;64(4):266–72.
10. Wohleb ES, McKim DB, Shea DT, Powell ND, Tarr AJ, Sheridan JF, Godbout JP. Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain. Biol Psychiatr. 2014;75(12):970–81.
11. Jacobsen DP, Eriksen MB, Rajalingam D, Nymoen I, Nielsen MB, Einarsen S, Gjerstad J. Exposure to workplace bullying, microRNAs and pain; evidence of a moderating effect of miR-30c rs928508 and miR-223 rs3848900. Stress. 2019;23(1):77–86.
12. Cano G, Sved AF, Rinaman L, Rabin BS, Card JP. Characterization of the central nervous system innervation of the rat spleen using viral transneuronal tracing. J Comp Neurol. 2001;439(1):1–18.
13. Kesse WK, Parker TL, Coupland RE. The innervation of the adrenal gland. I. The source of pre- and postganglionic nerve fibres to the rat adrenal gland. J Anatomy. 1988;157:33–41.
14. Badder EM, Santen R, Samojlik E, Harrison TS. Adrenal medullary epinephrine secretion: effects of cortisol alone and combined with aminoglutethimide. J Lab Clin Med. 1980;96(5):815–21.
15. Nezu M, Miura Y, Adachi M, Adachi M, Kimura S, Toriyabe S, Ishizuka Y, Ohashi H, Sugawara T, Takahashi M, et al. The effects of epinephrine on norepinephrine release in essential hypertension. Hypertension. 1985;7(2):187–95.
16. Wamsteeker Cusulin JI, Fuzesi T, Watts AG, Bains JS. Characterization of corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus of Crh-IRES-Cre mutant mice. PLoS ONE. 2013;8(5):e64943.
17. Osterlund CD, Rodriguez-Santiago M, Woodruff ER, Newsom RJ, Chadayammuri AP, Spencer RL. Glucocorticoid fast feedback inhibition of stress-induced ACTH secretion in the male rat: rate independence and stress-state resistance. Endocrinology. 2016;157(7):2785–98.
18. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. J Immunol. 1985;135(2 Suppl):755s–65s.
19. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci USA. 2003;100(4):1920–5.
20. Grisanti LA, Evanson J, Marchus E, Jorissen H, Woster AP, DeKrey W, Sauter ER, Combs CK, Porter JE. Pro-inflammatory responses in human monocytes are beta1-adrenergic receptor subtype dependent. Mol Immunol. 2010;47(6):1244–54.
21. Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Stress-induced changes in blood leukocyte distribution role of adrenal steroid hormones. J Immunol. 1996;157(4):1638–44.
22. Engler H, Dawils L, Hoves S, Kurth S, Stevenson JR, Schauenstein K, Stefanski V. Effects of social stress on blood leukocyte distribution: the role of alpha- and beta-adrenergic mechanisms. J Neuroimmunol. 2004;156(1–2):153–62.
23. Engler H, Bailey MT, Engler A, Sheridan JF. Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. J Neuroimmunol. 2004;148(1–2):106–15.
24. Wohleb ES, Hanke ML, Corona AW, Powell ND, Stiner LM, Bailey MT, Nelson RJ, Godbout JP, Sheridan JF. beta-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J Neurosci. 2011;31(17):6277–88.
25. Hanke ML, Powell ND, Stiner LM, Bailey MT, Sheridan JF. Beta adrenergic blockade decreases the immunomodulatory effects of social disruption stress. Brain Behav Immun. 2012;26(7):1150–9.
26. Turney TH, Harmsen AG. Splenomegaly and other hematological parameters in the socially dominant mouse. Physiol Behav. 1984;33(4):559–62.
27. Powell ND, Bailey MT, Mays JW, Stiner-Jones LM, Hanke ML, Padgett DA, Sheridan JF. Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. Brain Behav Immun. 2009;23(2):225–31.
28. Gao H, Sun Y, Wu Y, Luan B, Wang Y, Qu B, Pei G. Identification of beta-arrestin2 as a G protein-coupled receptor-stimulated regulator of NF-kappaB pathways. Mol Cell. 2004;14(3):303–17.

29. Luan B, Zhang Z, Wu Y, Kang J, Pei G. Beta-arrestin2 functions as a phosphorylation-regulated suppressor of UV-induced NF-kappaB activation. EMBO J. 2005;24(24):4237–46.
30. Kaidanovich-Beilin O, Lipina T, Vukobradovic I, Roder J, Woodgett JR. Assessment of social interaction behaviors. J Vis Exp. 2011;48:2473.
31. Bergh MS, Bogen IL, Andersen JM, Oiestad AML, Berg T. Determination of adrenaline, noradrenaline and corticosterone in rodent blood by ion pair reversed phase UHPLC-MS/MS. J Chromatogr B Anal Technol Biomed Life Sci. 2018;1072:161–72.
32. Iniguez SD, Riggs LM, Nieto SJ, Dayrit G, Zamora NN, Shawhan KL, Cruz B, Warren BL. Social defeat stress induces a depression-like phenotype in adolescent male c57BL/6 mice. Stress. 2014;17(3):247–55.
33. Faldt J, Wernstedt I, Fitzgerald SM, Wallenius K, Bergstrom G, Jansson JO. Reduced exercise endurance in interleukin-6-deficient mice. Endocrinology. 2004;145(6):2680–6.
34. Landgraf D, Long J, Der-Avakian A, Streets M, Welsh DK. Dissociation of learned helplessness and fear conditioning in mice: a mouse model of depression. PLoS ONE. 2015;10(4):e0125892.
35. Palminteri S, Justo D, Jauffret C, Pavlicek B, Dauta A, Delmaire C, Czernecki V, Karachi C, Capelle L, Durr A, et al. Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. Neuron. 2012;76(5):998–1009.
36. Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. NeuroImage. 2003;19(4):1439–48.
37. Tsai Cabal A, Ioanas HI, Seifritz E, Saab BJ. Selective amotivation deficits following chronic psychosocial stress in mice. Behav Brain Res. 2017;317:424–33.
38. Stark JL, Avitsur R, Padgett DA, Campbell KA, Beck FM, Sheridan JF. Social stress induces glucocorticoid resistance in macrophages. Am J Physiol Regul Integr Comp Physiol. 2001;280(6):R1799–805.
39. Patel D, Anilkumar S, Chattarji S, Buwalda B. Repeated social stress leads to contrasting patterns of structural plasticity in the amygdala and hippocampus. Behav Brain Res. 2018;347:314–24.
40. McKim DB, Niraula A, Tarr AJ, Wohleb ES, Sheridan JF, Godbout JP. Neuroinflammatory dynamics underlie memory impairments after repeated social defeat. J Neurosci. 2016;36(9):2590–604.
41. Mouri A, Ukai M, Uchida M, Hasegawa S, Taniguchi M, Ito T, Hida H, Yoshimi A, Yamada K, Kunimoto S, et al. Juvenile social defeat stress exposure persistently impairs social behaviors and neurogenesis. Neuropharmacology. 2018;133:23–37.
42. Vyas A, Pillai AG, Chattarji S. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience. 2004;128(4):667–73.
43. Conrad CD, LeDoux JE, Magarinos AM, McEwen BS. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci. 1999;113(5):902–13.
44. Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. J Neurosci. 1996;16(15):4787–98.
45. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci. 2002;22(15):6810–8.
46. Saygin D, Wanner N, Rose JA, Naga Prasad SV, Tang WHW, Erzurum S, Asosingh K. Relative quantification of beta-adrenergic receptor in peripheral blood cells using flow cytometry. Cyto Part A J Int Soc Anal Cytol. 2018;93(5):563–70.
47. Hadcock JR, Malbon CC. Down-regulation of beta-adrenergic receptors: agonist-induced reduction in receptor mRNA levels. Proc Natl Acad Sci USA. 1988;85(14):5021–5.
48. Kizaki T, Izawa T, Sakurai T, Haga S, Taniguchi N, Tajiri H, Watanabe K, Day NK, Toba K, Ohno H. Beta2-adrenergic receptor regulates Toll-like receptor-4-induced nuclear factor-kappaB activation through beta-arrestin 2. Immunology. 2008;124(3):348–56.
49. Xiao W, Hodge DR, Wang L, Yang X, Zhang X, Farrar WL. NF-kappaB activates IL-6 expression through cooperation with c-Jun and IL6-AP1 site, but is independent of its IL6-NFkappaB regulatory site in autocrine human multiple myeloma cells. Cancer Biol Ther. 2004;3(10):1007–17.
50. Luo Y, Zheng SG. Hall of fame among pro-inflammatory cytokines: interleukin-6 gene and its transcriptional regulation mechanisms. Front Immunol. 2016;7:604.
51. Libermann TA, Baltimore D. Activation of interleukin-6 gene expression through the NF-kappa B transcription factor. Mol Cell Biol. 1990;10(5):2327–34.
52. Schwaninger M, Sallmann S, Petersen N, Schneider A, Prinz S, Libermann TA, Spranger M. Bradykinin induces interleukin-6 expression in astrocytes through activation of nuclear factor-kappaB. J Neurochem. 1999;73(4):1461–6.
53. Fu X-L, Duan W, Su C-Y, Mao F-Y, Lv Y-P, Teng Y-S, Yu P-W, Zhuang Y, Zhao Y-L. Interleukin 6 induces M2 macrophage differentiation by STAT3 activation that correlates with gastric cancer progression. Cancer Immunol Immunother. 2017;66(12):1597–608.
54. McLoughlin RM, Jenkins BJ, Grail D, Williams AS, Fielding CA, Parker CR, Ernst M, Topley N, Jones SA. IL-6 trans-signaling via STAT3 directs T cell infiltration in acute inflammation. Proc Natl Acad Sci USA. 2005;102(27):9589–94.
55. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, Achong MK. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Investig. 1998;101(2):311–20.
56. Chen Q, Wang WC, Bruce R, Li H, Schleider DM, Mulbury MJ, Bain MD, Wallace PK, Baumann H, Evans SS. Central role of IL-6 receptor signal-transducing chain gp130 in activation of L-selectin adhesion by fever-range thermal stress. Immunity. 2004;20(1):59–70.
57. Fielding CA, McLoughlin RM, McLeod L, Colmont CS, Najdovska M, Grail D, Ernst M, Jones SA, Topley N, Jenkins BJ. IL-6 regulates neutrophil trafficking during acute inflammation via STAT3. J Immunol. 2008;181(3):2189–95.
58. Hurst SM, Wilkinson TS, McLoughlin RM, Jones S, Horiuchi S, Yamamoto N, Rose-John S, Fuller GM, Topley N, Jones SA. Il-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. Immunity. 2001;14(6):705–14.
59. Diehl S, Anguita J, Hoffmeyer A, Zapton T, Ihle JN, Fikrig E, Rincon M. Inhibition of Th1 differentiation by IL-6 is mediated by SOCS1. Immunity. 2000;13(6):805–15.
60. Hirano T, Yasukawa K, Harada H, Taga T, Watanabe Y, Matsuda T, Kashiwamura S, Nakajima K, Koyama K, Iwamatsu A, et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature. 1986;324(6092):73–6.
61. Yang Y, Ochando J, Yopp A, Bromberg JS, Ding Y. IL-6 plays a unique role in initiating c-Maf expression during early stage of CD4 T cell activation. J Immunol. 2005;174(5):2720–9.
62. Animal Welfare Act In. https://lovdata.no/lov/2009-06-19-97.
63. Regulation on the use of animals in research In. https://lovdata.no/forskrift/2015-06-18-761.

Publisher's Note

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, Leif E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, Kjell, Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, Jon C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, Fred, Dr. philos.	Essays on explanation in psychology.
	Ellertsen, Bjørn, Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.
1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.

	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.
	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.

	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.
1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.

H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.
	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.
2001 V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.

	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.
	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 V	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.

	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.

	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints

	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skolelederes og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leversen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes
	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
	Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
	Hynninen, Kia Minna Johanna	Anxiety, depression and sleep disturbance in chronic obstructive pulmonary disease (COPD). Associations, prevalence and effect of psychological treatment.

	Flo, Elisabeth	Sleep and health in shift working nurses
	Aasen, Elin Margrethe	From paternalism to patient participation? The older patients undergoing hemodialysis, their next of kin and the nurses: a discursive perspective on perception of patient participation in dialysis units
	Ekornås, Belinda	Emotional and Behavioural Problems in Children: Self-perception, peer relationships, and motor abilities
	Corbin, J. Hope	North-South Partnerships for Health: Key Factors for Partnership Success from the Perspective of the KIWAKKUKI
	Birkeland, Marianne Skogbrott	Development of global self-esteem: The transition from adolescence to adulthood
2013 H	Gianella-Malca, Camila	Challenges in Implementing the Colombian Constitutional Court's Health-Care System Ruling of 2008
	Hovland, Anders	Panic disorder – Treatment outcomes and psychophysiological concomitants
	Mortensen, Øystein	The transition to parenthood – Couple relationships put to the test
	Årdal, Guro	Major Depressive Disorder – a Ten Year Follow-up Study. Inhibition, Information Processing and Health Related Quality of Life
	Johansen, Rino Bandlitz	The impact of military identity on performance in the Norwegian armed forces
	Bøe, Tormod	Socioeconomic Status and Mental Health in Children and Adolescents
2014 V	Nordmo, Ivar	Gjennom nåløyet – studenters læringserfaringer i psykologutdanningen
	Dovran, Anders	Childhood Trauma and Mental Health Problems in Adult Life
	Hegelstad, Wenche ten Velden	Early Detection and Intervention in Psychosis: A Long-Term Perspective
	Urheim, Ragnar	Forståelse av pasientaggresjon og forklaringer på nedgang i voldsrate ved Regional sikkerhetsavdeling, Sandviken sykehus
	Kinn, Liv Grethe	Round-Trips to Work. Qualitative studies of how persons with severe mental illness experience work integration.
	Rød, Anne Marie Kinn	Consequences of social defeat stress for behaviour and sleep. Short-term and long-term assessments in rats.
	Nygård, Merethe	Schizophrenia – Cognitive Function, Brain Abnormalities, and Cannabis Use
	Tjora, Tore	Smoking from adolescence through adulthood: the role of family, friends, depression and socioeconomic status. Predictors of smoking from age 13 to 30 in the "The Norwegian Longitudinal Health Behaviour Study" (NLHB)
	Vangsnes, Vigdis	The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens.

	Nordahl, Kristin Berg	Early Father-Child Interaction in a Father-Friendly Context: Gender Differences, Child Outcomes, and Protective Factors related to Fathers' Parenting Behaviors with One-year-olds
2014 H	Sandvik, Asle Makoto	Psychopathy – the heterogenety of the construct
	Skotheim, Siv	Maternal emotional distress and early mother-infant interaction: Psychological, social and nutritional contributions
	Halleland, Helene Barone	Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD). From basic mechanisms to functional outcome.
	Halvorsen, Kirsti Vindal	Partnerskap i lærerutdanning, sett fra et økologisk perspektiv
	Solbue, Vibeke	Dialogen som visker ut kategorier. En studie av hvilke erfaringer innvandrerungdommer og norskfødte med innvandrerforeldre har med videregående skole. Hva forteller ungdommenes erfaringer om videregående skoles håndtering av etniske ulikheter?
	Kvalevaag, Anne Lise	Fathers' mental health and child development. The predictive value of fathers' psychological distress during pregnancy for the social, emotional and behavioural development of their children
	Sandal, Ann Karin	Ungdom og utdanningsval. Om elevar sine opplevingar av val og overgangsprosessar.
	Haug, Thomas	Predictors and moderators of treatment outcome from high- and low-intensity cognitive behavioral therapy for anxiety disorders. Association between patient and process factors, and the outcome from guided self-help, stepped care, and face-to-face cognitive behavioral therapy.
	Sjølie, Hege	Experiences of Members of a Crisis Resolution Home Treatment Team. Personal history, professional role and emotional support in a CRHT team.
	Falkenberg, Liv Eggset	Neuronal underpinnings of healthy and dysfunctional cognitive control
	Mrdalj, Jelena	The early life condition. Importance for sleep, circadian rhythmicity, behaviour and response to later life challenges
	Hesjedal, Elisabeth	Tverrprofesjonelt samarbeid mellom skule og barnevern: Kva kan støtte utsette barn og unge?
2015 V	Hauken, May Aasebø	«*The cancer treatment was only half the work!»* A Mixed-Method Study of Rehabilitation among Young Adult Cancer Survivors
	Ryland, Hilde Katrin	Social functioning and mental health in children: the influence of chronic illness and intellectual function
	Rønsen, Anne Kristin	Vurdering som profesjonskompetanse. Refleksjonsbasert utvikling av læreres kompetanse i formativ vurdering

	Hoff, Helge Andreas	Thinking about Symptoms of Psychopathy in Norway: Content Validation of the Comprehensive Assessment of Psychopathic Personality (CAPP) Model in a Norwegian Setting
	Schmid, Marit Therese	Executive Functioning in recurrent- and first episode Major Depressive Disorder. Longitudinal studies
	Sand, Liv	Body Image Distortion and Eating Disturbances in Children and Adolescents
	Matanda, Dennis Juma	Child physical growth and care practices in Kenya: Evidence from Demographic and Health Surveys
	Amugsi, Dickson Abanimi	Child care practices, resources for care, and nutritional outcomes in Ghana: Findings from Demographic and Health Surveys
	Jakobsen, Hilde	The good beating: Social norms supporting men's partner violence in Tanzania
	Sagoe, Dominic	Nonmedical anabolic-androgenic steroid use: Prevalence, attitudes, and social perception
	Eide, Helene Marie Kjærgård	Narrating the relationship between leadership and learning outcomes. A study of public narratives in the Norwegian educational sector.
2015 H	Wubs, Annegreet Gera	Intimate partner violence among adolescents in South Africa and Tanzania
	Hjelmervik, Helene Susanne	Sex and sex-hormonal effects on brain organization of fronto-parietal networks
	Dahl, Berit Misund	The meaning of professional identity in public health nursing
	Røykenes, Kari	Testangst hos sykepleierstudenter: «Alternativ behandling»
	Bless, Josef Johann	The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention.
	Løvvik, Camilla Margrethe Sigvaldsen	Common mental disorders and work participation – the role of return-to-work expectations
	Lehmann, Stine	Mental Disorders in Foster Children: A Study of Prevalence, Comorbidity, and Risk Factors
	Knapstad, Marit	Psychological factors in long-term sickness absence: the role of shame and social support. Epidemiological studies based on the Health Assets Project.
2016 V	Kvestad, Ingrid	Biological risks and neurodevelopment in young North Indian children
	Sælør, Knut Tore	Hinderløyper, halmstrå og hengende snører. En kvalitativ studie av håp innenfor psykisk helse- og rusfeltet.
	Mellingen, Sonja	Alkoholbruk, partilfredshet og samlivsstatus. Før, inn i, og etter svangerskapet – korrelater eller konsekvenser?
	Thun, Eirunn	Shift work: negative consequences and protective factors

	Hilt, Line Torbjørnsen	The borderlands of educational inclusion. Analyses of inclusion and exclusion processes for minority language students
	Havnen, Audun	Treatment of obsessive-compulsive disorder and the importance of assessing clinical effectiveness
	Slåtten, Hilde	Gay-related name-calling among young adolescents. Exploring the importance of the context.
	Ree, Eline	Staying at work. The role of expectancies and beliefs in health and workplace interventions.
	Morken, Frøydis	Reading and writing processing in dyslexia
2016 H	Løvoll, Helga Synnevåg	Inside the outdoor experience. On the distinction between pleasant and interesting feelings and their implication in the motivational process.
	Hjeltnes, Aslak	Facing social fears: An investigation of mindfulness-based stress reduction for young adults with social anxiety disorder
	Øyeflaten, Irene Larsen	Long-term sick leave and work rehabilitation. Prognostic factors for return to work.
	Henriksen, Roger Ekeberg	Social relationships, stress and infection risk in mother and child
	Johnsen, Iren	«Only a friend» - The bereavement process of young adults who have lost a friend to a traumatic death. A mixed methods study.
	Helle, Siri	Cannabis use in non-affective psychoses: Relationship to age at onset, cognitive functioning and social cognition
	Glambek, Mats	Workplace bullying and expulsion in working life. A representative study addressing prospective associations and explanatory conditions.
	Oanes, Camilla Jensen	Tilbakemelding i terapi. På hvilke måter opplever terapeuter at tilbakemeldingsprosedyrer kan virke inn på terapeutiske praksiser?
	Reknes, Iselin	Exposure to workplace bullying among nurses: Health outcomes and individual coping
	Chimhutu, Victor	Results-Based Financing (RBF) in the health sector of a low-income country. From agenda setting to implementation: The case of Tanzania
	Ness, Ingunn Johanne	The Room of Opportunity. Understanding how knowledge and ideas are constructed in multidisciplinary groups working with developing innovative ideas.
	Hollekim, Ragnhild	Contemporary discourses on children and parenting in Norway. An empirical study based on two cases.
	Doran, Rouven	Eco-friendly travelling: The relevance of perceived norms and social comparison
2017 V	Katisi, Masego	The power of context in health partnerships: Exploring synergy and antagony between external and internal ideologies in implementing Safe Male Circumcision (SMC) for HIV prevention in Botswana

	Jamaludin, Nor Lelawati Binti	The “why” and “how” of International Students’ Ambassadorship Roles in International Education
	Berthelsen, Mona	Effects of shift work and psychological and social work factors on mental distress. Studies of onshore/offshore workers and nurses in Norway.
	Krane, Vibeke	Lærer-elev-relasjoner, elevers psykiske helse og frafall i videregående skole – en eksplorerende studie om samarbeid og den store betydningen av de små ting
	Søvik, Margaret Ljosnes	Evaluating the implementation of the Empowering Coaching™ program in Norway
	Tonheim, Milfrid	A troublesome transition: Social reintegration of girl soldiers returning ‘home’
	Senneseth, Mette	Improving social network support for partners facing spousal cancer while caring for minors. A randomized controlled trial.
	Urke, Helga Bjørnøy	Child health and child care of very young children in Bolivia, Colombia and Peru.
	Bakhturidze, George	Public Participation in Tobacco Control Policy-making in Georgia
	Fismen, Anne-Siri	Adolescent eating habits. Trends and socio-economic status.
2017 H	Hagatun, Susanne	Internet-based cognitive-behavioural therapy for insomnia A randomised controlled trial in Norway.
	Eichele, Heike	Electrophysiological Correlates of Performance Monitoring in Children with Tourette Syndrome. A developmental perspective.
	Risan, Ulf Patrick	Accommodating trauma in police interviews. An exploration of rapport in investigative interviews of traumatized victims.
	Sandhåland, Hilde	Safety on board offshore vessels: A study of shipboard factors and situation awareness
	Blågestad, Tone Fidje	Less pain – better sleep and mood? Interrelatedness of pain, sleep and mood in total hip arthroplasty patients
	Kronstad, Morten	Frå skulebenk til deadlines. Korleis nettjournalistar og journaliststudentar lærer, og korleis dei utviklar journalistfagleg kunnskap
	Vedaa, Øystein	Shift work: The importance of sufficient time for rest between shifts.
	Steine, Iris Mulders	Predictors of symptoms outcomes among adult survivors of sexual abuse: The role of abuse characteristics, cumulative childhood maltreatment, genetic variants, and perceived social support.
	Høgheim, Sigve	Making math interesting: An experimental study of interventions to encourage interest in mathematics

2018 V	Brevik, Erlend Joramo	Adult Attention Deficit Hyperactivity Disorder. Beyond the Core Symptoms of the Diagnostic and Statistical Manual of Mental Disorders.
	Erevik, Eilin Kristine	User-generated alcohol-related content on social media: Determinants and relation to offline alcohol use
	Hagen, Egon	Cognitive and psychological functioning in patients with substance use disorder; from initial assessment to one-year recovery
	Adólfsdóttir, Steinunn	Subcomponents of executive functions: Effects of age and brain maturations
	Brattabø, Ingfrid Vaksdal	Detection of child maltreatment, the role of dental health personnel – A national cross-sectional study among public dental health personnel in Norway
	Fylkesnes, Marte Knag	Frykt, forhandlinger og deltakelse. Ungdommer og foreldre med etnisk minoritetsbakgrunn i møte med den norske barnevernstjenesten.
	Stiegler, Jan Reidar	Processing emotions in emotion-focused therapy. Exploring the impact of the two-chair dialogue intervention.
	Egelandsdal, Kjetil	Clickers and Formative Feedback at University Lectures. Exploring students and teachers' reception and use of feedback from clicker interventions.
	Torjussen, Lars Petter Storm	Foreningen av visdom og veltalenhet – utkast til en universitetsdidaktikk gjennom en kritikk og videreføring av Skjervheims pedagogiske filosofi på bakgrunn av Arendt og Foucault. *Eller hvorfor menneskelivet er mer som å spille fløyte enn å bygge et hus.*
	Selvik, Sabreen	A childhood at refuges. Children with multiple relocations at refuges for abused women.
2018 H	Leino, Tony Mathias	Structural game characteristics, game features, financial outcomes and gambling behaviour
	Raknes, Solfrid	Anxious Adolescents: Prevalence, Correlates, and Preventive Cogntive Behavioural Interventions
	Morken, Katharina Teresa Enehaug	Mentalization-based treatment of female patients with severe personality disorder and substance use disorder
	Braatveit, Kirsten Johanne	Intellectual disability among in-patients with substance use disorders
	Barua, Padmaja	Unequal Interdependencies: Exploring Power and Agency in Domestic Work Relations in Contemporary India
	Darkwah, Ernest	Caring for "parentless" children. An exploration of work-related experiences of caregivers in children's homes in Ghana.
	Valdersnes, Kjersti Bergheim	Safety Climate perceptions in High Reliability Organizations – the role of Psychological Capital

2019 V	Kongsgården, Petter	Vurderingspraksiser i teknologirike læringsmiljøer. En undersøkelse av læreres vurderingspraksiser i teknologirike læringsmiljøer og implikasjoner på elevenes medvirkning i egen læringsprosess.
	Vikene, Kjetil	Complexity in Rhythm and Parkinson's disease: Cognitive and Neuronal Correlates
	Heradstveit, Ove	Alcohol- and drug use among adolescents. School-related problems, childhood mental health problems, and psychiatric diagnoses.
	Riise, Eili Nygard	Concentrated exposure and response prevention for obsessive-compulsive disorder in adolescents: the Bergen 4-day treatment
	Vik, Alexandra	Imaging the Aging Brain: From Morphometry to Functional Connectivity
	Krossbakken, Elfrid	Personal and Contextual Factors Influencing Gaming Behaviour. Risk Factors and Prevention of Video Game Addiction.
	Solholm, Roar	Foreldrenes status og rolle i familie- og nærmiljøbaserte intervensjoner for barn med atferdsvansker
	Baldomir, Andrea Margarita	Children at Risk and Mothering Networks in Buenos Aires, Argentina: Analyses of Socialization and Law-Abiding Practices in Public Early Childhood Intervention.
	Samuelsson, Martin Per	Education for Deliberative Democracy. Theoretical assumptions and classroom practices.
	Visted, Endre	Emotion regulation difficulties. The role in onset, maintenance and recurrence of major depressive disorder.
2019 H	Nordmo, Morten	Sleep and naval performance. The impact of personality and leadership.
	Sveinsdottir, Vigdis	Supported Employment and preventing Early Disability (SEED)
	Dwyer, Gerard Eric	New approaches to the use of magnetic resonance spectroscopy for investigating the pathophysiology of auditory-verbal hallucinations
	Synnevåg, Ellen Strøm	Planning for Public Health. Balancing top-down and bottom-up approaches in Norwegian municipalities.
	Kvinge, Øystein Røsseland	Presentation in teacher education. A study of student teachers' transformation and representation of subject content using semiotic technology.
	Thorsen, Anders Lillevik	The emotional brain in obsessive-compulsive disorder
	Eldal, Kari	Sikkerheitsnettet som tek imot om eg fell – men som også kan fange meg. Korleis erfarer menneske med psykiske lidingar ei innlegging i psykisk helsevern? Eit samarbeidsbasert forskingsprosjekt mellom forskarar og brukarar.

	Svendsen, Julie Lillebostad	Self-compassion - Relationship with mindfulness, emotional stress symptoms and psychophysiological flexibility
2020 V	Albæk, Ane Ugland	Walking children through a minefield. Qualitative studies of professionals' experiences addressing abuse in child interviews.
	Ludvigsen, Kristine	Creating Spaces for Formative Feedback in Lectures. Understanding how use of educational technology can support formative assessment in lectures in higher education.
	Hansen, Hege	Tidlig intervensjon og recoveryprosesser ved førsteepisode psykose. En kvalitativ utforsking av ulike perspektiver.
	Nilsen, Sondre Aasen	After the Divorce: Academic Achievement, Mental Health, and Health Complaints in Adolescence. Heterogeneous associations by parental education, family structure, and siblings.
	Hovland, Runar Tengel	Kliniske tilbakemeldingssystemer i psykisk helsevern – implementering og praktisering
	Sæverot, Ane Malene	Bilde og pedagogikk. En empirisk undersøkelse av ungdoms fortellinger om bilder.
	Carlsen, Siv-Elin Leirvåg	Opioid maintenance treatment and social aspects of quality of life for first-time enrolled patients. A quantitative study.
	Haugen, Lill Susann Ynnesdal	Meeting places in Norwegian community mental health care: A participatory and community psychological inquiry
2020 H	Markova, Valeria	How do immigrants in Norway interpret, view, and prefer to cope with symptoms of depression? A mixed method study
	Anda-Ågotnes, Liss Gøril	Cognitive change in psychosis
	Finserås, Turi Reiten	Assessment, reward characteristics and parental mediation of Internet Gaming Disorder

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230866467 (print)
9788230844526 (PDF)