Biological mechanisms underlying susceptibility to traumatic stress

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An Ning

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Dedication

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Chapter 1

General introduction

The current thesis revolves around determinants and biological mechanisms underlying differential susceptibility to the impact of stress on mental health.

The first question addressed in this thesis is "what is stress"? Based on the critical findings from Walter B. Cannon and Hans Selye, the modern concept of stress came into being as *a consciously or unconsciously sensed threat to homeostasis*. Homeostasis, coined by Cannon, refers to the organism's steady internal environment. Threats to homeostasis evoke a "fight" or "flight" reaction, which is the initial stage of "alarm reaction" for the stress process proposed by Selye, followed by a stage of "adaptation," and eventually (in some cases) by a stage of "exhaustion" (reviewed in [1]).

The type of stress people may experience after exposure to a traumatic event, which imposes actual or threatens death, serious physical injury, or threat to physical well-being, is termed 'traumatic stress.' Exposure to several forms of stress, including traumatic stress, may be followed by failure to adapt and eventual exhaustion, resulting in physical or mental illness (reviewed in [2]).

Although many individuals experience stressful and potentially traumatizing events during life, only a (relatively) small part of the exposed population develops stress-related pathologies, including mental disorders such as post-traumatic stress disorder (PTSD), depression, and anxiety disorders. Thus, there are striking inter-individual differences in susceptibility to the effects of stress, including traumatic stress. However, the biological mechanisms of this differential susceptibility are mainly unknown. This knowledge would provide a basis for understanding stress mechanisms and facilitate therapeutic or preventive strategies for mental health-related disorders.

This thesis aimed to elucidate (some of) the biological mechanisms underlying susceptibility to traumatic stress. This chapter will:

- Introduce the concepts of differential susceptibility and resilience.
- Provide a summary of the current knowledge on the relevant physiological and biological processes involved in susceptibility to traumatic stress.
- Provide background information on the animal models used in this thesis to study traumatic stress and
- Introduce the main research questions and specific aims of the different chapters.

1.1 Concept of differential susceptibility and resilience to the effects of traumatic stress

Susceptibility refers to individuals displaying dysfunctional behavioural and physiological characteristics in response to traumatic event exposure or a specific process [3, 4]. Susceptibility could also be factors that could be detectable and manipulated before trauma, and manipulation of these factors alters the likelihood of developing PTSD [5]. This thesis mainly focuses on the first definition.

While resilience refers to avoiding negative social, psychological, and biological consequences of extreme stress that would otherwise compromise their psychological or physical well-being [6]. Resilience could also be an adaptive response or swift recovery from those effects, and psychological growth after experiencing trauma [7, 8, 9]. This thesis conceptualizes "resilience" as an active and dynamic process through which a person adaptively overcomes a stressful event [10].

1.2 Biological processes are involved in the stress response and susceptibility to traumatic stress

The response to traumatic stress involves the "fight-flight or freeze" reactions [11], which refer to the behavioral responses of animals exposed to a nearby threat. Exposure activates the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The autonomic nervous system and the sympathetic and parasympathetic nervous systems have been linked with other biological components such as hormones, cytokines, neuropeptides, and neurotransmitters [12, 13].

1.2.1 HPA axis

Activation of the HPA axis and its hormones are the most studied subjects of the stress response mechanism. The hormone corticotropin-releasing hormones (CRH) and arginine vasopressin (AVP) are released from the paraventricular nucleus (PVN) of the hypothalamus upon stress. The hormones stimulate the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) into the blood circulation. In the adrenal glands, ACTH induces the synthesis of glucocorticoids, such as cortisol, in humans and corticosterone in rodents (Figure 1).

Glucocorticoids are essential hormones that impact protein, fat, and sugar metabolism, which support the nutrient requirements of the central nervous system during stress. Glucocorticoids can enhance muscle protein breakdown, adipose tissue lipolysis, and hepatic gluconeogenesis, and they can reduce glucose utilization to elevate circulating glucose concentrations. Excessive glucocorticoids have been linked with insulin resistance, obesity, and cardiovascular diseases [14].

Circulating glucocorticoids can bind to two types of receptors: glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). They are ligand-gated transcription factors mediating the expression of a group of genes. The MR has a higher glucocorticoid binding affinity than GR. Thus, MRs are nearly saturated with low basal glucocorticoid concentrations, while high glucocorticoid concentrations during stress occupy MRs and GRs (Figure 1) [15].

During a high-stress level, the binding of a glucocorticoid to GR terminates the stress response and maintains predetermined hormone levels, including cortisol in humans or corticosterone in rodents, and homeostasis via a negative feedback loop [16].

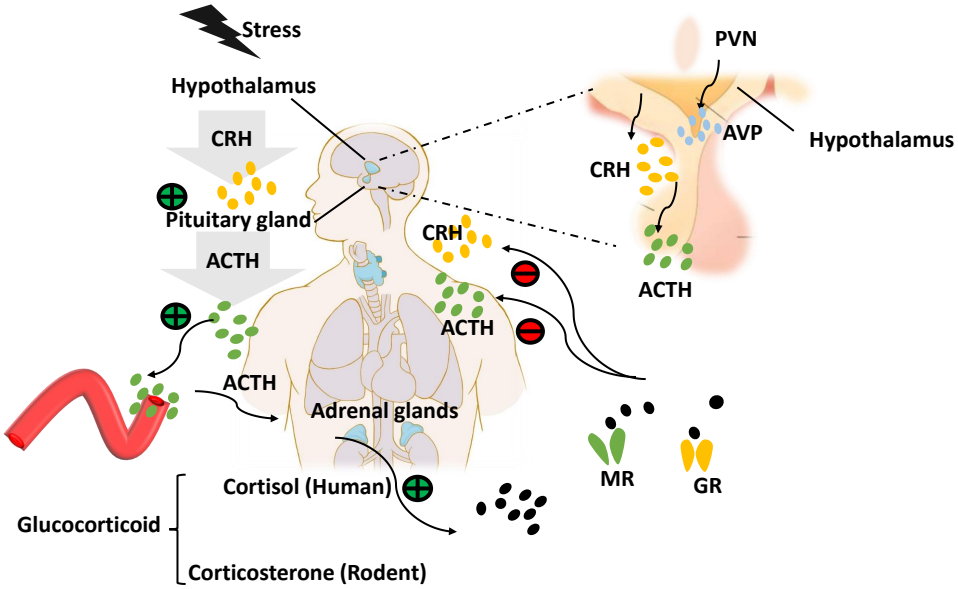

Figure 1: Schematic representation of the HPA axis. Stress induces AVP release from PVN, stimulating CRH release from the hypothalamus and activating ACTH release in the pituitary gland. ACTH binds to receptors in adrenal glands to induce glucocorticoid release in the circulation to modulate physiological response to stress through binding to both MR and GR receptors, which may provide negative feedback to the HPA axis.

Disruption of the HPA axis has been linked with many psychiatric disorders, such as PTSD, depression, bipolar disorder, and schizophrenia [17, 18, 19, 20, 21].

It has been observed that PTSD patients displayed a less robust ACTH response compared to controls in response to the cold pressor task [22] and exhibited lower basal cortisol levels compared to healthy controls [23] or trauma-exposed healthy controls [24]. In addition, PTSD veterans who were Met allele carriers of BDNF Val66Met polymorphism exhibited significantly stronger cortisol suppression and higher skin conductance response magnitudes in the startling sounds condition and an annoying (but not painful) 2.5 mA shock conditions than controls with no threat conditions in the sample [25]. Furthermore, PTSD veterans who carry T alleles of the fk506-binding protein 51 (*fkbp51*) gene displayed significantly lower cortisol levels at baseline. FKBP5 protein is involved in the regulation of GR sensitivity and the translocation of glucocorticoids [26].

Studies on HPA-axis reactivity have identified candidate endophenotypes with two clinically and biologically distinct HPA-axis reactivity. One subgroup, "non-responders," showed a blunted HPA-axis response, distinct clinical and biological characteristics, and abnormal expression kinetics of the genes encoding the MRs and FKBP5 [27].

1.2.2 Olfactory system and stress

The olfactory and emotional systems are highly intervened, and stress can impact the olfactory systems. One study on healthy humans showed that cortisol is associated with better odor identification performance [28]. On the other hand, the stimulation of the olfactory system can influence stress levels. Numerous studies demonstrated aroma's stress-suppressing effects, while predator odor's effects induce stress in experimental animals [29].

1.2.3 Neurotransmitter

Neurotransmitters interacted with the HPA axis in stress-related brain regions, including limbic brain areas like the prefrontal cortex (PFC), amygdala, hippocampus, and nucleus accumben [30]. Besides, the HPA axis heavily interacts with the neurotransmitter system, including serotonin [31], dopamine [32], glutamate, GABA, and norepinephrine [33]. The primary HPA axis hormone, corticosterone, is essential in modulating the release of different neurotransmitters in limbic areas to mediate coping behavior [30].

For example, one study on urines indicated that trauma-exposed mothers with PTSD symptoms had higher urinary dopamine levels than trauma-exposed mothers without PTSD symptoms or controls [34]. Besides dopamine disturbance, dopamine receptors are correlated with PTSD symptoms. Another study added evidence for the involvement of the dopaminergic system in PTSD, as the study reported that PTSD patients with at least one copy of the dopamine receptor type 4 long allele had more intense PTSD symptoms than patients who did not have these alleles in genotype [35]. Besides dopamine, other studies have indicated the involvement of epinephrine, norepinephrine, and serotonin in PTSD-related symptoms, including hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood, and suicidality [36].

1.2.4 Epigenetic mechanisms

Epigenetics mechanisms are reversible chemical modifications to the chromatin structure that alter gene transcription without altering the DNA sequence, including DNA methylation, DNA hydroxymethylation, histone modifications (i.e., methylation, acetylation, and phosphorylation), and microRNAs which act as translational repressors [37]. This thesis focuses on the DNA methylation of epigenetic mechanisms in stress response.

DNA methylation is an epigenetic process in which a methyl group is added to nucleotides of DNA without any alterations to the DNA sequence, which modulates gene expression by regulating the accessibility of transcription factors to their binding sites and influencing chromatin structure. DNA methylation has been implicated in many psychiatric disorders, including depression, bipolar disorder, schizophrenia [38], and PTSD [39].

Accumulating evidence suggests that epigenetic processes play an essential role in the onset of PTSD [39]. One recent study found that military personnel with elevated PTSD symptoms showed that 119 genes exhibited reduced DNA methylation levels in peripheral blood, and 8 genes exhibited increased DNA methylation [40]. A recent study

coordinated by our group showed that increased PTSD symptom scores in combat-trauma-exposed military soldiers deployed to Afghanistan were associated with hypomethylation of loci in the dual specific phosphatase 22 (*dusp22*), myelin basic protein (*mbp*), and myelin transcription factor 1 like (*myt1l*) genes measured in whole blood samples [41]. These three genes formed a basis for this thesis.

The *dusp 22* gene-encoded enzyme DUSP22 belongs to a family of atypical small molecular mass dual-specificity phosphatases (DSPs) that dephosphorylate both tyrosine and serine/threonine residues. Few studies show the association between DUSP22 and mental health; little is known about these associations. Therefore, this thesis provides an overview of DUSP22 and its DUSP family members concerning mental health and diseases.

MBP is an oligodendrocyte-specific protein essential for oligodendrocyte morphogenesis [42], contributing to the balanced production of myelin proteins and lipids [43]. Evidence from human brain imaging studies and large-scale mRNA profiling analyses indicate that defects in myelin and abnormal expression of myelin genes, like *mbp* and their regulators, are common in many psychiatric disorders [44]. Among schizophrenia patients, the *mbp* mRNA in the primary visual cortex was reduced compared to healthy controls in the post-mortem brain tissue [45]. Among women with PTSD, the *mbp* mRNA was downregulated with several oligodendrocyte-related genes in the ventromedial PFC compared to healthy controls [46]. In animal stress models, *mbp* mRNA was reduced in medial prefrontal cortex (mPFC) and hippocampus of mice one month after exposure to 24-hour restraint stress compared to controls [47]. MBP protein expression was reduced in the mPFC of mice exposed to social defeat [48]. The MBP immunoreactivity was low in the pre-limbic and orbitofrontal cortex of rats exposed to chronic, unpredictable stress [49]. However, the MBP protein and mRNA were markedly increased in the cerebrospinal fluid, the hypothalamus, and the hippocampus of trauma-exposed dogs [50].

Variations in *myt1l*, a gene encoding a transcription factor expressed in the brain, have been associated with autism, intellectual disability, and schizophrenia [51]. These neurodevelopmental disorders show loss of function mutations in *myt1l*, including deletions, frameshift, and single nucleotide variations. These mutations are predicted to cause decreases in mRNA production or aberrant protein functions [52].

1.3 Research methodology for studying differential susceptibility to traumatic stress in rodent models

Rodent models can be instrumental in identifying molecular and cellular factors and mechanisms involved in differential behavioral responses to the effects of traumatic stress. Research on the effects of severe stress in animal models has a long history which has been reviewed elsewhere [53, 54, 55]. The following paragraphs introduce a few relevant aspects that form a basis for these studies.

1.3.1 Levels of analysis

The level of the analysis includes behavior, (electro) physiology, morphology and structure, and gene expression.

Behavior tests can give direct behavior outcomes of the stress event. These behavior tests include anhedonia tests like the sucrose preference test [56], anxiety tests like the elevated zero maze test [57], social behavior tests like the social interaction test [58], and depressive behavior tests like the forced swim test [59]. Electrophysiology can record local field potentials from populations of neurons and action potentials from single neurons in acute brain slices [60], the brain of anesthetized rodents [61], and even in awake-behaving rodents [62]. The following paragraphs overview the current research methodologies in susceptibility and resiliency.

1.3.2 Experimental stress paradigm used in this thesis

Stress paradigms are commonly and widely used in laboratory animal studies. For example, stress induced by electric foot shock, stress induced by restrainment (restraint stress; RS), stress induced by social defeat (SD), early life stress, e.g., via a range of stressors, or predator-based stress, may induce both acute and chronic responses and impact. These stress paradigms and their advantages and disadvantages have been reviewed elsewhere [63]. In this thesis, we employed the SD and predator-based stress paradigm.

Social defeat (SD)

SD has been widely used to examine the impact of chronic and severe social stress on physical and behavioral conditions. Moreover, SD models show symptoms similar to psychiatric disorders in humans, including depression- and anxiety-like behavior [64]. The current paradigm of SD is developed using CD-1 mice as the resident and C57BL/6J mice as the intruder [65].

Researchers modified the SD paradigm due to severe injuries during physical attacks. Some studies have reduced the duration of physical contact from 5 min to 30 s each day [63]. A later developed SD paradigm created a set-up in which the C57BL/6J mice witnessed (rather than experienced) the social defeat of another C57BL/6J mouse without physical contact, and this paradigm successfully induced a stress phenotype by isolating physical stress and psychological stress in mice [64, 66]. However, this paradigm induced a more modest phenotype [67]. Besides, housing conditions (single versus group housing) could also moderate the behavioral response of individual mice exposed to social defeat stress [68].

Repeated social defeat stress results in a spectrum of behavioral alterations. Based on the social interaction ratio score, the animals' responses have been categorized into either 'susceptible' or 'resilient' groups [65]. The 'susceptible' mice spend significantly more time in the corner than in the interaction zone. In contrast, resilient mice spend more time in the interaction zone than control mice that have never undergone a defeat procedure [65]. Numerous scholars have used this experimental paradigm and discovered substantial evidence on different levels of analysis [53].

Predator-based stress

Rats show many ultrasonic cries and modified eating patterns in the presence of a predator cat [69]. Predator odor alone can induce fear [70]. The unconditioned fear of a predator odor paradigm employs four steps. First, researchers acclimated the mice to the testing chamber for 3 min and then presented predator odor to the mice. Lastly, researchers measure freezing behavior immediately after predator odor presentation and 24 hours later in a retention test [71]. Exposure to soiled cat litter induces PTSD-like behavior in rats [72]. Maternal exposure to predator odor induces increased anti-predator behavior and a predator-odor-induced decrease in activity in mice [73].

As evidence has accumulated that animals (also non-humans) show differential responses to stress stimuli, it may be attractive (for scientific purposes) to take this differential response into account, for example, by splitting the clearly "maladapted" and clearly "well-adapted" animals. Such cutoff behavioral criteria, similar to the splitting in social defeat [65], have provided a basis for identifying biomarkers of differential susceptibility in response to stress [74].

1.4 Overview of the thesis

Susceptibility is a dynamic and complex phenomenon that depends not only on a person's personality, genotype, or brain architecture, but also on the nature of the stressor(s), the complex and time-varying constellations of intra-, inter-, and extra-individual circumstances present during and after stressor exposure.

It has become clear that the study of susceptibility should evolve from a static to a dynamic and process-oriented conceptualization, for instance, through a prospective longitudinal study on differential susceptibility and resilience [10].

A recent study provided the first biological evidence of some genetic and epigenetic mechanisms underlying stress and resilience. By conducting a longitudinal study using a differential susceptibility approach in its analysis, a recent study involving Dutch soldiers deployed to the Afghanistan war has demonstrated that increases in PTSD symptom scores were associated with hypomethylation of loci in the *dusp22*, *mbp*, and *myt1l* genes (as measured in whole blood samples). These genes thereby pinpoint candidate molecules that may mediate differential susceptibility to the effects of traumatic stress [41].

While these findings provide valuable novel insights, it is crucial to analyze the localization and function of the genes concerning the stress response. This thesis first investigates the role of the *dusp22* and the entire dusp family of genes in mental and neurodegenerative disorders and reviews the available evidence in **Chapter 2**. Given the limited knowledge of the localization and the function of DUSP22 in the brain, this thesis investigates in **Chapter 3** the expression pattern of DUSP22 in mice brain, with a particular focus on the brain regions with an established link to the stress response, i.e., PFC, hippocampus, and amygdala.

The *mbp* gene also showed different methylation patterns in response to another stressor, i.e., prenatal restraint stress [75], thereby underscoring the potential importance of differential susceptibility to severe stress. Therefore, this thesis aimed to investigate MBP protein expression profiles in a prime brain region involved in the stress response, i.e., the hippocampus. This thesis includes immunohistochemical analyses in mouse hippocampal subregions and tests whether exposure to social defeat stress was associated with altered MBP protein expression patterns in the mouse hippocampus. This study is in **Chapter 4**.

A third novel candidate gene from the human PTSD study was *myt1l*, a transcription factor involved in the formation of myelin and the nervous system [76]. Findings from several groups have shown links between *myt1l* and other stress-related mental disorders [77, 78], spurring us to explore links between *myt1l*, the impact of traumatic stress, and differential susceptibility to traumatic stress. **Chapter 5** describes a study aiming to understand the localization of protein MYT1L in the brain (through immunohistochemical investigation of MYT1L protein expression in the mouse brain) and investigate differences in expression profiles concerning SD exposure.

In order to increase the toolbox to perform experimental studies on the mechanisms mediating or moderating the impact of stress, this thesis includes experiments done using a Microdrive array recording the activity of neural circuitries in the presence of stressful odor presentation. The activity focuses on local field potentials and action potentials in single neuron fire in response to stress in vivo. It employs the recently developed construction of Microdrive arrays [62]. **Chapter 6** illustrates the firing pattern in the olfactory neurons of mice in response to predator odor-induced stress, which was recorded by the Microdrive array implanted in the olfaction brain regions of the mice.

The thesis includes experiments using the social defeat stress model to understand the potential role of the identified genes in regulating the short-and long-term impact of exposure to severe stress on behavior, gene expression, and morphology. While doing so, the experiments test the hypothesis that physical activity would be protective (physical activity before stress would reduce the impact of the stress exposure) against the short- and long-term impact of social defeat stress in rodents, which is described in **Chapter 7**.

Chapter 8 summarizes the main research findings and discusses them in light of broader scientific developments.

Chapter 9 provides an outlined summary and future perspectives in rodent models on stress susceptibility.

Chapter 2

A potential role for the dusp family of genes in mental and neurodegenerative disorders

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Abstract

The dual-specificity phosphatase (DUSP) family includes a heterogeneous group of protein phosphatases that dephosphorylate both phospho-tyrosine and phospho-serine/phospho-threonine residues within a single substrate. These protein phosphatases have many substrates and modulate diverse neural functions, such as neurogenesis, differentiation, and apoptosis. *Dusp* genes have furthermore been associated with mental disorders such as depression and neurological disorders such as Alzheimer's disease.

Herein, we review the current literature on the DUSP family of genes concerning mental and neurological disorders. This review i) outlines the structure and general functions of *dusp* genes, and ii) overviews the literature on *dusp* genes concerning mental and neurological disorders, including model systems, while furthermore providing perspectives for future research.

Keywords: DUSP, Mental health, neurological diseases, phosphatase, psychiatric disorders.

2.1 Introduction

Mental and neurological disorders are becoming highly prevalent and, in turn, exert significant socioeconomic and personal burdens [79, 80]. For instance, mental disorders are often associated with a reduced quality of life and also reduced maximal life expectancy [81], possibly due to the early onset of these disorders, the impact on social interactions, and their frequent occurrence as a comorbidity with other physiological health issues, i.e., cardiovascular, metabolic and immune-related disorders [82].

Recent progress in the study of mental and neurological disorders has allowed for a better understanding of critical underlying determinants, as well as associated molecular and cellular mechanisms. The etiology of mental and neurological disorders is associated with an interplay between genetic predisposition and epigenetic mechanisms that are influenced by environmental exposures throughout life [83, 38]. Developments in the fields of psychiatric genetics and epigenetics have enabled the first wave of genome-wide analyses on groups of people diagnosed with specific mental and neurological disorders compared to control populations. These analyses have provided critical initial insights, suggesting the involvement of distinct genes and biological processes in the onset and course of mental and neurological disorders. Increasing evidence from various genetic and epigenetic studies has identified associations between several genes in the dual-specificity phosphatases (DUSP) family and various mental and neurological disorders [84, 85].

These phosphatases are characterized by removing a phosphorus group from phospho-tyrosine and phospho-serine/phospho-threonine residues within a single substrate, leading to conformational protein changes. This process that can be reversed by kinase phosphorylation. Additionally, these protein phosphatases have a variety of substrates and, as such, can modulate diverse cellular functions, such as neurogenesis, neuronal differentiation, and apoptosis via three main signaling pathways, including MAP kinase pathways [86], Phosphatidylinositol 3-kinase (PI3K)/AKT [87], and BDNF [88].

While a range of studies on *dusp* genes has linked these genes to cancer [89, 90, 91] and disorders of the immune system [92], accumulating evidence for links between *dusp* genes and mental disorders, such as depression, as well as neurological disorders such as Alzheimer's disease, is increasingly documented [84].

Herein, we aim to summarize, converge, and critically review the current literature on the DUSP family of genes implicated in mental and neurological disorders.

2.2 Structure, expression, and function of DUSP family members

DUSPs' primary mode of action is the dephosphorylation of tyrosine and/or serine/threonine residues and the resulting activity regulation of their substrates. The physiological outcomes of DUSPs' functions thus hinge on their substrate specificity and phosphatase activity. However, the substrates for DUSPs are not precisely defined. The archetypical DUSP, DUSP1/MKP1, was initially discovered to regulate the activities of MAP kinases by

dephosphorylating the TXY motif in the kinase domain. However, although DUSPs were discovered more than a decade ago, only in the past few years have their various functions begun to be described. DUSPs can be categorized into typical DUSPs and atypical DUSPs based on the presence or absence of a MAP kinase-interacting domain. A subset of DUSPs contains an N-terminal region composed of two CDC25 homology 2 (CH2) domains and an intervening cluster of basic amino acids known as the MAP kinase-binding (MKB) motif. All DUSP proteins contain a common phosphatase domain consisting of conserved Asp, Cys, and Arg residues forming the catalytic site [93].

The subcategorization of DUSPs into subgroups is supported by the phylogenetic tree of DUSP sequences similarities with consideration of substrate preferences [93]. Based on this, the DUSP family members can be categorized into the following subgroups: 1) slingshot homolog (SSH) family of phosphatases, 2) phosphatases of regenerating liver (PRL) family, 3) cell division cycle 14 (CDC14) phosphatases, 4) phosphatase and tensin homologs deleted on chromosome 10 (PTEN), 5) myotubularins, 6) mitogen-activated protein kinase phosphatases (MKPs) and 7) atypical DUSPs [86]. DUSP family members and synonyms can be found in Table A.1 of the Appendix, while atypical DUSPs are presented in Table A.2 of the Appendix.

In the following paragraphs, we will review the current knowledge about the structure, tissue expression, and function of the DUSP family members. A summary of DUSP Protein or RNA expression in animal and human brains is presented in Table A.3 of the Appendix, while their expression in non-brain tissues is shown in Table A.5. The function of DUSP proteins is summarized in Table A.4. The structure of the DUSP members are illustrated in A.6 of the Appendix.

2.2.1 Slingshot homolog (SSH) family of phosphatases

- Structure and Homologues

Slingshot homolog (SSH), encoded by the *ssh* gene, was initially recognized as a cofilin phosphatase in genetic studies performed in Drosophila [94]. Cofilin is an actin-depolymerizing factor (ADF) abundant in human and other mammalian brains [95]. In mammals, three SSH homologs have been identified and denoted as SSH-1, SSH-2, and SSH-3 [94].

The sequence alignment of the three SSH phosphatases shows more than 80% sequence similarity [94]. For instance, SSH proteins from human, mouse, and Drosophila possess three highly conserved domains, A, B, and P (a phosphatase domain) in the N-terminal region [96]. Amino acid sequences of the P domain of the SSH family are distantly related to those of a family of MKPs and share a Dual Specific Phosphatase (DSP) active site (HCxxGxxR) conserved within both DSP and protein tyrosine phosphatases (PTP) [97, 98]. The short serine-rich sequence motif (S domain) is conserved only in SSH-1 and SSH-2 in mouse and human but not in SSH-3 of the mouse, human, or Drosophila SSH protein (Figure Appendix) [96].

- Expression and Function

At the cellular level, human SSH (hSSH)-1 is primarily expressed in the plasma membrane, cytosol, and nucle-

oplasm, while hSSH-2 and hSSH-3 reside in the cytoplasm [the Human Protein Atlas (www.proteinatlas.org)] [99]. At the tissue level, hSSH-1 proteins were expressed in the frontal cortex and cerebellum of human post-mortem brain tissue of healthy elderly persons [100, 101] as well as in human keratinocytes [102].

SSH phosphatases modulate actin separation and reunion by regulating the ADF /cofilin complex in vivo [98]. SSH phosphatases remove a phosphorus group from ADF/cofilin to activate this complex [103, 104, 105, 106]. The activated ADF/cofilin complex depolymerizes and dismantles actin filaments to drive the protraction of growth cones and neurite extensions, as observed in rat hippocampal neurons. In contrast, activated LIM domain kinase 1, a negative regulator of actin-polymerization dynamics, adds a phosphorus group to ADF/cofilin, inhibiting the formation of this complex. This inhibition then drives actin polymerization, which reduces the protraction of growth cones and neurite extensions [107]. The balance between SSH and LIM domain kinase 1 is responsible for modulating actin filament assembly at the tip of the growth cone and is essential for driving the repulsive or attractive responses of growth cones and neurite extensions, which in turn leads to modifications in neuronal morphology and sprouting [103, 108, 109, 110]. Specifically, SSH1, along with Cofilin1 modulated growth cone extension in rodents [111, 112] and chick [104]. SSH2 reverse actin-severing defects and improves actomyosin parameters in interneurons of mice [113]. Furthermore, SSH phosphatases play a pivotal role in controlling AMPA receptor trafficking and the number, size, and morphology of dendritic spines in cortical neurons by controlling the actin cytoskeleton via ADF/cofilin activation. Interestingly, AMPA receptor trafficking and the morphology of dendritic spines in cortical neurons are strongly associated with synaptic plasticity, which underlies cognitive functions such as learning and memory processes [114].

2.2.2 Phosphatases of regenerating liver (PRLs) family

- Structure and Homologues

While the cellular functions of this family remain yet to be uncovered, we currently know that PRLs are oncogenes [115]. Within this subgroup, three protein subtypes, PRL-1, PRL-2, and PRL-3, have been identified based on their amino acid sequences [116], which share greater than 50% homology in humans [117].

PRLs carry the CAAX motif and are the only CAAX proteins in the DUSP family [117]. CAAX proteins involve global cellular functions, such as proliferation and differentiation. A polybasic region localizes next to the CAAX box and mediates membrane or nuclear localization of PRLs. The catalytic or protein phosphatase (PTP) domain is responsible for enzymatic activity, requiring the P-loop residues and the WPD loop (conserved in the PTP family) residues for the transfer of a phosphate group (Figure Appendix) [117].

- Expression and Function

At the cellular level, PRLs localize in the plasma membrane and nucleus, whereas at the tissue level, human PRLs (hPRLs) subtypes differ depending on the type and severity of the tumor in question. *hprl-1* and *hprl-2* mRNA expression patterns are widespread in healthy adult human tissues. hPRL-2 is expressed at higher levels in

the brain than hPRL-1, especially in the granular layer of the cerebellum [118]. *hprl-3* mRNA is expressed in both skeletal muscle and the heart during development [119]. Similarities exist compared to other mammalian tissue, such as mouse tissue. For instance, mouse PRL (mPRL)-1 is 100% identical to hPRL-1 in the number of amino acid subunits [120]. *mprl-2* mRNA is expressed in skeletal muscle, and *mprl-3* is expressed in skeletal muscle and heart tissue [120].

PRLs promote cell proliferation, migration, invasion, tumor growth, and metastasis via multiple signaling pathways, including extracellular signal-regulated kinase (ERK) 1/2 pathways [121, 122], the mechanistic target of the rapamycin [123], and the phosphatidylinositol 3-kinase (PI3K)/AKT pathways [124]. It has been observed that PRL-1 and PRL-2 induce cell invasion and motility through the activation of ERK 1/2. Moreover, PRL-3 stimulates cell proliferation and epithelial-mesenchymal transition, a crucial developmental process, by acting upstream of PI3K. Interestingly, ERK1/2 and PI3K are common signaling pathways in cell proliferation, migration, invasion, tumor growth, and metastasis [117].

2.2.3 Cell division cycle 14 (CDC14) phosphatases

- Structure and Homologues.

CDC14 phosphatases, encoded by the *cdc14* gene, are the subgroup mainly involved in cell cycle regulation [125, 126]. CDC14 comprises three isoforms, CDC14A, CDC14B, and CDC14C [127]. The isoform CDC14B encodes four splice variants, including CDC14Bpar, CDC14B1, CDC14B2, and CDC14B3 [128]. Interestingly, the isoform CDC14C (also known as CDC14Bretro) is produced by the CDC14B splice variant CDC14Bpar by gene retroduplication, a process that occurs in hominoids [128, 129].

CDC14A contains a core domain and a nuclear export signal responsible for the translocation of CDC14A from the nucleus to the cytoplasm. The core domain contains two structurally similar domains, A and B [130]. The protein structure of human hCDC14A shares 65% compatibility with hCDC14B except for the nucleolar targeting sequence (N-terminal 44 amino acids) that is responsible for localizing CDC14B to the nucleolus throughout interphase during cell division [130]. CDC14C structure is similar to hCDC14B except for the C-terminus (Figure Appendix) [128].

- Expression and Function

At the cellular level, CDC14A localizes on the centrosomes of cells during interphase [131]. CDC14B1 is expressed in the nucleoli, and CDC14B2 in nuclear speckles localized within the nucleus, as demonstrated in COS7-cells. Moreover, CDC14B3 and CDC14Bpar exhibit co-localization with microtubules in COS7-cells [128]. It has also been demonstrated that CDC14C co-localizes with an endoplasmic reticulum marker in COS7 cells, human HeLa, or LN229 cell lines [128].

At the tissue level, hCDC14A and hCDC14B are found in the cerebral cortex, lymph nodes, liver, colon, kidneys, and testis (www.proteinatlas.org) [99]. While *hcdc14bpar* mRNA is predominantly expressed in the adult and fetal brain, *hcdc14b1*, *hcdc14b2*, and *hcdc14b3* mRNAs are expressed in the adult brain, including the hippocampus,

prefrontal cortex, amygdala, and hypothalamus [128]. *hcdc14c* mRNA is found in the adult brain and embryonic forebrain, including the dorsal telencephalon [128].

The CDC14 family is conserved within eukaryotes and plays a role in inactivating mitotic cyclin-dependent kinase via dephosphorylation. While activation of cyclin-dependent kinase drives cells into mitosis, their inactivation promotes mitotic exit and cytokinesis. Furthermore, CDC14 regulates various other cellular events, such as DNA recombination, telomere segregation, mitotic spindle dynamics, and cytokinesis [127, 132].

2.2.4 Phosphatase and tensin homologs deleted on chromosome 10 (PTENs) family

- Structure and Homologues

The *pten* gene codes for the PTEN protein, a protein in which tumor suppression functions due to its phosphatase activity [133, 134]. PTEN carries two isoforms: a CUG-initiated isoform designated PTENα and an AUG-initiated isoform referred to as PTENβ with a smaller molecular weight than PTENα [135]. The N-terminal domain of PTEN contains the catalytic N-terminal PIP2-binding domain and PTP domain. The C-terminal domain consists of the following subdomains: C2, C-tail, and the PDZ, with the active catalytic site being HCxxGxxR (Figure Appendix) [136, 137]. PTEN's phosphatase domain carries a similar structure to protein phosphatases but with a more significant active site, allowing it to bind other substrates such as phosphoinositide (PI). Additionally, PTEN's C2 domain has been shown to bind phospholipid membranes in vitro and thus aid in the steering and anchoring of PTEN to the cellular membrane [138]. Together, this interplay between both domains carries implications for suppressing and stimulating tumor cell growth.

- Expression and Function

At the cellular level, PTENα is expressed in the cytoplasm and the mitochondrial inner membrane, while PTENβ is in the nucleolus [135, 139]. In neurons, PTEN is dynamically localized to specialized subcellular compartments, such as the neuronal growth cone, dendritic spines, and the nucleus [140, 141].

At the tissue level, PTEN protein and mRNA expression have been observed in the human pancreas [142] and in the human brain, including the cerebral cortex, cerebellum, and hippocampus (www.proteinatlas.org) [99]. PTEN exhibits differential distribution in the rat brain, with the highest levels found in the anterior olfactory nucleus, cerebral cortex, amygdaloid nucleus, hippocampus, purkinje cells, and several nuclei in the basal ganglia, thalamus, midbrain, and pons [143].

PTEN regulates cellular proliferation, survival, energy metabolism, cell architecture, and motility [137]. PTEN modulates cell proliferation and neuronal growth during development by dephosphorylating PIP3 and antagonizing PI3K signaling. PI3K signaling mediates responses to cellular stimuli, including hormones and growth factors [144, 145, 146]. On the other hand, the inhibition of PTEN causes axonal regeneration and neural repair [147]. PTEN is fundamental in maintaining chromosomal stability through physical interactions with centromeres and controls DNA repair [148].

2.2.5 Myotubularins

- Structure and Homologues

Myotubularins can be found in almost all eukaryotes, from yeast to mammals. In humans, 14 clearly defined myotubularin paralogs have been described, with MTM1 being the first recognized myotubularin. Subsequently, 13 myotubularin-related proteins were identified, labeled MTMR1 to MTMR13 [149].

All myotubularins share the PH-GRAM (Pleckstrin Homology - Glucosyltransferase, Rab-like GTPase Activator, and Myotubularins) domain and catalytically active or inactive phosphatase domains. Additionally, myotubularins can also carry other functional domains, including the PDZ binding site, the PH (Pleckstrin homology) and FYVE (Fab1-YOTB-Vac1-EEA1) domains, and the DENN (Differentially Expressed in Normal and Neoplastic cells) domain. Except for MTMR10, all myotubularins comprise a coiled-coil domain (Figure Appendix) [149, 150].

- Expression and Function

Myotubularins do not show any nuclear expression at the cellular level but are primarily localized in the cytoplasm as a richly-formed network. Myotubularins have also been shown to localize to Rac1-inducible plasma membrane ruffles. This localization to Rac1-induced ruffles seems to be associated with a highly conserved myotubularin domain referred to as RID [151].

At the tissue level, *myotubularin* mRNA expression has been documented for various human organs, including the spinal cord and substantia nigra (SN) of the central nervous system, skin, lungs, and vagina [149]. At the protein level, myotubularins are expressed in the brain, including the cerebral cortex, hippocampus, and cerebellum, as well as non-brain tissues like lungs, muscles, endocrine tissue, bone marrow, immune system, liver, gallbladder, and pancreas (www.proteinatlas.org) [99].

Myotubularins are involved in several cellular processes, including autophagy, apoptosis, the actin cytoskeleton, and intermediate filaments dynamic and PI metabolism. Active myotubularin can remove phosphate on carbon number 3 of PtdIns3P or PtdIns(3,5)P2 and turn it into PtdIns or PtdIns5P, respectively [152]. Additionally, they are also involved in myelin formation in neurons. For instance, MTMR2 is present in the nucleus and cytoplasmic compartments of Schwann cells and motor neurons but not in the nucleus of sensory neurons. Moreover, MTMR2 interacts with the neurofilament light chain protein NF-L in Schwann cells and neurons [153]. Schwann cell/dorsal root ganglion neuron co-cultures from *mtmr2* knock-out mice exhibit excessive redundant myelin, also known as myelin outfolding, and MTMR2 replacement was shown to rescue this myelin outfolding phenotype [154]. Interestingly, the deletion of MTMR2 phospholipid phosphatase in humans causes childhood onset of an autosomal recessive demyelinating neuropathy, also known as Charcot–Marie–Tooth type 4B1 [155].

2.2.6 Mitogen-activated protein kinase phosphatases (MKPs)

- Structure and Homologues

The *mkp* genes encode phosphatases that dephosphorylate MAP kinase (MAPK) signaling elements in vivo

deactivating them [156]. In turn, this leads to the modulation of several physiological processes via a conformational change of their substrates.

MKPs comprise the MAPK-binding (MKB) domain in the N-terminal end and the DSP domain in the C-terminal end. The N-terminal MAPK-binding domain regulates enzymatic specificity through docking interaction with MAPK. The binding of phosphorylated MAPK to the MAPK-binding domain alters the structure of the DUSP domain. This alteration in the conformation of the protein, in addition to the interaction of the catalytic domain with MAPK, increases MKPs' catalytic activity (Figure Appendix).

- Expression and Function

MKPs seem highly expressed in various tissue types, including the brain, endocrine tissues, lung, digestive tract, liver, gallbladder, kidneys, male and female reproductive tissues, and adipose tissue (www.proteinatlas.org)[99].

The MKP family can bind to substrates from MAPK signaling pathways, including ERK, JNK, and p38 [156, 157]. The DSP domain of MKPs inactivates MAPK by docking into phospho-MAPK [156]. MAPK signaling converts extracellular stimuli into various intracellular responses, such as proliferation, differentiation, survival, apoptosis, and migration [158, 159, 160]. MAPK signaling pathways have many predominant kinases, including JNK, ERK, and p38, which can be inactivated by different MKPs [161].

2.2.7 Atypical DUSPs

- Structure and Homologues

Atypical DUSP genes have multiple nomenclatures and remain poorly characterized [91, 93]. The HUGO (Human Genome Organization) Gene Nomenclature Committee includes 16 atypical DUSPs genes [162]. Patterson et al. identify 20 members of atypical DUSPs [86], and Huang and Tan 15 atypical DUSP members [93]. Moreover, phylogeny analysis has shown that atypical DUSPs are not derived from a common proximal ancestor [86, 93]. Atypical DUSPs encode proteins with a molecular weight of less than 27 kDa [86, 91]. All the members of atypical DUSPs are listed in the Appendix. Atypical DUSPs predominantly contain the consensus DSP catalytic domain. Some atypical DUSPs contain a CH2 domain, a carbohydrate-binding domain, and an Arginine-rich or Proline-rich region (Figure Appendix) [86].

- Expression and Function

Most atypical DUSPs are localized in the cytoplasm at the cellular level, with some in the nucleus, another subset in the mitochondria, and Golgi in various cell types [86]. At the tissue level, the brain expression of atypical DUSPs is presented in the Appendix, while their localization in other tissues is described in the Appendix.

Some atypical DUSPs regulate MAPK, playing a role in cell proliferation and apoptosis. In addition to MAPK protein substrates, several substrates of atypical DUSPs include nucleic acids (such as RNA) and phosphorylated carbohydrates (such as amylopectin and glycogen). Nonetheless, the physiological substrates of many atypical DUSPs remain unknown [86, 163].

2.3 DUSP genes and mental disorders

Accumulating evidence from the current literature on the link between DUSP genes and mental disorders such as depression, bipolar disorder, autism spectrum disorder (ASDs), schizophrenia, post-traumatic stress disorder (PTSD), and substance abuse disorders are described in the following section. The summary of the pathological implication of DUSP family members in mental disorders is presented in Table A.4 of the Appendix.

2.3.1 Depression

Depression is characterized by psychological and physiological symptoms, including negative thinking, anhedonia, fatigue, memory impairment, insomnia, extreme weight loss, or weight gain. The World Health Organization (WHO) reported that depression is a leading cause of disability worldwide. The neurobiological mechanisms underlying depression are complex, however, first-line antidepressants are effective in a subset of patients by reversing some of the symptoms of depression [164]. However, not all individuals benefit from current antidepressants, and genetic factors have been shown to contribute to the risk of treatment-resistant depression [165].

PTEN and Depression

Genetic studies have demonstrated an association between three distinct *pten* single nucleotide polymorphisms, rs701848, rs2735343, and rs112025902, and increased risk of depression in a Chinese cohort [166]. Other studies have provided evidence that PTEN protein levels are higher in postmortem lysates of the ventral prefrontal cortex (Brodmann's area 11) from suicide victims diagnosed with depression when compared to non-depressed healthy controls [167]. Besides, the enzymatic activity of the kinases PI3K and AKT1 were found to be decreased in the ventral prefrontal cortex (Brodmann's area 11) of suicide victims diagnosed with depression, while their protein levels did not differ. Conversely, PTEN protein levels in the ventral prefrontal cortex were observed to be increased in patients with a depressive disorder. This attenuation of PI3K and AKT1 activity in suicide victims with a depressive disorder may be related to elevated levels of PTEN, which in turn may result in insufficient phosphorylation of second lipid messengers PI3-phosphate, PIP2 and PIP3 [167].

PI3K and AKT are also involved in mediating depressive-like behavior in mice induced by stress [168, 169] and inhibitors of PI3K/ AKT have been shown to prevent antidepressant-like effects (characterized by decreased immobility time) induced by creatine in mice following the stress-inducing tail suspension test [170, 171]. Together, these results highlight that the phosphorylation of AKT and the downstream effects might be of interest as a potential treatment of depression. Previous work has indicated that deficits in vital cellular processes such as cell survival and neuroplasticity are observed in major depression [172]. Therefore, looking into the enzymatic activity of PTEN and PI3K and their association with abnormalities in neurotrophic signaling is pertinent [167].

DUSP1 and Depression

DUSP1 has also been documented to play a role in the pathophysiology of depression in human subjects [173]. For instance, *dusp1* mRNA expression was shown to be increased in the hippocampus of depressed patients when compared to healthy controls [174]. As negative regulators of DUSP1, MAPK and its downstream kinases were decreased in the prefrontal cortical areas and the hippocampus of suicide subjects with depression [158, 175, 176]. Recent evidence from animal studies suggests the involvement of MKPs in depression-like behavior. For instance, in one study, DUSP1 protein levels were observed to be increased in the hippocampus of stressed rats when compared to controls in the resident-intruder paradigm. Kinase substrates of DUSP1, including phosphorylated MEK1/2 and ERK1/2, were decreased in the hippocampus of stressed rats when compared to controls [177]. In another stress model – the chronic unpredictable stress (CUS) model - the upregulated protein levels of DUSP1 in the hippocampus was rescued by the antidepressant fluoxetine, two weeks after inducing depressive-like behaviors in rodents [174]. Similarly, the upregulated protein level of DUSP1 in the ventrolateral orbital cortex of rats subjected to chronic unpredictable mild stress was attenuated by enhancing miR-101 expression, and so was the depressive-like behavior [178]. miR-101 is a functional silencing small RNA targeting *dusp1* [179, 180] and the amyloid precursor protein (APP) [181]. Moreover, overexpression of DUSP1 in the hippocampus induced anhedonia-like behavior, including a reduced preference for sucrose and increased frequency of failure-to-escape in the active avoidance test [174]. *Dusp1* knockout mice were also resistant to CUS-induced depressive-like behaviors [174].

Antidepressant treatments have an impact on the expression of DUSP1 in healthy animal subjects. For example, the administration of fluoxetine reduced *dusp1* mRNA expression in the prefrontal cortex of healthy rats [182]. Moreover, electroconvulsive therapy (ECT), a treatment for drug-resistant depression, induced upregulation of *dusp1* mRNA levels in all hippocampal subregions, and the prefrontal cortex of healthy rats [182].

These results together strengthen the association between DUSP1 and depression. Future studies looking into treatments for depression should consider targeting DUSP1 as a therapeutic strategy by, for example, making use of small RNAs, particularly miRNAs, to silence the expression of DUSP1 hence reversing signs and symptoms of depression.

DUSP4 and Depression

Analyses of postmortem brain tissue samples indicated increased protein levels of DUSP4 (aliases MKP-2, the ERK1/2 phosphatase) in prefrontal cortical areas and the hippocampus of patients with major depressive disorder following the death by suicide compared to non-psychiatric control subjects. This increase was accompanied by decreased expression of mRNA and protein levels of ERK1 and ERK2, resulting in reduced MAPK activity [158]. Another study showed sex-dependent differential expression of *dusp4* mRNA in the ventral subiculum of patients with depression compared to healthy controls; with differences observed in male but not in female subjects [183].

DUSP4 protein expression remained unchanged in the hippocampus and the frontal cortex of rats subjected

to prenatal stress [184] and in a male rat model of depression, which was induced by neonatal treatment with clomipramine [185]. Treatments, including antidepressants and ECT, have led to changes in DUSP4 expression in healthy animals. For instance, ECT treatment in healthy male rats induced increased expression of *dusp4* mRNA in the dentate gyrus (DG) of the hippocampus and the prefrontal cortex [182].

Although these findings suggest DUPS4 changes in both human patients and animals subjected to antidepressant treatments ECS, the available studies do not show DUSP4 change in the stress paradigm in animals, like the prenatal stress and depression model of neonatal treatment with clomipramine. These unchanged results might be due to the limitations of the stress paradigm in animals. Besides, even though studies show DUSP4 level is sex-dependent in human depression studies, no studies show that the DUSP4 level is sex-dependent in animal models of depression, which creates limitations in specifying the involvement of DUSP4 in depression.

DUSP6 and Depression

In post-mortem brain tissue, *dusp6* mRNA was shown to be differentially expressed in the ventromedial prefrontal cortex of patients with depressive disorder in a sex-specific manner [183]. Besides, the DUSP6 substrates, phospho-ERK1/2, showed elevated protein expression in the prefrontal cortex of female patients with depressive disorder [183]. Downregulation of DUSP6 mediated by virus injection in the ventromedial prefrontal cortex of chronic stressed induced depressive-like phenotype in female mice, but not male mice. The overexpression of *dusp6* mediated by a Herpes simplex virus vector rescued the depressive-like behavior in female mice [183]. This sex-differential response of the stressed mice suggests that DUSP6 exerts a sex-specific role in the stress response, possibly via an interaction with sex-specific hormones.

Moreover, viral-mediated downregulation of *dusp6* was accompanied by increased phosphorylated ERK1/2 levels in the ventromedial prefrontal cortex of stressed female mice compared to control [183]. However, the total ERK1/2 protein levels in the DUSP6-downregulated female stressed mice remain unchanged in the ventromedial prefrontal cortex compared to control. These findings resemble findings observed in post-mortem brain tissue analyses of female patients diagnosed with depression. Females diagnosed with depression showed elevated levels of phospho-ERK1/2 in the prefrontal cortex compared to healthy female controls. Elevated phospho-ERK1/2-reactive cell density mainly localized in layers II/III and layers V/VI of the prefrontal cortex of female patients with depressive disorder [183].

Additionally, ECT and administration of antidepressants are shown to have an impact on DUSP6 expression. For instance, ECT induces the upregulation of *dusp6* mRNA levels in the prefrontal cortex and DUSP6 protein levels in the hippocampus and prefrontal cortex of healthy rats [182]. The administration of fluoxetine, however, reduced the mRNA expression of *dusp6* in the prefrontal cortex of healthy rats [182]. This discrepancy in results highlights the need to further investigate the involvement of DUSP6 in mood disorders such as depression.

DUSP2, DUSP12, DUSP19, DUSP23, DUSP24 and Depression

The subregions of the hippocampus exhibit differential RNA expression of *mkps* in post-mortem brain samples of patients diagnosed with depressive disorder. For instance, while DUSP2 and DUSP19 show higher expression in the hippocampal DG than in the CA1, mRNA levels of *dusp12* and *dusp24* are increased in the CA1 region of postmortem brain tissue of patients diagnosed with depression [174] as compared to healthy controls. Another study showed differential expression of *dusp19* mRNA in the ventral subiculum and of *dusp23* mRNA in the nucleus accumbens and the Broadman area of male patients with depressive disorder, but not in female patients [183]. These results indicate that distinct *dusp* genes may be linked with depression differently, including sex-specific effects. Despite these observations, further experimental studies are needed to better understand the involved of MKPs in depression and eventually target their expression to reverse depressive symptoms.

2.3.2 Bipolar disorder

Bipolar disorder is characterized by mood instability, with episodes of mania and depression. Bipolar disorder is a complex disorder with high estimated heritability. Despite the accumulating evidence of the etiology of bipolar disorder, the underlying biological mechanisms that give rise to this mood disorder remain elusive [186]. Besides underlying genetic factors, environmental risk factors have also been identified as being partly responsible for the onset of bipolar disorder [187]. Bipolar disorder is associated with multiple dysregulations including disturbed brain development, neuroplasticity, and chronobiology, specifically, neurotransmitter, neurotrophic factors, neuroinflammation, autoimmunity, cytokines, stress axis activity, oxidative stress, and mitochondrial dysfunctions [188].

DUSP2 and Bipolar disorder

It has been observed that patients diagnosed with bipolar disorder have increased proportions of monocytes in the blood or cerebrospinal fluid (CSF) compared to controls [189, 190]. It has also been found that the monocytes of patients with bipolar disorder and the offspring of bipolar parents show aberrant levels of *dusp2* mRNA expression. For instance, patients with bipolar disorder taking medication show elevated blood mRNA levels of *dusp2* compared to healthy controls. DUSP2 carries a strong correlation to the mRNA expression of inflammatory cytokines [191]. *Dusp2* mRNA expression has been shown to be significantly higher in monocytes of patients with mood disorder compared to healthy controls [192]. Furthermore, lithium carbonate- and antipsychotic-treated patients with bipolar disorder exhibited lower levels of expression of *dusp2* mRNA in monocytes compared to non-lithium- and non-antipsychotic-treated patients with bipolar disorder [192]. Thus, DUSP2 may be an attractive target for further analyses in patients with bipolar disorder.

DUSP6 and Bipolar disorder

There is a positive association between the *dusp6* gene and patients with bipolar disorder [193, 194]. A genetic study, including 160 patients with a diagnosis of schizophrenia, 132 patients with bipolar disorder, and 336 healthy controls, indicated that the G allele of the T/G polymorphism of the *dusp6* gene was significantly more common in patients with bipolar disorder than controls. However, there was no difference between schizophrenia patients and controls. This contrast suggests a specific association of the *dusp6* gene with bipolar disorder, but not with schizophrenia [194]. However, this association was not observed in male patients with bipolar disorder [194], hence suggesting a sex-specific effect.

The lower expression of *dusp6* gene observed in postmortem brain samples of patients with bipolar disorder has been found to show sex-specificity, with a reduced level of mRNA transcripts expression in female but not male patients with bipolar disorder [195]. Additionally, in vitro studies demonstrated functional Leu114Val and Ser144Ala polymorphisms in *dusp6* blunted the effects of lithium on ERK1/2 activation by using SH-SY5Y human neuroblastoma cells infected with recombinant adenoviruses [193]. Other evidence has suggested that DUSP6 may be linked with bipolar disorder, possibly via the involvement of the ERK pathway and circadian rhythm dysregulation [194].

Also, DUSP6, a negative regulator of ERK1/2, has been linked to the disruption of the circadian rhythm in cell cultures of fibroblasts derived from patients with bipolar disorder. The knock-down of *dusp6* in these fibroblasts has been shown to reverse lithium-induced increases in amplitude of circadian rhythm. That being said, the inability of lithium to regulate circadian rhythms in bipolar disorder may reflect reduced ERK activity, which is partially regulated by DUSP6 [196]. Thus, DUSP6 may be playing a crucial role in regulating circadian rhythms and in the onset and course of bipolar disorder [193].

2.3.3 Autism spectrum disorders (ASD)

Autism spectrum disorder is a developmental disorder characterized primarily by a lack of social reciprocity accompanied by repetitive behavior such as stereotypical or repetitive motor movements. The heritability of ASD is considerably high, and common genetic variants have been shown to play a role in conferring risk to ASD [197]. Besides, indirect evidence suggests a contribution of environmental factors in interaction with genetic factors in the development of ASD [198].

PTEN and ASD

Pten gene mutations have been shown to be risk factors for ASDs associated with macrocephaly [199, 200, 201]. This specific type of ASD associated with macrocephaly is termed PTEN-ASD, typically characterized by reduced levels of PTEN protein expression in conjunction with increased brain size and cognition impairment [202]. In the last decades, *pten* mutation frequencies in PTEN-ASD has been reported in ten human studies [203].

Moreover, *pten* loss in mice leads to alterations in synapses and cytoarchitecture [203]. Ablation of *pten* in neural stem cells in the subgranular zone of the hippocampus of mice leads to increased proliferation and differentiation rate of the stem cells, which later developed into hypertrophied neurons [204]. Several mouse models characterized by *pten* deficiency or dysfunction show autism-like behaviors, including social deficit and repetitive behavior [134]. One of these models, *pten(m3m4)*, exhibits the same disrupted genes as those in human ASD [205], including genes related to myelination such as myelin basic protein. Interestingly, *pten(m3m4)* animals present an enlarged corpus callosum, white matter abnormalities, and impaired learning and memory processes [202].

DUSP15 and ASD

The analysis of peripheral blood from 255 children affected by ASD and 427 healthy controls revealed that DUSP15 could be a susceptibility biomarker for ASD [206]. Additionally, recurrent identical de novo mutations of *dusp15* were found via exome sequencing using 175 samples from ASD cases and their parents [207]. Therefore, DUSP15 seems to carry a peculiar role in ASD risk and should be further investigated as a potential biomarker for ASD in children.

2.3.4 Schizophrenia

Schizophrenia is a debilitating disease affecting various daily functions, including self-care, social aspects, and occupational functions [208, 209]. The symptoms of schizophrenia include hallucination, delusion, bizarre behavior, anhedonia, and concentration problems [210]. Evidence shows that the factors contributing to schizophrenia include genetic factors, early environmental influences, and social factors (e.g. poverty) [208, 209]. Schizophrenia is a complex disease affecting 1-3 % of the population. It is also considered among the top ten causes of disability worldwide [208]. Dysfunction of dopaminergic neurotransmission and synaptic function seems to contribute to psychotic symptoms and abnormalities of neuronal connectivity, respectively [211]. Current first-line treatment mainly includes the administration of antipsychotic drugs (such as chlorpromazine and haloperidol) combined with psychotherapy, social support, and rehabilitation [211].

DUSP4 and Schizophrenia

A post-mortem brain study demonstrated decreased DUSP4 protein levels in the cerebellar vermis of the patient with schizophrenia compared to control [212]. This is particularly interesting given the increasing evidence showing the involvement of the cerebellum in psychiatric disorders, mainly schizophrenia. As substrates of DUSP4, ERK protein levels also seem to be disrupted in the postmortem brains of schizophrenia patients. For instance, ERK1 protein expression is reduced in the prefrontal cortex, while ERK2 is elevated in the thalamus [213].

DUSP22 and Schizophrenia

The hypermethylation of the *dusp22* promoter has been reported in a recent study investigating genetic vulnerability to schizophrenia [214]. The blood and brain tissue of patients exhibited significant hypermethylation at the *dusp22* gene promoter. Furthermore, the *dusp22* gene promoter showed higher DNA methylation levels in the famine-exposed schizophrenia patients compared to non-famine exposed groups. Thus, famine seemed to be a susceptible factor in the onset of schizophrenia. In an in vitro model of famine, nutritionally deprived patient-derived fibroblasts showed hypermethylated *dusp22*. These results suggest an association between epigenetic changes on the *dusp22* gene and increased susceptibility to the impact of an environmental risk factor on mental disorders [214]. Although no correlation was found to exist between DNA methylation and gene expression of the *dusp22*, these results suggest changes in gene expression regulation of *dusp22*, in response to extreme conditions like famine, may moderate or mediate risk for schizophrenia. Additionally, the hypermethylation of *dusp22* in the blood and brain of schizophrenia patients that were not exposed to famine, also suggests that dysregulations in *dusp22* methylation are associated with underlying mechanisms in the onset and development of schizophrenia. Further research on the involvement of DUSP22 in neuronal development is required to strengthen this association and better understand the changes that are brought by aberrant *dusp22* methylation.

MTMR2, MTMR9 and Schizophrenia

Mtmr9 mRNA level was found to be reduced approximately two-fold in peripheral blood lymphocytes from patients with schizophrenia compared to healthy controls [215]. Furthermore, *mtmr2* mRNA was shown to be lower in the superior temporal cortex of patients diagnosed with schizophrenia as compared to controls without a schizophrenia diagnosis [216]. These results suggest that further research into MTMR9 is required to investigate whether it would eventually be qualified as a biomarker for the diagnosis of schizophrenia.

2.3.5 Post-traumatic stress disorder (PTSD)

PTSD symptoms include intrusions, avoidance/numbing, hyperarousal, sensitization to stressors, and negative alterations in cognitions and mood. The cause of the PTSD remains elusive, and various factors have an impact on the pathology of PTSD, including genetic factors, trauma exposure, and interaction between gene and environment [217, 218]. The global burdens of PTSD in public health are substantial because the symptoms lead to impaired functions in several aspects of one's life, including health, social, and professional life [219]. Given the complexity of the pathology of PTSD, the treatment of PTSD consists of various methods, including pharmacologic approaches [220, 221], psychotherapies [222], and mindfulness [223].

DUSP22 and PTSD

Differential DNA methylation at the DUSP22 gene is receiving increased attention to psychiatric disorders such as schizophrenia and PTSD. A recent longitudinal study in a Dutch military cohort identified changes in DNA methylation at several differentially methylated positions, including DUSP22 [41]. Decreased DNA methylation around the DUSP22 gene was linked to increased PTSD symptoms [41]. Although this observation was not replicated in an independent replication study, a thorough understanding of the role of epigenetic changes around the DUSP22 gene in the face of extreme environmental conditions like traumatic stress and famine is required.

2.4 DUSP genes and neurological disorders

Accumulating evidence from the current literature on the link between DUSP genes and neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and epilepsy, is described in the following section. The summary of the pathological implication of DUSP family members in neurological disorders is presented in Appendix TableA.4.

2.4.1 Alzheimer's disease (AD)

AD is characterized by progressive memory loss, impairments in cognition, and neuropsychiatric disturbances such as mood and personality changes, anxiety, and aggression [224]. The prevalence of AD is 10–30 % in individuals over 65 years, with incidence doubling every ten years after 60 [225, 226]. The pathophysiological hallmarks of AD are the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated-tau that lead to neuronal loss due to neurotoxic effects. So far, there is no cure for AD, and the current treatment options have been shown to only slow down its progression [227].

DUSP1 and AD

The protein level of DUSP1 decreased in the hippocampus and temporal cortex of patients diagnosed with AD compared to aged match healthy controls [228]. Similarly, DUSP1 protein levels were decreased in the hippocampus of APP/PS1 transgenic AD model mice at the age of 9 months compared to control mice [228]. DUSP1 inhibits the amyloidogenic process through the ERK/MAPK signaling pathway, and DUSP1 reduces Aβ generation and plaque formation and alleviates synaptic and cognitive impairments in APP/PS1 mice [228]. In PC12 cell culture, DUSP 1 mitigates Aβ-induced apoptosis, oxidative stress, and neuroinflammation by inhibiting the JNK signaling pathway, thereby playing a neuroprotective role. From the animal and cell culture studies, DUSP1 alleviates amyloid beta-induced neurotoxicity [229]. The results suggest that DUSP1 impairment facilitates the pathogenesis of AD, whereas the upregulation of DUSP1 plays a neuroprotective role to reduce Alzheimer related phenotypes [228].

DUSP26 and AD

DUSP26 protein was observed to be elevated in the hippocampal of postmortem brain tissue of patients with AD compared to controls [230]. In the APP-expressing HEK293/APP695 cell lines, overexpression of DUSP26 increased Aβ42 levels by twofold [230], In contrast, the enzymatically inactive mutant of *dusp26* failed to induce Aβ oligomers or APP processing. Thus, DUSP26 has been linked to Aβ generation and APP processing in these cell lines [230], thereby suggesting the involvement of DUSP26 in the pathophysiology of AD.

SSH1, SSH3 and AD

SSH1 protein level showed a 45 % significant reduction in the frontal cortex of patients diagnosed with AD compared to healthy controls. This reduction was accompanied by unchanged pSSH1 levels, which led to the significant decrease of the pSSH1/SSH1 ratio indicative of the inactivation of SSH1 in human AD [100]. Besides, *ssh3* mRNA was shown to be differentially expressed in the hippocampus, the temporal and frontal cortex, as well as in the whole blood of patients diagnosed with AD in comparison with healthy controls [231]. SSH phosphatase dephosphorylates cofilin, and the reduced protein expression and inactivation of SSH1 were further accompanied by an increase in cofilin1 phosphorylation/inactivation in human and animal studies [100]. Hyperphosphorylation of cofilin can result in tau pathology, which can be induced by Aβ oligomers [232].

DUSP22 and AD

Analyses of blood/brain samples indicated that methylation of the region in *dusp22* correlated linearly and powerfully with the Braak stages of neuropathology, an index of AD progression (Pearson correlation coefficient $r = 0.95$, $p < 0.05$) [233]. In the hippocampus of patients diagnosed with AD, hypermethylation of the *dusp22* promoter and decreased protein expression of DUSP22 as compared to age-matched controls have been reported [233]. Reductions in DUSP22 levels may lead to increased tau phosphorylation due to weaker inhibitory control of protein kinase A-mediated tau-phosphorylation, at least as suggested by findings in neuronal cell lines [233]. Besides, it has been found in SK-N-BE(2) cell culture studies that are depleting DUSP22 through small hairpin RNA's resulted in a higher survival capability than cells with control or healthy and overexpression of DUSP22 [233]. It would be interesting for future studies on AD pathophysiology to establish the regulatory role of DUSP22 in tau phosphorylation, Aß accumulation, and neuronal death in AD.

PTEN and AD

AD is associated with excessive recruitment of PTEN into synapses, leading to aberrant synaptic depression [134]. It has furthermore been observed that layer III of the temporal cortex in patients with AD showed a 15 % loss of PTEN immunoreactive neurons compared to controls, while the majority of the layer III temporal cortex were PTEN immunoreactive in control cases [234]. PTEN protein levels decreased in the AD temporal cortex compared

with matched controls, and PTEN level has been negatively correlated with the severity of neurofibrillary pathology or senile plaques [235].

It has been observed in AD, that PTEN delocalizes from the nucleus to the cytoplasm and intracellular neurofibrillary tangles in postmortem brain tissues [236]. The nuclear PTEN immunoreactivity reduced in neurons of the CA1, subiculum, and entorhinal cortex of AD cases, while the PTEN immunoreactivity increased in apical dendrites in the CA1 and subiculum in AD cases compared with control [235]. However, in the temporal cortex, PTEN protein levels were not significantly different in either nucleus or membrane fractions in AD postmortem brains and controls [234]. Instead, the ratio of Ser380 p-PTEN / total PTEN protein reduced in temporal cortical homogenates in AD compared to control [234], which indicated reduced PTEN phosphorylation at residue Ser380 in AD. Decreased PTEN and increased tau phosphorylation were evident in frontal cortex brain slices of AD [237]. This suggests that PTEN phosphorylation is involved in AD pathology and that PTEN dynamics in AD brain might be region dependent.

PTEN contributes to AD pathology in animal and cell culture models [238]. Overexpression of PTEN induces synaptic depression, similar to Aß-induced depression in transgenic mice [239]. Additionally, the overexpression of the PTEN protein in Chinese hamster ovary cells reduces tau phosphorylation [240]. Another study demonstrated that overexpression of PTEN decreases the formation of tau aggregates in COS-7 cells.

In contrast, the phosphatase-null or inactive PTEN increases tau aggregation in rat cortical primary neurons transfected with a mutant form of *pten* [237]. The loss of PTEN causes neurodegeneration through the hyperphosphorylation of tau and neurofilaments in mouse cerebellar neurons [241]. However, induction of PTEN is accompanied by okadaic acid-induced tau phosphorylation, while the knockdown of PTEN reduced tau hyperphosphorylation in SH-SY5Y neuroblastoma cells, and increased cell proliferation and survival. Inhibition of PTEN reduces tau phosphorylation in SH-SY5Y neuroblastoma cells [242]. Furthermore, inhibition of PTEN via intracerebroventricular delivery of a PTEN inhibitor, VO-OHpic, rescued Aβ42-induced impairment in both basal synaptic transmission and LTP, as well as spatial learning tasks, in APP/PS1 transgenic mouse model of AD [239].

The PDZ-binding domain of PTEN is central to Aβ-induced synaptic toxicity and cognitive dysfunction [239]. Deletion of this PDZ-binding domain results in resistance to Aβ toxicity in postsynaptic neurons [239]. Overexpression of PTEN reduced tau phosphorylation in Chinese hamster ovary cells [240]. Thus, taken together, these findings indicate that PTEN may be centrally involved in moderating or mediating AD's pathophysiology.

2.4.2 Parkinson's disease (PD)

PD is a progressive disease with motor and non-motor symptoms, which consist of slow movements, tremors, rigidity, impaired balance during walking, various disturbances in autonomic functions with orthostatic hypotension, constipation, sleep disturbances, and a spectrum of neuropsychiatric symptoms [243]. The cause of PD is unknown but is believed to involve both genetic and environmental factors [244]. Parkinson's disease affects 1 % of the

population above 60 years old and is more frequently prevalent in men than women [245]. The main hallmarks of PD are Lewy bodies and the degeneration of dopaminergic neurons in the substantia nigra. However, recent findings suggest that PD's pathophysiology is heterogeneous. Other protein aggregates like α-synuclein, DJ-1 [246], tau, and β-amyloid also play a role [247] in the onset and progression of the disease.

PTEN and PD

Protein level of nuclear PTEN has been shown to be significantly increased by 5.6-fold in the substantia nigra of PD brain compared to the age-matched controls. PTEN downstream regulators, PI3K regulatory subunit p85, PIP3, and Akt1/2/3 protein levels decreased by two-fold in nuclear of substantia nigra region of PD brain samples compared to the age-matched controls [248].

Downregulation of PTEN inhibits elevated levels of intracellular reactive oxygen species and neuronal death in rat hippocampal and in human dopaminergic SH-SY5Y neurons caused by neurotoxin 1-methyl-4-phenylpyridinium iodide toxicity which mimic PD [249]. PTEN deletion in adult dopaminergic neurons protects these neurons from 6-hydroxydopamine (6-OHDA) neurotoxicity and restores striatal dopamine levels in mouse models of PD [250]. PTEN has been involved in response to DNA damage repair in PD [251]. Specific defects in DNA impact the dopaminergic system and are associated with PD pathology in both cell and animal models [252]. Thus, PTEN does play a role in DNA damage in PD.

DUSP1 and PD

There are currently few studies on DUSP1 in patients with PD. However, one study reported decreased *dusp1* mRNA expression in the dorsolateral prefrontal cortex of idiopathic PD patients [253]. In cell culture studies using neuronal PC12 cells, Serial Analysis of Gene Expression-based study showed that acute (8 hours) exposure to 6-OHDA, a dopaminergic neurotoxin commonly used to induce PD-like symptoms in experimental studies [254, 255], induced a 35-fold increase of *dusp1* mRNA levels [256]. Moreover, *dusp1* mRNA was transiently upregulated in the SN 4 days post-6-OHDA administration in the medial forebrain bundle lesion model in rats [257]. Besides, *dusp1* mRNA expression was increased in rat striatum treated with 6- OHDA followed by injection of SKF38393, a selective dopamine receptor D1 agonist [258]. DUSP1 has been shown to promote the growth and elaboration of dopaminergic neuronal processes, protecting them from the neurotoxic effects of 6-OHDA [259]. This study indicates that DUSP1 may have a neuroprotective effect, at least in PD rodent models [259].

2.4.3 Huntington's disease (HD)

HD is a devastating heritable neurological disease characterized primarily by progressive motor and cognitive impairments, as well as psychiatric symptoms, including affective disorder symptoms that often precede other symptoms [260]. HD is typically induced by a highly polymorphic CAG trinucleotide repeat expansion in exon-

1 of the gene encoding the huntingtin protein [261]. Huntingtin protein is widely expressed during development and exhibits a complex and dynamic distribution within cells [262]. Besides genetic factors, cerebral vitamin B5 deficiency is a potential cause of HD [263]. Most European populations show a relatively high prevalence (4-8 per 100,000), but HD is notably rare in Finland and in Japan [264]. The underlying neuropathology is characterized by neuronal loss, striatum microglial activation, and neuro-inflammation within the striatum [265, 266]. Many genetically modified animal models of HD recapitulate some of the pathophysiological features observed in humans, but many drug designs based on animal models of HD have failed in clinical trials [267].

DUSP1 and HD

Reduced DUSP1 levels were observed in animal models of HD [268], and enhancing DUSP1 expression has been shown to significantly reduce neuronal cell death in HD animal models induced by lentiviral infection and expression of a mutated *huntingtin* gene. In a cell culture studies comprising primary striatal rat neurons exposed to a pathological construct comprising the N-terminal fragment of polyglutamine-expanded huntingtin (Htt171–82Q), overexpression of DUSP1 inhibited apoptosis [269]. This DUSP1-mediated neuroprotection has been suggested to be dependent on the activity of phosphatases and occur through direct regulation of JNKs and p38s [269]. Mutant *dusp1* selectively targeting JNK or p38, preserves significantly fewer NeuN-positive cells in primary striatal neurons exposed to Htt171–82Q fragments than in wild-type DUSP1 primary neuron HD models, indicating that dual targeting of JNK and p38 by DUSP1 may exert neuroprotective effects [269]. These findings suggest that this DUSP1 regulated pathway may represent a novel candidate as a therapeutic target in HD.

PTEN and HD

Elevated PTEN expression, together with amplification of BDNF signaling, seems to result in neuroplasticity abnormalities in the indirect pathway of the spiny projection neurons from brain slice of the BACHD mouse model and Q175 knock-in mouse model of HD [270]. Furthermore, plasticity and LTP aberrations were rescued by inhibiting PTEN in indirect pathway spiny projection neurons of a transgenic HD mouse model [271].

P53 has been shown to transiently upregulate PTEN protein and mRNA levels in medium spiny neurons in the striatum of TIF-IA knock-out mice, a transgenic model of HD [272]. TIF-IA inactivation leads to nucleolar disruption, which is also a common finding in HD pathology [273]. TIF-IA deletion, together with PTEN or p53 deletion in mice, exhibited increased levels of apoptotic cells in the striatum [272]. However, TIF-IA deletion combined with PTEN and p53 deletion did not show increased apoptotic cells in the striatum. Thus, PTEN and p53 prolong neuronal survival upon nucleolar disruption [272]. The upregulation of PTEN impairs kinase mammalian/mechanistic target of rapamycin function in medium spiny neurons [272].

Future studies investigating PTEN regulation will contribute to understanding the etiology of HD and to the development of new therapeutic strategies targeting PTEN.

2.4.4 Epilepsy

Epilepsy is characterized by recurrent unprovoked seizures and accounts for the highest disability-adjusted life year rates among neurological disorders [274]. Epilepsy is caused by various factors, including genetic influence, head trauma, brain disease like brain tumors or strokes, infectious diseases, prenatal injury, or developmental disorders. Epilepsy affects more than 65 million people worldwide [275]. Gliosis, imbalance of ion and water homeostasis, increased extracellular glutamate, altered neural circuits, damaged blood-brain barrier are omnipresent in epilepsy in animal models or patients [276]. Antiepileptic drugs are the first-line treatment, but alternative treatments, including surgical resection of the seizure focus, ketogenic diets, vagus nerve stimulators, and implantable brain neurostimulators are available for patients with seizures that are not controlled with medication [277].

Laforin and Lafora disease (LD)

LD is a progressive neurological disorder characterized by intractable myoclonic seizures, emotional disturbance, and cognitive decline. Hallmarks of this disease are primarily attributed to the accumulation of hyperphosphorylated insoluble poly-glucosan called Lafora bodies (LBs). LBs are caused by mutations in either the atypical DUSP *laforin*, *emp2A*, or *nhlrc1*. *Laforin* genes encode phosphatases that dephosphorylate glycogen. Glycogen, a potent energy storage molecule in animals, is degraded by glycogen phosphorylase and glycogen debranching enzyme. In the brain, the accumulation of glycogen in neurons can lead to neuronal loss, locomotive defects, and neurodegeneration in mice and Drosophila. As such, a reduction of glycogen synthesis may prevent LBs formation and subsequent neurodegeneration and seizure susceptibility, thus preventing LD progression [278, 279, 280].

PTEN and Epilepsy

pten mutations have been observed in patients with epilepsy and a variety of comorbidities, including cancer [281, 282]. PTEN sequence analysis performed on a case where the individual suffered from both epilepsy and Cowden syndrome, an inherited disorder characterized by noncancerous growths, identified a heterozygous missense mutation in *pten* [283]. Resection of high-grade glioma tissue from patients with seizures exhibited reduced PTEN expression compared to patients with glioma without seizures [284]. *Pten* mutations have also been reported and used in several animal models of cortical dysplasia, which is also a contributor to epilepsy in adults [285]. For instance, the inhibition of PTEN rescued neuronal death in a mouse model of temporal lobe epilepsy, implying an excitotoxic role for PTEN. This inhibition has also been shown to exert potent anti-inflammatory and neuroprotective effects [286]. These results confer additional support to the role of PTEN in neuronal dysfunction.

DUSP1 and Epilepsy

A study on kainic acid-induced limbic seizures in rats reported that DUSP1 protein expression was transiently induced in the dentate granule cells of the hippocampus, outer layers of the neocortex, and neurons of the lateral

nucleus of the bed of the stria terminalis in rat with the seizures as compared to untreated controls [287]. On a subcellular level, DUSP1 colocalizes with its substrate, MAP kinase, in neuronal nuclei, which has been linked to inhibition of the seizure response in an animal model of temporal lobe epilepsy [287, 288]. Given these results, DUSP1 induction seems to have a partial role in the inhibition of MAP kinase activity following seizures.

2.5 Conclusions

This review provides an extensive overview of research findings on the role of several *dusp* genes and their involvement in the onset and development of certain mental and neurological disorders. The body of literature on *dusp* genes does show the great diversity of biological processes in which *dusp* genes are involved, and it is therefore not surprising that genomic variations in *dusp* genes have been linked to several mental and somatic disorders.

It is furthermore noteworthy that the first wave of epigenetic studies has identified epigenetic changes in particularly one *dusp* gene, i.e., *dusp22*, to be linked to a range of mental as well as neurological disorders, i.e., altered methylation in the *dusp22* gene has been observed in PTSD patients, in patients diagnosed with schizophrenia and in AD patients as compared to controls.

The current state of the literature is nevertheless in a very early stage, and our review of the literature indicated a plethora of findings that are most challenging to converge into a common pathway. We did find a more comprehensive line of converging evidence from human observational studies and experimental studies using and model systems on the DUSP family genes *ssh* and *pten* suggesting intricate links to neuroplasticity, cellular proliferation, survival, and cellular architecture.

To reiterate, it is reasonable to suggest that *dusp* genes are possibly involved in biological processes underlying and/or mediating the onset and course of mental health and neurological disorders. Because candidates from epidemiological cohort studies cannot be thoroughly tested for causality in observational studies, it would be interesting to consider targeting the next phase of experimental cell and animal studies on manipulating the expression of distinct DUSP mentioned above family genes, in a cell type- and/or circuit-specific as well as temporal- specific manner (e.g., by combining genetic editing with optogenetics) in order to better understand their involvement in the etiopathogenesis of neurological and mental disorders, and as potential promising therapeutic targets.

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Chapter 3

Immunohistochemical localization of dual specificity phosphatase 22 (dusp22) in the mouse brain, preliminary results

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Chapter 4

Protein expression of myelin basic protein (mbp) in the brain and associations with behavioral changes induced by chronic stress

Kohei Koike, An Nijs, Caroline Rommels, Lisa F. Lebherz, Ehsan Pishva, Harry W.M. Steinbusch, Gunter Kenis,

Daniel van de Hove, Laurence de Nijs, Bart P.F. Rutten

Chapter 5

Brain localization of myelin transcription factor 1 like protein (myt1l) expression

Kohei Koike, An Ning, Lawrence de Nijs, Daniel van de Hove1, Gunter Kenis, Harry W.M. Steinbusch,

Bart P.F. Rutten

Chapter 6

Neural activity in the anterior olfactory nucleus (aon) in response to predator and non-predator odors in awake mice

An Ning, Erik Böhm, Renata Medinaceli Quintela, Jennifer Bauer, Lutz Wallhorn, Kim Le, Daniela Brunert,

Markus Rothermel

Chapter 7

Short-term and long-term effects of social defeat stress in mice and the effects of physical activity as a potential modifier

Lisa Lebherz, Ali Nimpf-Hammels, Laurence de Nijs, Gunter Kenis, Daniel L.A. van den Hove,

Ehsan Pishva, Bart P.F. Rutten

Chapter 8

Discussion

This thesis describes my studies investigating the mechanisms underlying susceptibility to traumatic stress using rodent models. To address this aim, my thesis covered studies on the following four research questions:

- 1 Are *dusp* genes and other genes related to mental and neurodegenerative disorders? How is the DUSP22 protein expressed in the rodent brain?
- 2 How is stress-related protein MYT1L expressed in the mouse brain?
- 3 Does exposure to social defeat stress correlate with altered MBP protein expression patterns in the mouse hippocampus?
- 4 How does predator odor change the neural activity in the olfactory cortex AON compared to non-predatory odor?
- 5 How does social defeat affect the subjects along with time? Can physical activity increase resilience to traumatic stress?

While I introduced the concepts and research questions in **Chapter 1**, **Chapter 2** described my extensive and critical review of evidence from the literature on the links of DUSP family genes with mental and neurodegenerative disorders. I found that studies based on patients and rodents or cell models confirmed the putative role of *dusp* genes in mental and neurodegenerative disorders, and I found that dusp genes regulate MAPK signaling to mediate inflammatory response [90, 428], which is proposed to be centrally involved in the onset and course of mental disorders [71] and neurodegenerative disorders [507]. Most dusp family genes seem to be linked with mental and neurodegenerative disorders via a regulatory role in inflammatory responses. Thus, one could speculate that the aberrant functioning of DUSP proteins may alter the response to inflammation and thereby increase the vulnerability to developing mental ill-health. The review provided insight into the relationship between inflammation and mental/neurodegenerative disorders. Most *dusp* genes and their proteins were critical players mediating inflammation via MAPK signaling pathways in mental and neurodegenerative disorders [83]. Previous findings have confirmed the link between the inflammatory process and multiple mental disorders [70] and neurodegenerative diseases [508]. However, the intermediate mediators were unclear. Chapter 2 thus confirms the neuro-inflammation theory in mental/neurodegenerative disorders. This review also provides possible intermediate mediators, DUSP phosphatase, which dephosphorylate MAP kinases [91] and MAPK signaling pathways [156]. The MAPK family members, p38, JNK, and ERK, are activated to produce cytokines and inflammatory mediators.

The DUSP family controls the inflammatory response via modulating MAPK signaling [90]. A significant limitation of the review described in **Chapter 2** is that most studies did not consistently operate on different levels like proteins, mRNA, or DNA levels in the same samples. Thus, concluding how *dusp* genes change in response to trauma was hard. Besides, the absence of research on upstream and downstream regulators of DUSP proteins in patients or rodent models makes it difficult at the present moment to know how *dusp* genes function in response to

trauma. Further research is needed to unravel the changes in protein, mRNA, or DNA levels in response to stress in patients, rodents, or cell models. DUSP proteins and their upstream and downstream regulators must be studied to present an overview of the cascade of signaling processes. Also, further studies could address causal links between DUSP-mediated inflammation and diseases.

Chapter 3 addresses the research question, "How are DUSP22 proteins expressed in the mouse brain?". This Chapter reports on my study on the localization of DUSP22 in the mouse brain. My results showed the prevalent expression of DUSPP22 in mice's cerebellum, hippocampus, cortex, and thalamus. Immunofluorescent double labeling of DUSP22 with the neuronal marker NeuN showed strong co-localization, indicating the neuronal expression of DUSP22, while this was not the case for GFAP-marked astrocytes in mice tissue. Thus, my study indicated that DUSP22 proteins expressed prevalently in the mouse brain. Cellularly, DUSP22 is expressed in neurons rather than in astrocytes. *Dusp22* mRNA is expressed in adult mouse brains, and its protein is expressed lightly in mouse hippocampus and cerebellum [294]. These expression profiles align with the proposal that the neuronal expression of DUSP22 may mediate the onset of mental ill-health. Some studies have confirmed this by discovering that DUSP22 protein expression is decreased in the hippocampus of AD patients [233]. Furthermore, it has been reported that the Dusp22 gene promoter was significantly hypermethylated in the famine exposed in schizophrenia patients compared to controls [214]. My findings provide the first evidence of the neuronal expression patterns of DUSP22 protein in the mammalian brain. Even though one study showed a tissue expression profile of DUSP22 in the adult mouse via western blotting analyses [295], this does not give a direct overview of how DUSP22 is expressed in the mouse brain. Our study is a first attempt to provide more information concerning DUSP22 expression in the mouse brain, although our data are too limited to provide detailed and complete regional distribution patterns. As noticed by western blotting, our data partially confirmed a brain regional-dependent expression profile of DUSP22 in the adult mouse brain [295]. However, earlier findings in cell cultures have reported that endogenous DUSP22 was distributed throughout the cytoplasm and was partially co-localized with cortical actin and actin stress fibers but not in the nucleus of NIH3T3 cells [295]. These potentially conflicting observations might differ between NIH3T3 cells (mouse embryo fibroblast cells) and mouse neuronal cells. A drawback was a high non-specific background signal, which complicates the interpretation of the immunohistochemical data. The appropriate blocking experiments and the fixative procedures used in the mouse studies were lacking. Future studies should, therefore, consider antibody testing and drastically increase the number of mouse brain slices.

Chapter 4 addressed my research question, "Does exposure to social defeat stress correlate with altered MBP protein expression patterns in the mouse hippocampus?". This study investigates the protein expression of MBP in the brain and its change in the brain in response to chronic stress. Results showed that MBP protein was widely expressed in the hippocampus of the mouse brain. Compared to the control, SD mice showed increased MBP expression in the CA1 radiatum layer of the hippocampus of SD mice, where MBP expression correlated positively to sociability score and corticosterone level within SD groups. Thus, our analyses of MBP protein expression in the

SD model suggested that MBP in the CA1 region of the hippocampus may be involved in the impact of SD stress on sociability and stress response. This study partially met our hypothesis that MBP protein is prevalently expressed in the hippocampus. However, our results did not support the hypothesis of MBP reduction in the hippocampus in response to SD stress since human and animal studies had revealed that chronic stress resulted in a deficiency of MBP [344, 76]. Instead, MBP expression increased in the CA1 radiatum layer of the hippocampus of SD mice compared to controls. Thus, our study showed increased MBP expression in mice hippocampus in response to social defeat, while one other mouse study found evidence of reduced MBP-positive staining area of mPFC [344] and nucleus accumbens [509] in response to social defeat.

Similarly, another study showed a significant decrease of MBP-positive staining in mPFC immediately after the last session of intermittent social defeat stress exposure during early adolescence, which persisted until later in the early adulthood of mice [48]. These conflicting results might be due to several factors, including the regional specificity of the effects, the severity of the defeat, or the duration of follow-up. I found that the length of myelinated segments indicated by MBP immunoreactivity showed a significant positive correlation with social interaction in defeated mice but not in the unstressed control group [509]. This difference suggested that changes in myelinated segments' length represent an adaptive response to the social defeat stress [509]. Furthermore, social behavior is reduced in mice seven days after induced demyelination measured by MBP reduction via focal injection of lysolecithin into the mPFC. The social behavior is restored in mice 21 days after induced demyelination due to increased MBP [509]. This experiment demonstrates that MBP increases social behavior in non-stressful conditions and modulates social behavior under social defeat stress. One proteomic analysis of the frontal cortex showed a significant increase in MBP in the stress resilient group in response to social defeat [342]. However, one study does not support this MBP elevation in the mPFC of resilient mice in response to social defeat. The levels of MBP did not significantly differ between susceptible and resilient mice [509]. These unmatched results might be due to different sample sizes per group: while only three mice per group were used in the study by Valentina Bonnefil [509]. 12 mice per group were used in the study by Viktoria Stelzhammer [342]. Our findings were supported partially by a study that MBP immunoreactivity in mPFC was positively correlated with social interaction in SD mice but not in the control group [509]. Our study discovered a positive correlation between MBP expression in the hippocampus and social interaction ratios with the SD group but not with controls. However, MBP expression in the nucleus accumbens was not significantly correlated to social behavior [509]. Thus, MBP correlation to social score was region dependent, suggesting that MBP in mPFC and hippocampus represent an adapting and coping response to social defeat stress. Our research's significant limitations are that we did not evaluate the MBP expression in response to SD in other brain areas, like the prefrontal cortex. Hence, we cannot conclude that MBP increases in response to SD trauma. Future studies should focus on the MBP expression in various limbic brain regions in response to social defeat to provide an overview of MBP expression in response to stress. Besides, splitting the SD group into susceptible and resilient subgroups and investigating MBP expression in the subgroups can unravel the involvement of MBP in

social behavior.

MBP has a close relationship with MYT1L. MYT1L overexpression in rat oligodendrocyte precursor cells resulted in an elevation of MBP. Increased MBP-positive cells bind to the upstream MBP transcription initiation site [19]. I was interested in knowing how MYT1L is expressed in the mouse brain.

MYT1L was also found to be associated with mental disorders, including depression, schizophrenia [78, 368, 369, 370, 373, 374], intellectual disability [363, 378, 379, 377], autism [380], attention-deficit/hyperactivity disorder [381], epilepsy [382], and PTSD [451] in an attempt better to understand its role in mental and neurodegenerative disorders. In **Chapter 5**, I performed a study to address the research question, "Where is MYT1L protein expressed in the mouse brain?". My study investigated the expression patterns of MYT1L in the mouse brain. **Chapter 5** reports the findings of our immunohistochemistry analyses of MYT1L in the brains of mice. My results showed that MYT1L is widely expressed throughout the mouse brain, including the hippocampus, cortex, striatum, amygdala, and cerebellum. Thus, this expression pattern covers some limbic brain areas of mice's brains, including the hippocampus, cortex, and amygdala, which suggests that MYT1L might be involved in central circuitries involved in cognitive functioning and/or emotion processing. Evidence from other studies has supported our findings that MYT1L is expressed widely in the brain. *Myt1l* mRNA is expressed in the human adult brain's frontal cortex, hippocampus, basal ganglia, and hypothalamus [363].The expression of *myt1l* mRNA was detected in the brain during rat brain development and continued to be expressed at detectable levels in the adult rat brain. By developmental stage P15, MYT1L protein expression is observed in hippocampal formation. *Myt1l* mRNA is restricted to neurons in the CNS. However, *myt1l* mRNA does not exist in the forebrain cultures of the E16 rat. This culture is enriched in astrocytes and oligodendrocytes [355]. However, one study stated that MYT1L protein was expressed in cultured oligodendrocytes from P0 rat cerebra but not in GFAP-positive astrocytes [367]. These conflicting results might be due to the difference in developmental stages of rat brain cultures. None of the studies overviewed the MYT1L protein expression in the brain. Our study filled the gap with the immunohistochemistry study in the whole mouse brain. *Myt1l* mRNA expression reached a maximum on birthdays and decreased during development [355]. These high levels observed during embryonic stages might be related to its roles in pro-neuronal function by direct repression of many different somatic lineage programs except the neuronal program [358]. This pro-neuronal function is critical for the developmental brain. One of the study's significant limitations was the limited sample size and lack of double-labeling experiments. Besides, it is beyond the study to address how MYT1L brain expression changes in response to stress or any correlation to susceptibility because this was not studied. Future studies could focus on cell-type-specific labeling of MYT1L (i.e., performing co-labeling studies with markers of distinct neuronal populations) to see whether MYT1L expresses in various regional subtypes of neurons. Besides addressing the correlation between MYT1L and stress, future studies should investigate associations between MYT1L expression and differential behavioral phenotypes of stress-exposed animals.

Predator odor can successfully induce stress behavior. Moreover, the neural activity in the olfactory system

in the stress response remained unknown. In **Chapter 6**, I addressed the fourth research question of my thesis, "How does predator odor change the neural activity in the olfactory cortex AON compared to non-predatory odor?". In this study, we detect the (excitatory and inhibitor) firing patterns of AON brain regions in response to odor application. Most significant single-unit signals during non-odor application were excitatory compared to baseline activity without odor application. However, predator odor 2MT alone induced more inhibitory responses than excitatory ones.

Furthermore, 2MT induced less inhibitory response than VB and Secba and more inhibitory than IAA. This indicated that non-predator odor could induce an inhibitory response similar to predator odor, but the degree of inhibition varied across different odors. The results of the firing pattern in the AON in the presence of odor can be excitatory and inhibitory, which was supported by the fact that AON harbors excitatory pyramidal neurons and inhibitory interneurons [397]. Most studies used a chemical analog to fox feces, TMT, to test neuronal activity in response to predators [423, 422, 419]. However, the product was not available due to supply reasons. We used 2MT chemically, like TMT, which has been shown to induce fear and anxiety behavior in mice [510, 419]. However, how this product 2MT induces neuronal activity is unknown.

These results prove that AON brain regions are indispensable to odor processing. Our data have contributed to a further overview of how AON responds to odor presentation, including non-predator and predator odor. The AON response to an odor can be excitatory and inhibitory irrespective of the odor's innate meaning. Even though most non-predatory odors induce more excitatory response in AON than inhibitory response, predator odors induce more inhibitory response than the excitatory response in AON, and some non-predatory odors can induce an inhibitory response in AON similar to 2MT.

The study also had limitations. Since we did not test anxiety and depression behavior in the mice after odor presentation, we cannot conclude that the 2MT-induced AON response in our study indicated innate fear response directly, though 2MT successfully induced freezing behavior in other studies [510, 419]. In one session, the non-predator odors were only 3 (VB, Secba, and IAA) tested with predator odor 2MT. Due to the limited non-predator odor selection, we could only see the inhibitory response in both predator and non-predatory odors.

Future studies should perform a series of behavior tests after the 2MT odor presentation to confirm that the neuronal activity recorded corresponds to innate fear. Future experiments should test more non-predator odors and 2MT or other predator odors like cat urine in one session.

In **Chapter 7,** I addressed the research question, "How does social defeat affect the subjects along with time? Can physical activity increase resilience to traumatic stress?"

Using a large-scale animal study in which mice were exposed to social defeat stress, our analyses showed that SD has detrimental effects on behavior and stress physiology. Furthermore, the LT cohort showed a less pronounced SD effect than ST via different behavioral results. However, increasing physical activity before exposure to chronic social defeat did not show resilience-enhancing properties in response to SD exposure. Our findings suggest that

chronic social stress negatively impacts mice behavior and is differentially associated with behavioral outcomes in ST and LT follow-up groups. However, physical activity did not exert a stress-resistant impact on SD stress. Our study partially confirmed the hypothesis that SD negatively impacts mice's behavior and stress physiology. However, SD did not affect anxiety but increased social behavior and suppressed corticosterone concentration, which was not an appliance to our hypothesis. Besides, the LT follow-up cohort showed less SD impact than ST, which was fully confirmed in our study. Lastly, physical activity did not bring resilience to mice exposed to SD, which was out of our hypothesis.

Contrary to our study, many studies reported that social defeat would increase anxiety [511, 512]. These conflicting results might be due to the EZM test being performed for a longer time (14 days in ST) after the SD stress paradigm, which results in recovery to some degree in mice.

In our study, the SD mice in ST and LT showed more social behavior than their controls, contrary to other studies that reported that SD mice showed less social behavior than controls [441, 513, 48]. These conflicting results might be due to a compensatory mechanism in response to stress. Some studies reported overeating behavior in response to stress in humans [514] and mice [515]. One study reported that social and physical stress alone would reduce prosocial behavior. Furthermore, combining the two stressors could restore pro-sociality in healthy young participants [516]. Our SD stress paradigm in mice combined physical and social stress, like in human studies. The reason might be that social anxiety modulated trust behavior significantly, with higher social anxiety levels associated with increased trust [516].

Our study showed SD increased sucrose intake one month after the SD stress paradigm in the LT, which indicated reduced anhedonia behavior, but without a difference ten days after SD stress in the ST group between treatments. In contrast, many other studies reported that SD rodents showed reduced sucrose intake than controls immediately or two days after stress [488, 511]. One study showed that SD mice reduced sucrose intake during the SD paradigm but did not show sucrose preference seven days after stress [441]. These studies showed anhedonia behavior during SD or days after SD, while our study reported long-term follow-up compared to the earlier studies. Even the ST follow-up cohort was examined ten days after the SD stress paradigm, which was a long wait for recovery. It is reasonable to have no significant results in the Sucrose preference test in our ST cohort because the period is enough to recover from stress. Besides, our study indicated a long-term effect on SD stress in sucrose preference.

Furthermore, our study showed that physical activity did not exhibit resilience-enhancing properties in response to SD exposure. However, other studies discovered that voluntary wheel running promoted resilience to chronic social defeat stress in mice [470, 517]. This conflicting result might be because the running wheel for physical exercise was taken away from the cages during recovery time in our study, introducing stress. Another difference is that these studies monitor the wheel's speed instead of the time wheel stays in the cage. One limitation of our study was that the mice arrived at different time points, resulting in group differences.

Thus, the findings of our study suggested that social defeat increases social behavior, which might be due to a

combination of social stress and physical stress in the SD paradigm modulating social trust in mice and restoring or increasing social behavior. Besides increased social behavior in response to stress, we have reported increased sucrose intake one month after social defeat, indicating reduced anhedonia behavior after social defeat. Most studies only focus on hours, days, and weeks after social defeat. We tested sucrose intake more than one month after social defeat stress, which may reflect evidence of enhanced eating behavior or altered metabolism in response to stress in human studies [518].

Given that we did not see physical activity's effect on social defeat stress, it could be concluded that physical activity does not exert resiliency to stress. Lastly, whether social defeat increases social behavior remains controversial, and future studies should focus on the correlation between social trust and social defeat. I would recommend future studies to avoid batch differences and advise running wheels to remain in the cage throughout the experiment.

Concluding remarks

My study underscored many genetic and environmental factors linked to mental and neurodegenerative disorders, including DUSP and myelin-related genes. Dusp family genes encoded phosphatase play a role in mental and neurodegenerative disorders. One of the dusp genes, dusp22, may be particularly important as a candidate gene. I found that DUSP22 was prevalently expressed throughout the mouse brain.

The myelin-related genes, MBP, showed increased protein expression in the CA1 region of the mouse brain's hippocampus in response to the SD stress paradigm. Also, the myelin-related gene MYT1L showed prevalent expression in the mouse brain.

Predator odor is a natural threat to rodents and can induce anxiety or fear behavior [409, 387]. Contrary to cat odor effects in the amygdala [421], our study showed that fox odor analog, 2MT inhibited firing pattern rodents AON of the olfactory brain structure.

Social stress is one of the common environmental factors contributing to mental and neurodegenerative disorders. SD paradigm had an impact on behavior in mice. Contrary to other studies, our study showed that SD increased social behavior, and physical exercise did not promote social stress resilience.

Future studies of the dusp22 gene may focus on comparing its protein expression and its upstream or downstream regulators in the post-mortem human brains of various mental and neurodegenerative disorders. Moreover, manipulating *dusp22* in rodents could unravel the mechanism of the role DUSP22 played in stress-related behavior. For instance, the genetic knockout or knockdown of *dusp22* in rodents can observe behavioral changes in various behavior tests. Future studies of myelin-related genes should focus on how *myt1l* and *mbp* change in response to stress in all the limbic brain regions. Whether physical exercise promotes resilience to stress should have prolonged physical exercise time and running wheels throughout the various tests. Predator odor-induced stress should have behavior tests on these mice to confirm that they were stressed.

The findings reported in my thesis serve as an important step in elucidating the mechanisms underlying the response to several stressors.

Chapter 9

Impact and valorization

Mental health and neurodegenerative disorders pose enormous personal and socioeconomic burdens worldwide. Among the mental disorders, schizophrenia and bipolar disorder have the lowest prevalence. However, they are associated with severe impairment, while major depressive disorder has a median prevalence rate of more than 5 % of the population with an enormous impact, as measured in disability-adjusted life years. Over the past generation, the global burden of neurodegenerative disorders like Parkinson's and Alzheimer's disease has more than doubled due to the increasing number of older people. The neurodegenerative disease frequently disrupts emotional, cognitive, and social behavior. However, many patients and their families do not receive adequate care. Besides, neurodegenerative disorders are most common among older adults who usually have a pension, while stress-induced psychiatric disorders are most common among young and middle-aged people who should be the most productive power in society. Therefore, research on psychiatric disorders could potentially improve the lives of many of the most productive age groups and benefit a country's GDP.

Treating psychiatric disorders suppresses symptoms and may induce various side effects. Similarly, treating neurodegenerative diseases does not cure them but may (at best) reduce the progression. A better understanding of the mechanism underlying mental health and neurodegenerative disorders is needed to pave the way to better treatment and prevention.

The current widely accepted framework in stress-related mental disorders is the Gene-Environment interaction model. The idea of the framework results from two common findings: one is that mental disorders have environmental causes, and the other is that people respond differently to the same environmental stressors. Later, the model is better revised as poly-gene-environmental causation of mental illness. To fulfill the framework's potential, we join the forces of neuroscience. The work presented in this dissertation attempts to understand several genetic players underlying susceptibility to traumatic stress in the neurons of patients or rodent models. Besides, scientific work should always have societal implications. We discuss chapter by chapter.

In **chapter 2**, the review highlights that *dusp* family genes have a close relationship with mental and neurodegenerative diseases. The *dusp* family genes are not fully understood in the mechanism of mental disorders. Most studies are correlational, not causal. Therefore, this thesis highlights more research on the future causal relationship between *dusp* genes and mental disorders. Besides, the involvement of the *dusp* family gene in mental disorders fits the poly-gene-environmental framework. The poly-genetic causes of mental disorders could relieve a small amount of the blame game within families while treating adolescents diagnosed with mental disorders. For example, parental barriers are very common in providing health care to adolescents diagnosed with depression. More than half of the adolescents do not have access to treatment due to parental motivation and support. The major concern is that parents do not want to get blamed for their upbringing style (environmental factor) that might bring about their child's mental disorders. Although this thesis does not deny the environmental factors in the onset of mental disorders, the poly-genetic findings could partly relieve the guilty feelings of parents or the anger of the sick child.

In **chapter 3**, we focus on the protein expression pattern of these related genes and the change of their expres-

sion in response to stress in the brains of mice. One of the genes, *dusp22,* which belongs to the limbic brain regions involved in psychiatric disorders, is expressed prevalently in the mouse brain. This finding is another evidence of studying brain evolution: our brains evolved from vertebrates' simpler and smaller brains. The phylogenetic approach assumes that living mammals contain primitive traits or features maintained from a distant ancestor. Thus, traits common to clade members are considered to be most likely inherited from a common ancestor rather than independently evolved specializations. The common traits between mice and the human brain are likely to originate from the common ancestors of mammals. Stress-related gene *dusp22* and its translated protein DUSP22 are expressed prevalently in the stress-related brain regions, the prefrontal cortex. The common features of DUSP22 expression can be evidence of the common ancestor of humans and mice. In addition, this common feature legitimates studying the human brain via investigating mice brains alongside other common features. Although other primates are more closely related to humans, mice are more available and have fast reproductive rates, which is ideal for scientific research.

In **chapter 4**, MBP protein expression increased in the CA1 of the hippocampus of mice in response to social defeat. MBP is a marker of myelination, and many psychiatric disorders show alterations in myelin. Myelin ensheathment allows fast and efficient conduction of nerve impulses through the nodes of Ranvier, improving the overall function of neuronal circuits [569]. Our study demonstrates the myelin alterations in the hippocampus of mice exposed to social defeat, indicating that stress is associated with the myelin alterations in the brain. This gives insight into the impact of stress and the potential harm to the human brain in modern society. Morden humans are suffering from more chronic stress than ever before. Penn State researchers looked at data from 1,499 adults collected in 1995 and then from 782 different adults 17 years later in 2012. Both different groups were interviewed daily for eight straight days. They were asked about stressful experiences they had over the past 24 hours. Researchers found that day-to-day stress and a sense of lower overall well-being were much higher in the 2010s compared to the 1990s [519]. Reducing stress practices could be a healthy lifestyle in modern society.

In addition, our study shows brain alterations in the hippocampus, which might indicate memory deficits, and future research could focus on memory and MBP in the hippocampus for further understanding.

Besides the *mbp*genes, *myt1l* in **chapter 5** is expressed prevalently in the limbic brains of mice. Meanwhile, variations in *myt1l* have been associated with autism, intellectual disability, and schizophrenia in humans. This finding shows the common gene between humans and mice and could be a basic foundation for studying autism, intellectual disability, and schizophrenia via mouse models. Recent manipulation of *myt1l* in mice successfully mimics the human phenotype of autism-related social impairments, especially in males [520].

Chapter 6 tested the neuronal firing pattern in awake-behaving mice exposed to fox-urine odor chemicals 2MT. This study is different from previous studies because it tests the real-time neuronal reactions of mice to stress-related odors. With the availability problem of TMT fox odor in research materials, 2MT is a substitute for widely researched TMT. However, the related research literature is scarce, and this study provides a reference for

future research on fox-odor-induced stress in mice. In addition, AON is a brain structure receiving information from the hippocampus, and this connection gives a good foundation for researching traumatic experiences recalled by the odor. For instance, the burning BBQ might remind the combat soldiers of their traumatic memories of burning flesh during wartime. As we know, a war is going on in Ukraine, and the Ukrainian soldiers are traumatized by the odor in the warzone, including burning gasoline, bodies, and gun powders. I hope this study could benefit the research aimed at combat soldiers.

Furthermore, the study found that most non-predator odors induced excitatory responses in AON. In contrast, the predator odor 2MT induced predominantly inhibitory AON responses. This result indicates that predatory odor inhibits neuronal activity in AON, and this discovery does not show direct application but indirectly gives implications for future research, like neuronal response between natural innate fear and conditioned fear in mice.

We used the social defeat paradigm as a stress model. The social defeat paradigm is one stress paradigm that successfully induces psychiatric disorders-like behavior in rodents. In **chapter 7**, we did an animal experiment using social defeat, showing surprising results contrary to other studies. For instance, socially defeated mice showed increased social behavior. Physical exercise did not promote resilience to stress inflicted by social defeat.

Further investigation is needed to confirm the results by modifying the social defeat paradigm to avoid severe injuries or animal loss. Another modification of the experiment is the homogeneous control of mice or randomization. For example, the mice's arrival should be under the same circumstances between the long-term and short-term cohorts. The third modification is the daily handling of the control and stress groups to avoid bias between stress and non-stressed control groups. Lastly, the physical exercise should be arranged along with the experiment timeline until the end.

So, upon reflection on the impact of my work on various levels, I cannot find a once-and-for-all answer to mental disorders. The progression of a tiny step requires much work, which can not help the suffering people right now, but hopefully for the people in the future.

Chapter 10

Curriculum vitae

An Ning was born in Gansu, China, on October 20th, 1988. She obtained her high school degree in 2007 at Shenzhen Foreign Languages High School. In 2007, she started her education at Southern Medical University in Guangzhou, where she enrolled in the Applied Psychology Bachelor's program. She obtained her Bachelor's degree in 2011 and continued a Master's program in Physiology of neuroscience. During her Master's program, she researched adult neurogenesis in the rostral migration stream of Amyloid Precursor Protein knock-out mice. In 2015, she obtained her Master's degree. She went to Maastricht University to start her Ph.D. in the mental health and neuroscience department. She was under the supervision of Prof. Dr. Bart Rutten, Prof. Dr. Harry Steinbusch, Dr. Laurence de Nijs, and Prof. Dr. Markus Rothermel. During her Ph.D., she studied the expression of various genes related to psychiatric disorders in the mice brain and post-mortem tissue. Besides, she investigated how the social defeat paradigm changes mice's behavior and whether physical exercise promotes resilience to stress. Afterward, she went to Aachen University under the supervision of Prof. Dr. Markus Rothermel. She studied the firing pattern in the olfactory system in the presence of predator odor in mice.

Chapter 11

List of publications

1 **An, N**., Bassil, K., Al Jowf, G. I., Steinbusch, H. W., Rothermel, M., de Nijs, L., & Rutten, B. P. (2020). Dual-specificity phosphatases in mental and neurological disorders. Progress in Neurobiology, 101906.

2 Zwamborn, R. A., Snijders, C., **An, N**., Thomson, A., Rutten, B. P., & de Nijs, L. (2018). Wnt signaling in the hippocampus in relation to neurogenesis, neuroplasticity, stress and epigenetics. Progress in molecular biology and translational science, 158, 129-157.

3 Chai, J., Xu, H., **Ning, A**., Zhang, P., Liu, F., He, S., ... & Li, Y. The prevalence of mental health problems for Chinese children and adolescents during COVID-19 in China: A meta-analysis. Frontiers in Pediatrics, 872.

4 Li, Yanlin, Hu Deng, Huan Wang, Cody Abbey, Yi Zheng, Jingxu Chen, **Ning An** et al. "Building the mental health management system for children post COVID-19 pandemic: an urgent focus in China." European Child & Adolescent Psychiatry (2021): 1-4.

5 Al Jowf, G. I., Ahmed, Z. T., **An, N**., Reijnders, R. A., Ambrosino, E., Rutten, B. P., ... & Eijssen, L. M. (2022). A Public Health Perspective of Post-Traumatic Stress Disorder. International Journal of Environmental Research and Public Health, 19(11), 6474.

Chapter 12

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Appendix A

Appendix

A.1 DUSP genes family members

Table A.1: DUSP genes family members.

DUSP genes family members					
Family	Isoforms	Synonym	Gene ID	MIM*	Chromosome
Slingshot	SSH1	SSH1L	54434	606778	12q24.11
	SSH2	SSH2L	85464	606779	17q11.2
	SSH3	SSH3L	54961	606780	11q13.2
PRLs	PRL1	PTP4A1	7803	601585	6q12
	PRL2	PTP4A2	8073	601584	1p35.2
	PRL3	PTP4A3	11156	606449	8q24.3
CDC14s	CDC14A	hCDC14	8556	603504	1p21.2
	CDC14B	HCDC14B	8555	603505	9q22.33
	CDC14C	CDC14CP	168448	N/A	7p12.3
PTENs	PTENα	PTENα	N/A	N/A	N/A
	PTENβ	PTENβ	5728	601728	10q23.31
Myotubularin	MTM1	MTM1	4534	300415	Xq28
	MTMR1	MTMR1	8776	300171	Xq28
	MTMR2	MTMR2	8898	603557	11q21
	MTMR3	MTMR3	8897	603558	22q12.2
	MTMR4	MTMR4	9110	603559	17q22
	MTMR5	SBF1	6305	603560	22q13.33

Continuation of Table A.1

Family	Isoforms	Synonym	Gene ID	MIM*	Chromosome
	MTMR6	MTMR6	9107	603561	13q12.13
	MTMR7	MTMR7	9108	603562	8p22
	MTMR8	MTMR8	55613	N/A	Xq11.2
	MTMR9	MTMR9	66036	606260	8p23.1
	MTMR10	MTMR10	54893	N/A	15q13.3
	MTMR11	MTMR11	10903	N/A	1q21.2
	MTMR12	MTMR12	54545	606501	5p13.3
	MTMR13	SBF2	81846	607697	11p15.4
MKPs	MKP1	DUSP1	1843	600714	5q35.1
	MKP2	DUSP4	1846	602747	8p12
	MKP3	DUSP6	1848	602748	12q21.33
	MKP4	DUSP9	1852	300134	Xq28
	MKP5	DUSP10	11221	608867	1q41
	MKP7	DUSP16	80824	607175	12p13.2
	PAC1	DUSP2	1844	603068	2q11.2
	Hvhr3	DUSP5	1847	603069	10q25.2
	MKP-X	DUSP7	1849	602749	3p21.2
	Hvh5	DUSP8	1850	602038	11p15.5
	MK-STYX	STYX-L1	51657	616695	7q11.23
Atypical	Laforin	EPM2A	7957	607566	6q24
	STYX	STYX	6815	615814	14
	DUSP3	VHR	1845	600183	17q21
	DUSP11	PIR1	8446	603092	2p13.2
	DUSP12	YVH1	11266	604835	1q23.3
	DUSP13A	TMDP	51207	613191	10q22.2
	DUSP13B	MDSP	51207	613191	10q22.2
	DUSP14	MKP-L	11072	606618	17q12
	DUSP15	VHY	128853	616776	20q11.21
	DUSP18	LMWDSP20	150290	611446	20q12.2
	DUSP19	SKRP1	142679	611437	2q32.1
	DUSP21	LMWDSP21	63904	300678	Xp11.3
	DUSP22	JSP1	56940	616778	6p25.3

Continuation of Table A.1					
Family	Isoforms	Synonym	Gene ID	MIM*	Chromosome
	DUSP23	LDP-3	54935	N/A	1q23.22
	DUSP26	LDP-4	78986	N/A	8p12
	DUSP27	DUPD1	92235	N/A	10q22.2
End of Table					

Note: N/A:Not Available. MIM: Online Mendelian Inheritance in Man®

A.2 Atypical DUSP genes members

Table A.2: Atypical DUSP genes members

Atypical DUSP genes members		
HUGO	Patterson	Huang and Tan
DUSP3	DUSP3	DUSP3
DUSP11	DUSP11	DUSP11
DUSP12	DUSP12	DUSP12
DUSP13A	DUSP13A	DUSP13
DUSP13B	DUSP13B	
DUSP14	DUSP14	DUSP14
DUSP15	DUSP15	DUSP15
DUSP18	DUSP18	DUSP18 (DUSP20)*
DUSP19	DUSP19	DUSP19
DUSP21	DUSP21	DUSP21
DUSP22	DUSP22	DUSP22
DUSP23	DUSP23	DUSP23
DUSP26	DUSP26	DUSP26(DUSP28;DUSP24)*
DUSP27	DUSP27	DUSP27
Laforin	Laforin	
STYX	STYX	
	DUSP1	
	DUSP2	
	DUSP6	
	DUSP5	
End of Table		

Note:* DUSP18 was renamed to DUSP20 while DUSP24 and DUSP28 were changed to DUSP26.

A.3 DUSP protein or RNA expression in animal and human brain

Table A.3: DUSP Protein or RNA expression in animal and human brain

DUSP Protein or RNA expression in animal and human brain				
Isoforms	Expression	Protein/mRNA	Species	Ref.
SSH1	Frontal cortex	Protein	Human	[100, 101]
	Cerebellum			
	Primary cortical neurons	Protein	Mice	[100]
	Ganglion neurons	Protein	Chick	[104]
SSH2	Brain	mRNA	Mice	[521]
	Thalamus			
	Hippocampus			
SSH3	Hippocampus	mRNA	Human	[231]
	Temporal gyrus			
	Frontal gyrus			
	Prefrontal cortex	mRNA	Mice	[522]
	Hypothalamus			
	Amygdala	mRNA	Mice	[523]
PRL2	Cerebellum	mRNA	Human	[118]]
	Cerebral cortex			
	Neuronal lineages	mRNA	Zebrafish	[524]
CDC14A	Cortical slices	mRNA	Human	[525]
	Cerebral cortex	Protein	Human	*[296]
hCDC14Bpar	Adult/fetal brain	mRNA	Human	[128]
hCDC14B1	Hippocampus	mRNA	Human	[128]
	Prefrontal cortex			
	Amygdala			
	Hypothalamus			
hCDC14B2	Hippocampus	mRNA	Human	[128]
	Prefrontal cortex			
	Amygdala			
	Hypothalamus			
hCDC14B3	Hippocampus	mRNA	Human	[128]
	Prefrontal cortex			

Continuation of Table A.3				
Isoforms	Expression	Protein/mRNA	Species	Ref.
	Amygdala			
	Hypothalamus			
hCDC14C	Adult brain	mRNA	Human	[128]
	Embryonic forebrain,			
	Dorsal telencephalon			
PTENs	Cerebral cortex	Protein	Human	*[296]
	Cerebellum			
	Hippocampus			
	Anterior olfactory nucleus	Protein	Rat	[143]
	Cerebral cortex			
	Amygdaloid nucleus			
	Hippocampus			
	Purkinje's cells			
	Basal ganglia			
	Thalamus			
	Midbrain Pons			
	Ventral prefrontal cortex	Protein	Human	[167]
	Layer III temporal cortex	Protein	Human	[234]
	Frontal cortex	Protein	Human	[237]
Myotubularin	Spinal cord	mRNA	Human	[149]]
	Substantia nigra			
	Cerebral cortex	Protein	Human	*[296]
	Hippocampus			
	Cerebellum			
MKP1	Hippocampus	Protein/mRNA	Human/Mice	[174]
(DUSP1)	Caudate	mRNA	Human	[269]
	Temporal cortex	Protein	Human	[228]
	Cerebral cortex	Protein	Human	[158]
	Cerebellum			
	Striatum	mRNA	Mice	[269]
	Striatum	mRNA	Rat	[526]
	Thalamus Cortex			

Continuation of Table A.3

Isoforms	Expression	Protein/mRNA	Species	Ref.
	Neocortex	Protein	Rat	[287]
	BNST			
MKP2	Cerebellar vermis	Protein	Human	[212]
(DUSP4)	Cortex	Protein	Human	[158]
	Hippocampus			
	Cerebellum			
	The medial prefrontal cortex	mRNA	Rat	[182]
	Lateral frontal cortex			
	Parietal cortex			
	Hippocampus			
MKP3	The medial prefrontal cortex	mRNA	Rat	[182]
(DUSP6)	Lateral frontal cortex			
	Parietal cortex			
	Hippocampus			
	Ventromedial PFC	mRNA	Human/Mice	[183]
	Striatum	mRNA	Rat	[526]
	Cortex			
	Hippocampus			
PAC1	Hippocampus	Protein/mRNA	Mice	[527]
(DUSP2)	Hippocampus	mRNA	Human	[174]
Hvhr3	Brain (not specified)	mRNA	Mice	[528]
(DUSP5)	Nucleus accumbens	mRNA	Mice	[529]
	Medial prefrontal cortex	mRNA	Rat	[530]
MKP-X	Whole-brain	mRNA	Mice	[531]
(DUSP7)				
Hvh5	Amygdala	mRNA	Human	[532]
(DUSP8)	caudate nucleus			
	Corpus callosum			
	Hippocampus			
	Hypothalamus Thalamus			
	Subthalamic nucleus			
	Substantia nigra			

Continuation of Table A.3

Isoforms	Expression	Protein/mRNA	Species	Ref.
MTMR2	Cortex	Protein/mRNA	Rat	[533]
	Hippocampus			
	Cerebellum			
MTMR5	Brain	Protein	Mice	[534]
	The sciatic nerve			
Laforin	Cerebellum	mRNA	Mice	[535]
(EPM2A)	Hippocampus			
	Cerebral cortex			
	Olfactory bulb			
DUSP12	Hippocampus	mRNA	Human	[174]
DUSP14	Retinal ganglion cells	mRNA	Rat	[536]
DUSP15	Schwann cell	mRNA	Rat	[537]
	Myelinating Oligodendrocytes	mRNA	Rat	[538]
DUSP18	Fetal brain	mRNA	Human	[539]
DUSP19	Hippocampus	mRNA	Human	[174]
	Ventral subiculum	mRNA	Human	[183]
DUSP22	Hippocampus	Protein	Human	[233]
DUSP23	Nucleus accumbens	mRNA	Human	[183]
	The Broadman area			
DUSP26	Hippocampus	Protein/mRNA	Human	[230, 174]

End of Table

Note:* (www.proteinatlas.org)

BNST:The bed nucleus of the stria terminalis

A.4 DUSP genes in normal and pathological brain function

Table A.4: DUSP genes in normal and pathological brain function

DUSP genes in normal and pathological brain function		
Isoforms	Function in Normal Brain	Function in Pathological Brain
SSH1	SSH1 along with Cofilin1 promoted dynamic changes in the cytoskeleton needed for axon engagement like growth cone collapse and neurite outgrowth, and myelination in Schwann cells in rat [111, 112]	SSH1 reduced and remained inactive as Cofilin1 in the frontal cortex of sporadic AD in human [100].
	SSH1 increases growth cone motility and extension, and the growth cone becomes slender and branchy in chick [104]	SSH1 reduced protein level and became inactive as Cofilin1 in the brain of APP/PS1 mice model of AD [100].
SSH3		SSH3 mRNA is differentially regulated gene in hippocampus tissue, temporal gyrus tissue, frontal gyrus tissue and whole blood in patients diagnosed with AD [231]. SSH3 mRNA has been found to be downregulated in central amygdala Drd2-expressing population following foot shock fear conditioning compared to controls in mice [523]. SSH3 mRNA is over expressed in prefrontal cortex, and hypothalamus in mice subjected to maternal separation for 3 h per day and lasted for 14 days [522].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
PRL3		PRL3 promotes cell proliferation, migration, and invasion in glioblastoma cells in Human [540, 541]
CDC14A	CDC14A involved in cell cycle regulation of human brain vascular endothelial cells following injury induced by high glucose, free fatty acids, and hypoxia [542].	Upregulated in response to Amyloid-Oligomers in adult human cortical brain slices [525].
CDC14B	Regulates RNA polymerase II and represses cell cycle transcription in primary mouse embryonic fibroblasts [543].	Involved in glioblastoma growth in human [544]
PTENs		PTEN single nucleotide polymorphisms associated with increased risk of depression in a Chinese cohort [166].
		PTEN protein levels are higher in post-mortem lysates of the ventral prefrontal cortex from suicide victims diagnosed with depression when compared to non-depressed healthy controls [167].
	PTEN moved to nucleus and promoted neuron survival in mice [545]	PTEN recruitment controls synaptic and cognitive function in AD model App/Psen1 mice [239].
	PTEN and β-catenin signaling regulates normal brain growth trajectory by controlling cell number, and imbalance in this relationship can result in abnormal brain growth in mice [546].	PTEN mediates brain growth during development and PTEN mutation-induced Autism-like behavior in mice [546, 547, 548, 549, 550].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
		PTEN mutations are late events in the malignant progression of glioma, and the occurrence of PTEN mutations are significantly correlated to patients' short-term survival [551]. PTEN mutation coexisted with autism behavior and macrocephaly in human [552].
MKP1(DUSP1)	MKP1 controls axon branching induced by BDNF signaling via mediating JNK deactivation in mice [553]. MKP-1 functions in light-dependent and time-of-day-dependent manners in the mice central clock structure-the suprachiasmatic nucleus [554].	Depression mice model showed increased hippocampal MKP1 expression, which can be normalized by antidepressant, while mice lacking MKP1 are resilient to stress [174]. MKP1 mRNA increased in the DG and CA1 of human diagnosed with depression [174]. Increased MKP-1 expression levels could be the cause of the high resistance to conventional chemotherapeutics in human glioblastoma multiforme in human [555] DUSP1 protein levels increased in the hippocampus [177] and the ventrolateral orbital cortex [178] of stressed rats when compared to controls.

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
MKP2(DUSP4)	MKP2 promotes neuroplasticity and memory, and its deletion impairs synaptic plasticity and hippocampal-dependent memory in mice [556]	MKP2 were significantly decreased in cerebellar vermis from schizophrenic patients compared to control subjects [212]. MKP2 was increased in BAs 8, 9, 10, and hippocampus, without any change in the cerebellum of depressed suicide subjects compared with control subjects [158].
MKP3(DUSP6)	DHA-enriched fish-oil induced MKP3 that enhance GFAP in developing rat brain astrocytes [557]	DUSP6 mRNA was differentially expressed in post-mortem tissue ventromedial PFC of patients with depressive disorder in a sex-specific manner [183].
Hvhr3(DUSP5)	Regulate the signaling of pressure-dependent myogenic cerebral arterial constriction in rat [558]	DUSP5 served as transcriptional target of tumor suppressor p53 in glioblastoma in human [559].
MKP-X(DUSP7)	The expression of DUSP7 was mediated by ERK1/2 activity both in resting and LPS-stimulated microglia in rat [560].	DUSP7 mRNA expression was reduced in the whole brain after chronic amphetamine injections in mice [531].
Hvh5(DUSP8)	Abundant in human and mice brain and inactivate mitogen-activated protein kinase [532]	Hvh5 mRNA was induced in the nucleus accumbens, caudate putamen, frontal cortex, and hippocampus by i.p. Injection of cocaine and fluoxetine in rat [561].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
MK-STYX (STYX-L1)	MK-STYX induced neurite extensions through the Rho signaling pathway and forms synapse in PC-12 cells. MK-STYX altered their morphology in primary hippocampal neurons in rat [562, 563]	MK-STYX missense mutation was identified in intellectual disability, accompanied by seizures and behavioral problems in human [564]. MK-STYX was differentially expressed in the blood of depression patients [565, 566] or depressive-like behavior in mice [566].
MTMR2	MTMR2 contributes to the maintenance of excitatory synapses by inhibiting excessive endosome formation and destructive endosomal traffic to lysosomes in rat [533] MTMR2 interacted with the neurofilament light chain protein, NF-L, in both Schwann cells and neurons in rat and human [153].	Loss of MTMR2 in Schwann cells causes CMT4B1 neuropathy, which is characterized by a dysmyelinating neuropathy with myelin outfoldings in mice [567] Mutation in the MTMR2 gene is a causative mutation in patients with Charcot-Marie-Tooth Disease Type 4B1 [568].
MTMR4		MTMR4 was differentially expressed between grade II-III gliomas and (grade IV) glioblastomas in human [569].
MTMR5(SBF1)	MTMR5 suppress neurite growth in hippocampal neurons in rat. Overexpression of MTMR5 reduce hippocampal neurite outgrowth [570].	SBF1 mutations may cause a syndromic form of autosomal recessive axonal neuropathy (AR-CMT2) in addition to CMT4B3 in Human [571].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
MTMR7		An intronic variant was identified in the genetic locus of MTMR7 linked to variant Creutzfeldt-Jakob disease susceptibility in human [572]. MTMR7 was differentially expressed in the substantia nigra of patients with PD in the GWAS study [573].
MTMR8		The copy number loss for MTMR8 was identified in 65 % of the glioblastoma multiforme patient sample [574].
MTMR10		MTMR10 was affected via 15q13.3 microdeletion and displayed strong phenotypes related to autism-like behavior [575, 576] and autism like behavior in mice. MTMR10 was affected via 15q13.3 deletion and was present in ADHD patients [577].
MTMR11		MTMR11 was frameshift mutated in children with epileptic encephalopathies [578]
MTMR13		Mtmr13-/- mice show both the initial dysmyelination and later degenerative pathology of [579, 580].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
		Mutation in the MTMR13 gene associated with a classical Charcot-Marie-Tooth 4B2 phenotype in human [581, 582]
Laforin(EPM2A)		The phosphatase activity of laforin is dispensable to rescue Epm2a -/- mice from Lafora disease [583]. EPM2A gene was expressed lower to control cells in fibroblasts from Lafora disease in human [584]. EPM2A gene has 11 kinds of mutations in the patients of Lafora disease in human [585].
DUSP11		DUSP11 mRNA was downregulated in the model of nicotine-induced seizures in mice [586].
DUSP13A		DUSP13A interacts with the N-terminal domain of Apoptosis signal-regulating kinase 1 in an oxidative stress-independent manner in brain neuroblastoma. The knock-down of DUSP13A decreased the phosphorylation and activation of apoptosis signal-regulating kinase 1 [587].
DUSP14	DUSP14 is a direct negative-feedback mechanism of MDMA-induced ERK signaling in the striatum of mice [588].	DUSP14 mRNA was upregulated in the frontal cortex in response to Environmental chronic mild stress in mice [589].

Continuation of Table A.4		
Isoforms	Function in Normal Brain	Function in Pathological Brain
	DUSP14 was a gene target limiting axon growth and regeneration downstream of Krűppel-like transcription factor 9 (KLF9)'s ability to suppress axon growth in retinal ganglion cells of rat [536].	DUSP14 was the delayed primary response genes downregulated in DG neurons of mice experienced foot shock after 24 hours in mice [590]. DUSP14 was decreased in HD mice and can be enriched after pridopidine treatment in mice [591]
DUSP15	DUSP15 is necessary for full activation of ERK1/2 phosphorylation and represses expression of several myelin genes, including myelin basic protein, in Schwann cells of rat [537]. DUSP15 influences oligodendroglial differentiation and myelin gene expression in rat [538]	The SNP (rs3746599) of DUSP15 was significantly associated with autism in human [206].
DUSP19		The mRNA levels of DUSP19 were increased in the dentate gyrus from depression postmortem tissue [174].
DUSP22		The promoter hypermethylation of the DUSP22 gene was identified in the hippocampus from controls and AD patients. DUSP22 inhibits PKA activity and thereby determines tau phosphorylation status and CREB signaling [233].

Continuation of Table A.4

Isoforms	Function in Normal Brain	Function in Pathological Brain
		DUSP22 gene promoter showed higher DNA methylation levels in the famine-exposed schizophrenia patients compared to non-famine exposed groups [214]. Increased DNA methylation within/around the DUSP22 gene was linked to increased PTSD symptoms in human [41]
DUSP23	DUSP23 affected neuronal differentiation in mice. The knock-down of DUSP23 decreased neuronal differentiation in terms of neuronal outgrowth and the expression of neuronal marker proteins [592].	The mRNA expression of the gene DUSP23 was significantly lower in patients that have died from the disease compared with neuroblastoma patients with no evidence of disease [593].
DUSP26	DUSP26 suppresses receptor tyrosine kinases and regulates neuronal development in zebrafish [594].	DUSP26 was differentially expressed between grade II-III gliomas and (grade IV) glioblastomas in human [569]. DUSP26 inhibition via NSC-87877 function in neuroblastoma, resulting in decreased tumor growth and increased p53 and p38 activity in mice [595]. DUSP26 expression and JNK activation were enhanced in the hippocampus of AD patients [230].
DUSP27		The variant rs950302 of cytosolic gene DUSP27 associate with heroin addiction vulnerability in African Americans [596].

End of Table

AD: Alzheimer's disease; HD: Huntingdon's disease; CMT4: Charcot-Marie-Tooth Neuropathy Type 4.

A.5 DUSP genes expression in non-brain tissues in animal and human

Table A.5: DUSP genes expression in non-brain tissues in animal and human

DUSP genes expression in non-brain tissues in animal and human				
Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
SSH1	PC-3 Cell	Human	Protein	[597]
	aortas	Mice	Protein	[598]
	keratinocytes	Human	Protein	[102]
SSH2	carcinoma cell lines	Human	Protein/mRNA	[599]
	vascular smooth muscle cell	Rat	mRNA	[600]
	PC12 Cell	Human	Protein	[601]
	CD4+ T cells	Human	Protein	[602]
	keratinocytes	Human	Protein	[102]
SSH3	colorectal cancer	Human	Protein/mRNA	[603]
	prostate cancer	Human	Protein	[604]
	blood	Human	mRNA	[231]
PRL1	liver, intestine	Mice	Protein/mRNA	[605]
	mid guts	Drosophila	mRNA	[524]
	testis	Mice	Protein	[606]
	prostate	Human	mRNA	[607]
	ovarian cancer	Human	Protein/mRNA	[608]
PRL2	lung cancer	Human	Protein/mRNA	[609]
	ovarian cancer	Human	Protein/mRNA	[608]
	testis	Mice	Protein	[606]
	thymocyte	Mice	mRNA	[610]
	skeletal muscle	Mice	Protein/mRNA	[611, 120]
PRL3	colon cancer	Mice/Human	Protein/mRNA	[612, 613]
	prostate cancer	Human	Protein/mRNA	[614]
	ocular melanoma cells	Human	Protein	[615]
	breast cancer	Human	Protein/mRNA	[616]
	skeletal muscle, heart	Human	mRNA	[119]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
	skeletal muscle, heart	Mice	mRNA	[120]
CDC14A	brain vascular endothelial cell	Human	Protein	[542]
	oocytes	Mice	Protein	[617]
	gastric tissue	Human	mRNA	[618]
	HeLa cells	Human	Protein	[131]
	lymph nodes, liver, colon, kidneys, testis	Human	Protein	[296]
CDC14B	HeLa cells	Human	Protein	[619]
	bone osteosarcoma epithelial cells (U2OS Line)	Human	Protein	[620]
	lymph nodes, liver, colon, kidneys, testis	Human	Protein	[296] *
	oocytes	Mice	Protein/mRNA	[617]
CDC14C	vulva precursors	C. elegans	Protein	[621]
	mononuclear cells	Human	mRNA	[622]
PTENs	endometrial cancer	Human	Protein	[623]
	pancreas	Human	Protein/mRNA	[142]
	colorectal cancer	Human	Protein	[624]
	cochlear lateral wall	Mice	Protein	[625]
	uterus	Mice	Protein	[626]
	ovary cells	Chinese hamster	Protein	[240]
Myotubularins	lung, muscles, endocrine tissue, bone marrow, immune system, liver, gallbladder, and pancreas	Mice	Protein	[296] *
	skin, lung, vagina	Human	mRNA	[149]
	lung, muscles, endocrine tissue, bone marrow, immune system, liver, gallbladder, and pancreas	Human	Protein	[296] *
DUSP1	atherosclerotic lesions	Mice	Protein/mRNA	[627]
	U937 Cells	Human	Protein	[628]
	liver	Mice	Protein/mRNA	[629]
	cardiomyocytes	Mice	Protein/mRNA	[630]
	ovarian carcinoma	Human	Protein/mRNA	[631]
	cochlea	Mice	mRNA	[632]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
DUSP4	T cells	Human	Protein/mRNA	[633]
	prostate, testis, pancreas, adrenal cortex, and stomach	Human	mRNA	[633]
	heart, spleen, lung, liver, kidney, testis, muscles	Rat	mRNA	[634]
	alveolar macrophage cell	Mice	Protein	[635]
	aortic endothelial cell	Rat	Protein	[636]
DUSP6	lung, heart, spleen,liver, kidney	Rat	mRNA	[637]
	breast cancer cell line	Human	Protein/mRNA	[638]
	Umbilical vein endothelial cell	Human	Protein/mRNA	[639]
	embryo	Mice	mRNA	[640]
DUSP9	placenta, kidney, Embryonic liver	Human	mRNA	[641]
	adipose tissue	Mice	mRNA	[642]
	placenta	Mice	Protein	[643]
	splenic dendritic cells	Mice	Protein/mRNA	[644]
DUSP10	heart, lung, liver, skeletal muscle, kidney	Mice	mRNA	[645]
	skeletal muscle, liver	Human	mRNA	[646]
	colon carcinomas	Human	mRNA	[647]
	CD4 T cells	Mice	mRNA	[648]
DUSP16	intestine	Mice	mRNA	[649]
	kidney, intestine, testis	Mice	mRNA	[650]
	CD4+ T cells	Mice	Protein	[651]
DUSP2	bone marrow-derived macrophage	Mice	Protein	[652]
	adipose tissue	Mice	mRNA	[653]
	primary colorectal cancer	Human	Protein	[654]
	monocyte	Human	mRNA	[191]
	blood	Human	mRNA	[192]
DUSP5	Cerebral arterial muscle	Rat	Protein/mRNA	[558]
	adipose tissue	Mice	Protein/mRNA	[655]
	colon-cancer cell lines	Human	Protein/mRNA	[559]
	skeletal muscle, adipose tissue	Human	mRNA	[656]
DUSP22	colorectal cancer	Human	mRNA	[657]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
	blood	Human	mRNA	[233]
	heart, skeletal muscle	Mice	Protein	[295]
	thymus, Spleen, Prostate, Testis, Blood lymphocytes	Mice	mRNA	[658]
	T cell	Mice	Protein	[299]
DUSP8	heart, skeletal muscle	Human	mRNA	[532]
	pancreatic islets	Human	Protein	[659]
	cardiac myocytes	Mice/Rat	Protein	[166]
	kidney	Mice	Protein	[660]
MK-STYX	ovarian cancer	Human	Protein	[661]
	HeLa cell	Human	Protein	[662]
	PC12 cells	Rat	Protein	[563]
	blood	Mice	Protein	[566]
MTM1	skeletal muscle, testis	Human	mRNA	[663]
	blood platelets	Human	Protein	[664]
	blood platelets	Mice	Protein	[664]
MTMR1	muscles	Human	Protein/mRNA	[665]
	muscles , heart	Mice	Protein	[666]
MTMR2	C2C12 cells	Mice	mRNA	[667]
	blood leukocytes	Human	mRNA	[568]
	liver, nerve	Mice	mRNA	[668]
	muscle	Mice	mRNA	[567]
	superior temporal cortex	Human	mRNA	[216]
MTMR3	oral cancer	Human	Protein	[669]
	Gastric / colon carcinoma	Human	mRNA	[618]
	monocyte-derived macrophages	Human	Protein/mRNA	[670]
	breast cancer	Human	Protein	[671]
MTMR4	COS1 cells	Monkey	Protein	[672]
	heart, kidney, spleen, liver, colon, testis, muscle, placenta, thyroid gland, pancreas, ovary, prostate, skin, peripheral blood, bone marrow, fetal liver	Human	mRNA	[673]
	HeLa cell	Human	Protein	[674]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
	papillary thyroid cancer	Human	Protein	[675]
MTMR5	NIH 3T3	Mice	Protein	[676]
	blood, buccal swab	Human	Protein	[677]
	testis, brain, colon	Mice	mRNA	[678]
	testis	Human	Protein/mRNA	[678]
MTMR6	ovarian cancer cells	Human	Protein	[671]
	heart, brain, spleen, lung, liver, muscle, kidney	Mice	Protein	[679]
MTMR7	brain, liver, kidney, and testis	Mice	mRNA	[680]
	brain	Mice	Protein	[680]
	myoblasts	Mice	Protein/mRNA	[681]
	colorectal cancer	Human	Protein/mRNA	[682]
MTMR8	heart, spleen, kidney, liver, leukocyte, ovary, muscle, testis, lung, skin, small intestines, prostate	Human	mRNA	[683]
	Megakaryocytic MEG-01 cells	Human	mRNA	[664]
	muscle, artery	Zebra fish	mRNA	[684, 685]
MTMR9	blood	Human	mRNA	[686]
	peripheral blood leukocyte	Human	mRNA	[687]
	Megakaryocytic MEG-01 cells	Human	mRNA	[664]
	peripheral blood lymphocytes	Human	mRNA	[215]
MTMR10	peripheral blood	Human	mRNA	[688]
	lymphoblastoid cell lines	Human	mRNA	[689]
MTMR11	breast tumor	Human	mRNA	[690]
	blood	Human	Protein	[691]
	inner ear hair	Mice	mRNA	[692]
MTMR12	skeletal muscle	Zebra fish	Protein/mRNA	[693]
MTMR13	placenta, testis, fetal brain	Human	mRNA	[694]
	sciatic nerves	Mice	Protein	[579]
	spinal cord, sciatic nerve, lymph node, adrenal gland, bone marrow, stomach	Human	mRNA	[695]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
Laforin	brain, skeletal muscle, placenta, lung, kidney, pancreas, heart, liver	Human	mRNA	[696]
	spleen, thymus, prostate, testis, ovary, small intestine, colon, peripheral blood lymphocytes, heart, brain, placenta, lung, liver, skeletal, muscle, kidney, pancreas	Human	mRNA	[697]
	Heart, liver, skeletal muscle, brain	Mice	Protein	[583]
STYX	colorectal cancer	Human	Protein	[698]
	Testis	Mice	Protein	[699]
	HeLa cell	Human	mRNA	[700]
DUSP3	endothelial cells	Human	Protein	[701]
	prostate cancer	Human	Protein/mRNA	[702]
	platelets	Human	Protein	[703]
	brain, lung, heart, stomach, liver, kidney, testis, spleen, skeletal muscle, small intestine	Mice	Protein	[704]
	platelets	Mice	Protein	[703]
DUSP11	colonic mucosa	Human	mRNA	[705]
	HEK293T	Human	Protein	[706]
	WI38 fibroblasts	Human	mRNA	[707]
DUSP12	A549 cells, MCF-7 cells	Human	Protein	[708]
	liver	Mice	Protein	[709]
	adipose tissue	Mice	Protein	[710]
DUSP13A	skeletal muscle	Human	Protein/mRNA	[711]
	diaphragm, Muscle	Mice	mRNA	[711]
DUSP13B	testis	Mice/Rat	Protein/mRNA	[711, 712]
	skeletal muscle, testis, spermatocytes, round spermatids, testicular germ cells	Mice	mRNA	[713]
DUSP14	bone marrow-derived cells	Mice	Protein	[714]
	myocardial tissue	Mice/Human	Protein	[715]
	liver	Human/Mice	Protein/mRNA	[716]

Continuation of Table A.5

Protein	Tissue/ Cell line	Species	Protein/ mRNA	Ref.
	blood	Human	mRNA	[717]
DUSP15	testis	Human	mRNA	[718]
	spinal cord	Mice	mRNA	[538]
DUSP18	brain, pancreas, kidney, liver, skeletal muscle, heart, lung, placenta, spleen, peripheral blood, testis, leukocyte, colon, thymus, small intestine, prostate, ovary	Human	mRNA	[539]
	breast, lung, colon, prostate, ovary human cancer cell line	Human	mRNA	[719]
DUSP19	heart, lung, liver, pancreas	Human	mRNA	[720]
	brain, placenta, lung, small intestine, heart, liver, kidney and testis	Mice	mRNA	[721]
	cartilage	Human	mRNA	[722]
DUSP21	testis	Human	mRNA	[723]
	colorectal cancer	Human	mRNA	[724]
DUSP22	blood	Human	mRNA	[214]
DUSP23	spleen, prostate, colon, adrenal gland, mammary gland, thyroid, trachea, uterus, bladder	Human	mRNA	[718]
	CD4+ T cells	Human	mRNA	[725]
	breast cancer	Human	Protein	[726]
	heart, liver, spleen, testis	Mice	mRNA	[727]
DUSP26	liver	Mice	mRNA	[728]
	kidney	Human	Protein	[729]
	normal thyroid tissue	Human	mRNA	[730]
	brain tumour, neuroblastoma, ovarian cancer cell lines	Human	mRNA	[731]
DUSP27	somites	Zebra fish	mRNA	[732]
	tonsils	Human	mRNA	[733]
	skeletal muscle, liver, kidney	Human	mRNA	[734]
	skeletal muscle, liver, and fat	Mice	Protein	[734]

End of Table

Note:* (www.proteinatlas.org)

BNST:The bed nucleus of the stria terminalis

A.6 Schematic representations of the structure of the family members of the DUSP proteins

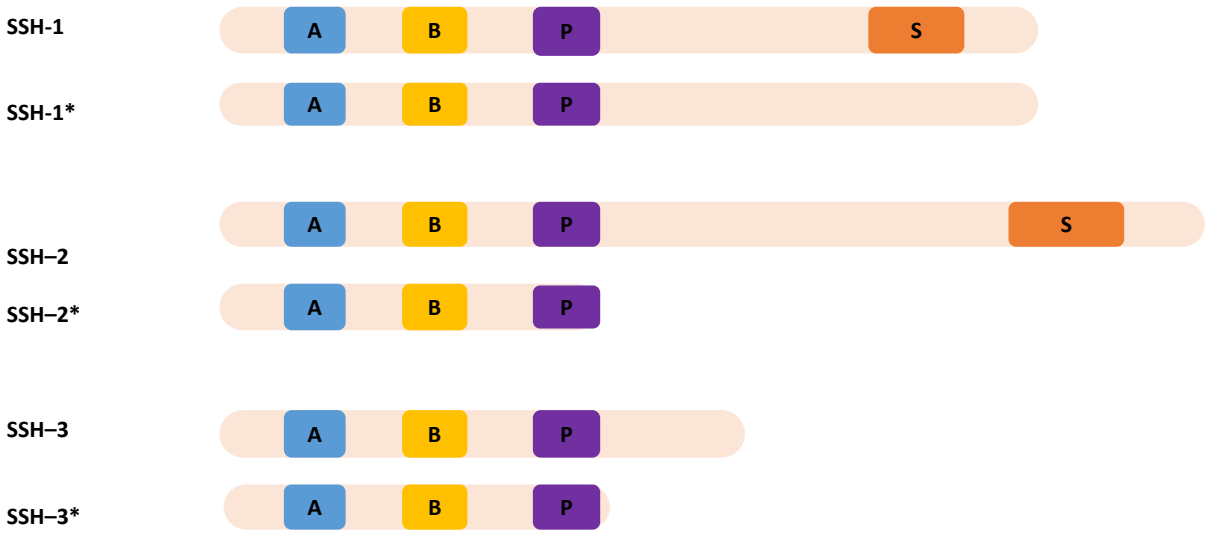

Figure 1: Structures of SSH family phosphatases. The schematic diagrams show protein structures of mouse (m), human (h), and Drosophila (D) SSHs. The highly conserved regions between SSH family proteins are indicated as A, B, P (protein phosphatase) and S (serine-rich) domains (adapted [98, 96])

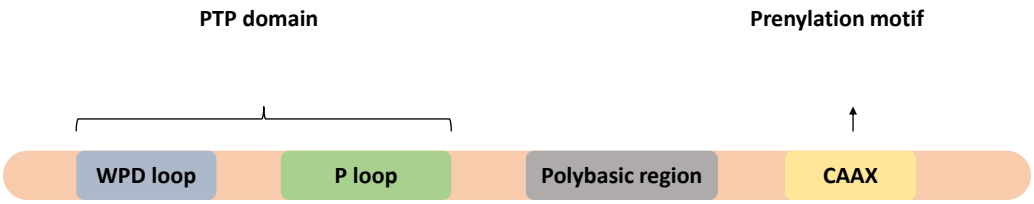

Figure 2: Simplified schematic diagram of the PRL proteins. The PTP domain is responsible for enzymatic activity, requiring the P-loop residues and the WPD loop residues for phosphate transfer. A polybasic region localizes next to the PTP domains and mediates membrane or nuclear localization of PRLs. The CAAX protein prenylation anchors the PRLs to the cellular membrane (simplified from [735])

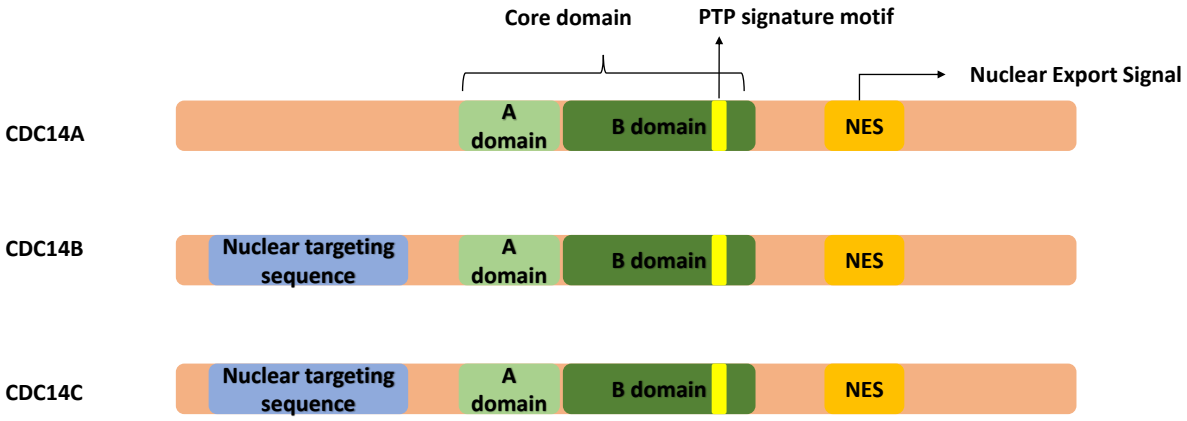

Figure 3: Schematic of the primary structure of CDC14 in humans. The conserved domain is depicted in blue (adapted from [130, 128])

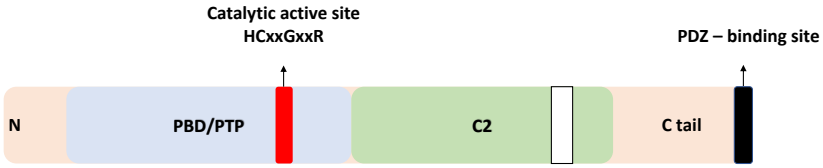

Figure 4: The domain architecture of PTEN. PTEN is composed of four domains: the PIP2-binding domain (PBD)/PTP, C2 domain, C tail domain, and a PDZ binding domain. The active catalytic site is HCxxGxxR (adapted from review [136, 137])

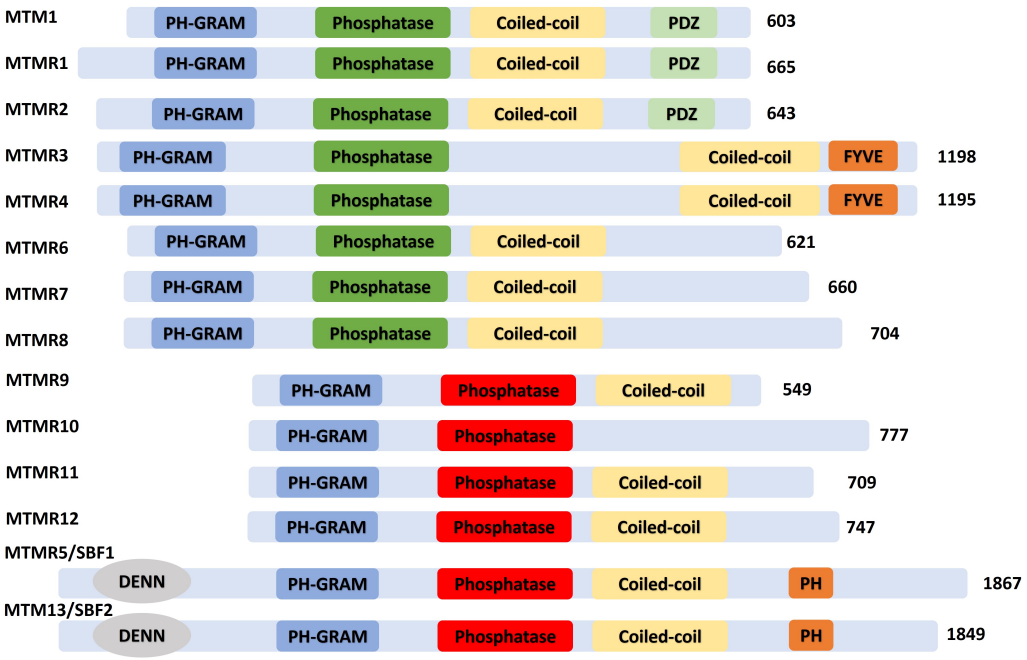

Figure 5: Scaled representation of the protein domains of human myotubularins. All myotubularins share the PH-GRAM and phosphatase (active or dead) domains. Additionally, myotubularins can also carry other functional domains, including the PDZ binding site, the PH (Pleckstrin homology) and FYVE (Fab1-YOTB-Vac1-EEA1) domains, as well as the DENN (Differentially Expressed in Normal and Neoplastic cells) domain. Except for MTMR10, all myotubularins are composed of a coiled-coil domain. For each myotubularin, the amino acid length for the most described protein isoform is indicated (adapted from review [150, 149])

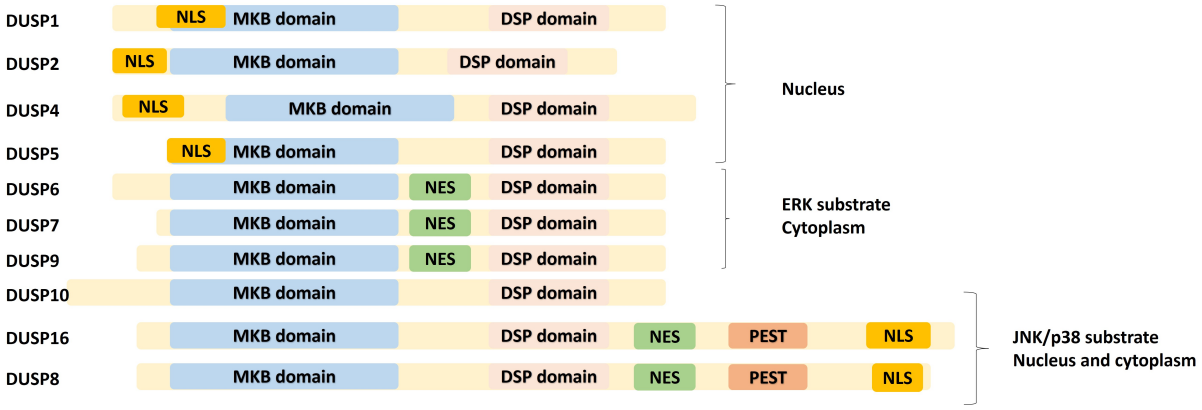

Figure 6: Classification and domain structure of the MKP family. The three subgroups are based on substrates and subcellular localization. In addition to the MAPK binding (MKB) domain and dual-specificity phosphatase (DSP) domain, the nuclear localization signal (NLS), nuclear export signal (NES), and PEST sequences are shown in the figure. (adapted from [157, 156])

Figure 7: Atypical DUSPs predominantly contain the consensus DSP catalytic domain, whereas some atypical DUSPs contain the CH2 domain, the carbohydrate-binding domain, and is an Arginine-rich or Proline-rich region (adapted from [86])

A.7 Weight comparison between all factors over the course of the experiment

Table A.6: Weight Comparison between all Factors over the Course of the Experiment.

	df	F - value	pη2	P - value
Time of Measurement (ST vs LT)	1	58.240**	0.284	0
ToM ×SD	1	7.025**	0.046	0.009
ToM ×PhA	1	0.13	0.001	0.719
Time of Measurement×SD×PhA	1	0.347	0.002	0.557
SD	1	1.046	0.007	0.308
PhA	1	0.133	0.001	0.716
SD×PhA	1	0.569	0.002	0.452
Error	147			

Note:ToM = Time of Measurement

$p < .05$ = *, $p < .01$ = **

A.8 Baseline behavioral measurements

Table A.7: Baseline Locomotion (cm)

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.027	0.000	0.870	control	1100 ± 237	24
					SD	1108 ± 193	54
PhA	1	8.291**	0.101	0.005	PhA-	1163 ± 188	39
					PhA+	1047 ± 209	39
SD ×PhA	1	1.713	0.023	0.195			
Error	74						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	1.109	0.015	0.296	Control	1405 ± 225	23
					SD	1461 ± 223	54
PhA	1	25.147**	0.256	0.000	PhA-	1564 ± 189	38
					PhA+	1327 ± 194	39
SD ×PhA	1	0.071	0.001	0.790			
Error	73						

Table A.8: Baseline SIR

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.194	0.003	0.661	Control	117.16 ± 38.1	24
					SD	122.07 ± 58.5	51
PhA	1	2.280	0.031	0.136	PhA-	131.74 ± 52.99	36
					PhA+	110.12 ± 50.07	39
SD×PhA	1	669.481	0.003	0.621			
Error	71						
LT	df	F - value	pη2	p - value		M ± StD	N
SD	1	0.301	0.005	0.585	Control	136.81 ± 41.13	23
					SD	131.59 ± 40.44	45
PhA	1	1.896	0.029	0.173	PhA-	140.12 ± 45.8	34
					PhA+	126.58 ± 33.6	34
SD×PhA	1	0.038	0.001	0.846			
Error	64						

Table A.9: Baseline Sociability score

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.643	0.009	0.425	Control	0.36 ± 0.09	24
					SD	0.38 ± 0.08	54
PhA	1	0.981	0.013	0.325	PhA-	0.38 ± 0.07	39
					PhA+	0.36 ± 0.09	39
SD×PhA	1	0	0	0.882			
Error	74						
LT	df	F - value	pη2	p - value		M ± StD	N
SD	1	0	0	0.984	Control	0.35 ± 0.07	23
					SD	0.35 ± 0.06	53
PhA	1	7.119**	0.09	0.009	PhA-	0.34 ± 0.06	37
					PhA+	0.37 ± 0.06	39
SD×PhA	1	1.682	0.023	0.199			
Error	72						

Table A.10: Baseline Sucrose (proportion)

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	3.78	0.051	0.056	Control	0.73 ± 0.06	22
					SD	0.71 ± 0.06	53
PhA	1	4.227*	0.056	0.043	PhA-	0.73 ± 0.07	36
					PhA+	0.7 ± 0.046	39
SD ×PhA	1	0.002	0.01	0.407			
Error	71						
LT	df	F - value	pη2	p - value		M ± StD	N
SD	1	4.118*	0.055	0.05	Control	0.74 ± 0.04	23
					SD	0.76 ± 0.06	52
PhA	1	0.73	0.01	0.396	PhA-	0.76 ± 0.05	36
					PhA+	0.74 ± 0.05	39
SD×PhA	1	3.152	0.043	0.08			
Error	71						

A.9 Descriptives and statistics of the behavioural measurements

Table A.11: Locomotion

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	8.009**	0.104	0.006	Control	1215.85 ± 329.98	24
					SD	1057.26 ± 201.46	49
PhA	1	20.387**	0.228	0	PhA-	1217.97 ± 270.81	36
					PhA+	1003.78 ± 200.95	37
SD×PhA	1	3.992	0.055	0.05			
Error	69						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.199	0.003	0.657	Control	1171.13 ± 205.88	23
					SD	1195.73 ± 201.44	45
PhA	1	0.751	0.012	0.389	PhA-	1213.76 ± 215.85	34
					PhA+	1161.06 ± 186.06	34
SD×PhA	1	0.154	0.002	0.696			
Error	64						

Table A.12: SIR

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.037	0.001	0.848	Control	91.26 ± 27.22	24
					SD	92.78 ± 34.49	48
PhA	1	0.679	0.01	0.413	PhA-	90.30 ± 28.93	35
					PhA+	94.13 ± 35.06	37
SD×PhA	1	1.135	0.016	0.29			
Error	68						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	3.468	0.051	0.067	Control	119.94 ± 38.51	23
					SD	143.85 ± 53.9	45
PhA	1	0.001	0	0.976	PhA-	135.71 ± 48.14	34
					PhA+	135.83 ± 52.99	34
SD×PhA	1	0.011	0	0.917			
Error	64						

Note: $p < .05$ = *, $p < .01$ = **

Table A.13: Sociability Score

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	5.056*	0.068	0.028	Control	0.35 ± 0.08	24
					SD	0.39 ± 0.08	49
PhA	1	0.094	0.001	0.76	PhA-	0.38 ± 0.09	36
					PhA+	0.38 ± 0.08	37
SD×PhA	1	1.125	0.016	0.293			
Error	69						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	3.149	0.048	0.081	Control	0.37 ± 0.06	23
					SD	0.40 ± 0.08	44
PhA	1	1.84	0.028	0.18	PhA-	0.40 ± 0.06	34
					PhA+	0.38 ± 0.06	33
SD×PhA	1	0.441	0.007	0.509			
Error	63						

Table A.14: SuP Sucrose Ratio

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	0.583	0.009	0.448	Control	0.79 ± 0.07	24
					SD	0.78 ± 0.066	47
PhA	1	0.461	0.007	0.5	PhA-	0.78 ± 0.06	36
					PhA+	0.78 ± 0.05	35
SD×PhA	1	3.46	0.049	0.067			
Error	67						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	67.133**	0.516	0	Control	0.63 ± 0.04	22
					SD	0.72 ± 0.04	45
PhA	1	0.16	0.003	0.691	PhA-	0.69 ± 0.05	33
					PhA+	0.69 ± 0.06	34
SD×PhA	1	0.037	0.001	0.848			
Error	63						

Table A.15: EZM Closed Arm (proportion)

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	1.038	0.015	0.312	Control	0.82 ± 0.05	24
					SD	0.81 ± 0.06	48
PhA	1	3.285	0.046	0.074	PhA-	0.80 ± 0.05	36
					PhA+	0.83 ± 0.05	36
SD×PhA	1	1.381	0.02	0.244			
Error	68						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	1.221	0.019	0.273	Control	0.87 ± 0.04	23
					SD	0.85 ± 0.05	45
PhA	1	0.105	0.002	0.747	PhA-	0.86 ± 0.03	34
					PhA+	0.86 ± 0.05	34
SD×PhA	1	0.06	0.001	0.807			
Error	64						

Table A.16: FST Immobility (proportion)

ST	df	F - value	pη2	P - value		M ±StD	N
SD	1	31.457**	0.33	0	Control	0.37 ± 0.14	23
					SD	0.54 ± 0.11	45
PhA	1	2.639	0.04	0.109	PhA-	0.46 ± 0.16	33
					PhA+	0.51 ± 0.13	35
SD×PhA	1	0.937	0.014	0.337			
Error	64						
LT	df	F - value	pη2	P - value		M ±StD	N
SD	1	5.683*	0.087	0.02	Control	0.47 ± 0.14	23
					SD	0.39 ± 0.11	41
PhA	1	6.733	0.101	0.012	PhA-	0.38 ± 0.14	31
					PhA+	0.45 ± 0.11	33
SD×PhA	1	1.436	0.023	0.236			
Error	60						

A.10 Descriptives of the basal, stress-induced, and recovery corticosterone concentration

Table A.17: Descriptives of the basal, stress-induced, and recovery corticosterone concentration

		ST		LT	
		Mean ± StD	N	Mean ± StD	N
Basal (µg/dl)	Control PhA-	51,65 ± 22,43	11	165,97 ± 78,46	11
	Control PhA+	160,87 ± 61,39	12	150,12 ± 59,76	12
	SD PhA-	92,95 ± 56,20	23	109,14 ± 39,57	22
	SD PhA+	85,54 ± 43,30	24	92,85 ± 46,63	21
Stress- induced (µg/dl)	Control PhA-	278,8 ± 46,57	12	239,01 ± 58,78	11
	Control PhA+	275,63 ± 37,96	12	228,47 ± 40,66	12
	SD PhA-	267,96 ± 52,85	19	236,25 ± 64,76	22
	SD PhA+	275,87 ± 66,64	23	223,32 ± 65,71	21
Recovery (µg/dl)	Control PhA-	71,57 ± 24,21	11	206,92 ± 91,13	11
	Control PhA+	84,46 ± 35,57	12	205,75 ± 81,8	12
	SD PhA-	54,19 ± 27,78	18	114,97 ± 60,44	22
	SD PhA+	54,59 ± 19,56	20	129,61 ± 45,07	20

Note: $p < .05$ = *, $p < .01$ = **

A.11 Correlations resilience groups and behavioural, physiological data

Table A.18: Descriptives of the basal, stress-induced, and recovery corticosterone concentration

	ST SIR			LT SIR		
	r2	sig.	df	r2	sig.	df
Locomotion	0	0.092	48	0.028	0.848	48
Sociability	0.347*	0.014	48	0.350*	0.014	47
Sucrose Preference	0	0.243	47	0.612**	0	47
Forced Swim Immobility	0.591**	0	43	-0.23	0.12	45
Elevated Zero Maze	0	0.932	47	-0.195	0.175	48
Basal Corticosterone	-0.322*	0.027	45	-0.377**	0.008	47
Stress-induced	0	0.483	44	-0.221	0.126	47
Recovery Corticosterone	-0.436**	0.004	39	-0.548**	0	46

Note: $p < .05$ = *, $p < .01$ = **

A.12 Pearson correlation analysis between behavioral measures and corticosterone parameters

Table A.19: Descriptives of the basal, stress-induced, and recovery corticosterone concentration

ST cohort		SIR	Soc	SuP	Immo	EZM
Baseline CORT	r	-0.07	-0.11	-0.09	0.06	0.03
	p	0.54	0.32	0.45	0.61	0.82
Stress-induced CORT	r	0.01	-0.08	-0.08	-0.18	0.05
	p	0.93	0.49	0.48	0.11	0.64
Recovery CORT	r	-0.02	-0.22	-0.05	-0.004	0.09
	p	0.84	0.05	0.66	0.97	0.45
LT cohort		SIR	Soc	SuP	Immo	EZM
Baseline CORT	r	-0.04	0.14	-0.25	-0.07	-0.01
	p	0.71	0.23	0.03*	0.54	0.96
Stress-induced CORT	r	-0.13	-0.17	-0.01	-0.01	-0.02
	p	0.25	0.15	0.94	0.90	0.84
Recovery CORT	r	-0.10	-0.28	-0.37	0.03	-0.01
	p	0.41	0.01*	0.0008**	0.80	0.93

Note: $p < .05$ = *, $p < .01$ = **

Bibliography

[1] David S. Goldstein and Irwin J. Kopin. Evolution of concepts of stress. *Stress*, 10(2):109–120, 1 2007.

[2] Petr Bob and Matthew Laker. Traumatic stress, neural self and the spiritual mind. *Consciousness and Cognition*, 46:7–14, 11 2016.

[3] Tamara B. Franklin, Bechara J. Saab, and Isabelle M. Mansuy. Neural Mechanisms of Stress Resilience and Vulnerability. *Neuron*, 75(5):747–761, 9 2012.

[4] Karl Ebner and Nicolas Singewald. Individual differences in stress susceptibility and stress inhibitory mechanisms. *Current Opinion in Behavioral Sciences*, 14:54–64, 4 2017.

[5] Khadijah S Alexander, Rebecca Nalloor, Kristopher M Bunting, and Almira Vazdarjanova. Investigating individual pre-trauma susceptibility to a PTSD-like phenotype in animals. *Frontiers in Systems Neuroscience*, 13:85, 2020.

[6] S J Russo, J W Murrough, M H Han, D S Charney, and E J Nestler. Neurobiology of resilience. *Nat Neurosci*, 15(11):1475–1484, 2012.

[7] C M Sheerin, K J Stratton, A B Amstadter, Tvmmir Education Clinical Center Mirecc Workgroup, and S D McDonald. Exploring resilience models in a sample of combat-exposed military service members and veterans: a comparison and commentary. *Eur J Psychotraumatol*, 9(1):1486121, 2018.

[8] Adriana Feder, Eric J Nestler, and Dennis S Charney. Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience*, 10(6):446–457, 2009.

[9] B P Rutten, C Hammels, N Geschwind, C Menne-Lothmann, E Pishva, K Schruers, D van den Hove, G Kenis, J van Os, and M Wichers. Resilience in mental health: linking psychological and neurobiological perspectives. *Acta Psychiatr Scand*, 128(1):3–20, 2013.

[10] Raffael Kalisch, Dewleen G. Baker, Ulrike Basten, Marco P. Boks, George A. Bonanno, Eddie Brummelman, Andrea Chmitorz, Guillén Fernàndez, Christian J. Fiebach, Isaac Galatzer-Levy, Elbert Geuze, Sergiu Groppa, Isabella Helmreich, Talma Hendler, Erno J. Hermans, Tanja Jovanovic, Thomas Kubiak, Klaus Lieb, Beat Lutz, Marianne B. Müller, Ryan J. Murray, Caroline M. Nievergelt, Andreas Reif, Karin Roelofs, Bart P. F. Rutten, David Sander, Anita Schick, Oliver Tüscher, Ilse Van Diest, Anne-Laura van Harmelen, Ilya M. Veer, Eric Vermetten, Christiaan H. Vinkers, Tor D. Wager, Henrik Walter, Michèle Wessa, Michael Wibral, and Birgit Kleim. The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour*, 1(11):784–790, 10 2017.

[11] Walter B Cannon. *The wisdom of the body*. W.W. Norton & Company, Inc., New York, 1932.

[12] Carlos Osório, Thomas Probert, Edgar Jones, Allan H. Young, and Ian Robbins. Adapting to Stress: Understanding the Neurobiology of Resilience. *Behavioral Medicine*, 43(4):307–322, 10 2017.

[13] Dennis S Charney. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *The American journal of psychiatry*, 161(2):195–216, 2 2004.

[14] Eliza B Geer, Julie Islam, and Christoph Buettner. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. *Endocrinology and metabolism clinics of North America*, 43(1):75–102, 3 2014.

[15] E R De Kloet, E Vreugdenhil, M S Oitzl, and M Joëls. Brain corticosteroid receptor balance in health and disease. *Endocrine reviews*, 19(3):269–301, 6 1998.

[16] Mary Ann C Stephens and Gary Wand. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. *Alcohol research : current reviews*, 34(4):468–83, 2012.

[17] Yong-Ku Kim, Meysam Amidfar, and Eunsoo Won. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. *Progress in neuro-psychopharmacology & biological psychiatry*, 91:103–112, 4 2019.

[18] Adwitia Dey and Pamela Hankey Giblin. Insights into Macrophage Heterogeneity and Cytokine-Induced Neuroinflammation in Major Depressive Disorder. *Pharmaceuticals*, 11(3):64, 6 2018.

[19] George Anderson and Michael Maes. Bipolar disorder: role of immune-inflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. *Current psychiatry reports*, 17(2):8, 2 2015.

[20] A Schuld, D Hinze-Selch, and Th Pollmächer. [Cytokine network in patients with schizophrenia and its significance for the pathophysiology of the illness]. *Der Nervenarzt*, 75(3):215–26, 3 2004.

[21] N Müller and M Ackenheil. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. *Progress in neuro-psychopharmacology & biological psychiatry*, 22(1):1–33, 1 1998.

[22] Elizabeth J Santa Ana, Michael E Saladin, Sudie E Back, Angela E Waldrop, Eve G Spratt, Aimee L McRae, Steven D LaRowe, Mary Ann Timmerman, Himanshu Upadhyaya, and Kathleen T Brady. PTSD and the HPA axis: differences in response to the cold pressor task among individuals with child vs. adult trauma. *Psychoneuroendocrinology*, 31(4):501–9, 5 2006.

[23] Randall D Marshall, Carlos Blanco, David Printz, Michael R Liebowitz, Donald F Klein, and Jeremy Coplan. A pilot study of noradrenergic and HPA axis functioning in PTSD vs. panic disorder. *Psychiatry research*, 110(3):219–30, 7 2002.

[24] Ellen R Klaassens, Erik J Giltay, Pim Cuijpers, Tineke van Veen, and Frans G Zitman. Adulthood trauma and HPA-axis functioning in healthy subjects and PTSD patients: a meta-analysis. *Psychoneuroendocrinology*, 37(3):317–31, 3 2012.

[25] Dmitri A Young, Thomas C Neylan, Aoife O'Donovan, Thomas Metzler, Anne Richards, Jessica A Ross, and Sabra S Inslicht. The interaction of BDNF Val66Met, PTSD, and child abuse on psychophysiological reactivity and HPA axis function in a sample of Gulf War Veterans. *Journal of affective disorders*, 235:52–60, 8 2018.

[26] Dmitri A Young, Sabra S Inslicht, Thomas J Metzler, Thomas C Neylan, and Jessica A Ross. The effects of early trauma and the FKBP5 gene on PTSD and the HPA axis in a clinical sample of Gulf War veterans. *Psychiatry research*, 270:961–966, 12 2018.

[27] Monika Zaba, Thomas Kirmeier, Irina A Ionescu, Bastian Wollweber, Dominik R Buell, Dominique J Gall-Kleebach, Christine F Schubert, Bozidar Novak, Christine Huber, Katharina Köhler, Florian Holsboer, Benno Pütz, Bertram Müller-Myhsok, Nina Höhne, Manfred Uhr, Marcus Ising, Leonie Herrmann, and Ulrike Schmidt. Identification and characterization of HPA-axis reactivity endophenotypes in a cohort of female PTSD patients. *Psychoneuroendocrinology*, 55:102–15, 5 2015.

[28] Matthias Hoenen, Oliver T Wolf, and Bettina M Pause. The Impact of Stress on Odor Perception. *Perception*, 46(3-4):366–376, 2017.

[29] Yoshinori Masuo, Tadaaki Satou, Hiroaki Takemoto, and Kazuo Koike. Smell and Stress Response in the Brain: Review of the Connection between Chemistry and Neuropharmacology. *Molecules*, 26(9):2571, 4 2021.

[30] Francisco Mora, Gregorio Segovia, Alberto Del Arco, Marta de Blas, and Pedro Garrido. Stress, neurotransmitters, corticosterone and body-brain integration. *Brain research*, 1476:71–85, 10 2012.

[31] Bing Mo, Na Feng, Kenneth Renner, and Gina Forster. Restraint stress increases serotonin release in the central nucleus of the amygdala via activation of corticotropin-releasing factor receptors. *Brain research bulletin*, 76(5):493–8, 7 2008.

[32] Zahra Bahari, Gholam H Meftahi, and Mohammad A Meftahi. Dopamine effects on stress-induced working memory deficits. *Behavioural pharmacology*, 29(7):584–591, 10 2018.

[33] Benjamin H Levy and Jeffrey G Tasker. Synaptic regulation of the hypothalamic-pituitary-adrenal axis and its modulation by glucocorticoids and stress. *Frontiers in cellular neuroscience*, 6:24, 2012.

[34] Dorie A Glover, Mark B Powers, Lyndsey Bergman, Jasper A J Smits, Michael J Telch, and Margaret Stuber. Urinary dopamine and turn bias in traumatized women with and without PTSD symptoms. *Behavioural brain research*, 144(1-2):137–41, 9 2003.

[35] Wojciech Ł Dragan and Włodzimierz Oniszczenko. The association between dopamine D4 receptor exon III polymorphism and intensity of PTSD symptoms among flood survivors. *Anxiety, stress, and coping*, 22(5):483–95, 10 2009.

[36] S M Southwick, S Paige, C A Morgan, J D Bremner, J H Krystal, and D S Charney. Neurotransmitter alterations in PTSD: catecholamines and serotonin. *Seminars in clinical neuropsychiatry*, 4(4):242–8, 10 1999.

[37] B C J Dirven, J R Homberg, T Kozicz, and M J A G Henckens. Epigenetic programming of the neuroendocrine stress response by adult life stress. *Journal of molecular endocrinology*, 59(1):R11–R31, 7 2017.

[38] E J Nestler, C J Pena, M Kundakovic, A Mitchell, and S Akbarian. Epigenetic Basis of Mental Illness. *Neuroscientist*, 22(5):447–463, 2016.

[39] Filomene G Morrison, Mark W Miller, Mark W Logue, Michele Assef, and Erika J Wolf. DNA methylation correlates of PTSD: Recent findings and technical challenges. *Progress in neuro-psychopharmacology & biological psychiatry*, 90:223–234, 3 2019.

[40] Christiana Martin, Young-Eun Cho, Hyungsuk Kim, Sijung Yun, Rebekah Kanefsky, Hyunhwa Lee, Vincent Mysliwiec, Ann Cashion, and Jessica Gill. Altered DNA Methylation Patterns Associated With Clinically Relevant Increases in PTSD Symptoms and PTSD Symptom Profiles in Military Personnel. *Biological research for nursing*, 20(3):352–358, 5 2018.

[41] B P F Rutten, E Vermetten, C H Vinkers, G Ursini, N P Daskalakis, E Pishva, L de Nijs, L C Houtepen, L Eijssen, A E Jaffe, G Kenis, W Viechtbauer, D van den Hove, K G Schraut, K-P Lesch, J E Kleinman, T M Hyde, D R Weinberger, L Schalkwyk, K Lunnon, J Mill, H Cohen, R Yehuda, D G Baker, A X Maihofer, C M Nievergelt, E Geuze, and M P M Boks. Longitudinal analyses of the DNA methylome in deployed military servicemen identify susceptibility loci for post-traumatic stress disorder. *Molecular psychiatry*, 23(5):1145–1156, 5 2018.

[42] M.R. Galiano, A. Andrieux, J.C. Deloulme, C. Bosc, A. Schweitzer, D. Job, and M.E. Hallak. Myelin basic protein functions as a microtubule stabilizing protein in differentiated oligodendrocytes. *Journal of Neuroscience Research*, 84(3):534–541, 8 2006.

[43] Eva-Maria Krämer-Albers, Niko Bretz, Stefan Tenzer, Christine Winterstein, Wiebke Möbius, Hendrik Berger, Klaus-Armin Nave, Hansjörg Schild, and Jacqueline Trotter. Oligodendrocytes secrete exosomes containing major myelin and stress-protective proteins: Trophic support for axons? *Proteomics. Clinical applications*, 1(11):1446–61, 11 2007.

[44] Philip R Lee and R Douglas Fields. Regulation of myelin genes implicated in psychiatric disorders by functional activity in axons. *Frontiers in neuroanatomy*, 3(JUN):4, 6 2009.

[45] Paul R. Matthews, Sharon L. Eastwood, and Paul J. Harrison. Reduced Myelin Basic Protein and Actin-Related Gene Expression in Visual Cortex in Schizophrenia. *PLoS ONE*, 7(6):e38211, 6 2012.

[46] Mark W. Logue, Zhenwei Zhou, Filomene G. Morrison, Erika J. Wolf, Nikolaos P. Daskalakis, Christos Chatzinakos, Foivos Georgiadis, Adam T. Labadorf, Matthew J. Girgenti, Keith A. Young, Douglas E. Williamson, Xiang Zhao, Jaclyn Garza Grenier, Bertrand Russell Huber, and Mark W. Miller. Gene expression in the dorsolateral and ventromedial prefrontal cortices implicates immune-related gene networks in PTSD. *Neurobiology of Stress*, 15:100398, 11 2021.

[47] Xixia Chu, Ying Zhou, Zhiqiang Hu, Jingyu Lou, Wei Song, Jing Li, Xiao Liang, Chen Chen, Shuai Wang, Beimeng Yang, Lei Chen, Xu Zhang, Jinjing Song, Yujie Dong, Shiqing Chen, Lin He, Qingguo Xie, Xiaoping Chen, and Weidong Li. 24-hour-restraint stress induces long-term depressive-like phenotypes in mice. *Scientific Reports*, 6(1):32935, 9 2016.

[48] H Zhang, G Yan, H Xu, Z Fang, J Zhang, J Zhang, R Wu, J Kong, and Q Huang. The recovery trajectory of adolescent social defeat stress-induced behavioral, (1)H-MRS metabolites and myelin changes in Balb/c mice. *Sci Rep*, 6:27906, 2016.

[49] José Javier Miguel-Hidalgo, Mohadetheh Moulana, Preston Hardin Deloach, and Grazyna Rajkowska. Chronic Unpredictable Stress Reduces Immunostaining for Connexins 43 and 30 and Myelin Basic Protein in the Rat Prelimbic and Orbitofrontal Cortices. *Chronic stress (Thousand Oaks, Calif.)*, 2, 2018.

[50] Qingsong Wang, Zhenggou Wang, Peifang Zhu, and Jianxin Jiang. Alterations of myelin basic protein and ultrastructure in the limbic system at the early stage of trauma-related stress disorder in dogs. *The Journal of trauma*, 56(3):604–10, 3 2004.

[51] Patricia Mansfield, John N. Constantino, and Dustin Baldridge. MYT1L: A systematic review of genetic variation encompassing schizophrenia and autism. *American journal of medical genetics. Part B, Neuropsy-*

chiatric genetics : the official publication of the International Society of Psychiatric Genetics, 183(4):227–233, 6 2020.

[52] Jiayang Chen, Allen Yen, Colin P. Florian, and Joseph D. Dougherty. MYT1L in the making: emerging insights on functions of a neurodevelopmental disorder gene. *Translational Psychiatry*, 12(1):292, 7 2022.

[53] Caroline Hammels, Ehsan Pishva, Jochen De Vry, Daniel L A van den Hove, Jos Prickaerts, Ruud van Winkel, Jean-Paul Selten, Klaus-Peter Lesch, Nikolaos P Daskalakis, Harry W M Steinbusch, Jim van Os, Gunter Kenis, and Bart P F Rutten. Defeat stress in rodents: From behavior to molecules. *Neuroscience and biobehavioral reviews*, 59:111–40, 12 2015.

[54] Nikolaos P Daskalakis and Rachel Yehuda. Principles for developing animal models of military PTSD. *European journal of psychotraumatology*, 5, 2014.

[55] N P Daskalakis, R Yehuda, and D M Diamond. Animal models in translational studies of PTSD. *Psychoneuroendocrinology*, 38(9):1895–1911, 2013.

[56] Meng-Ying Liu, Chun-Yu Yin, Li-Juan Zhu, Xian-Hui Zhu, Chu Xu, Chun-Xia Luo, Hongshan Chen, Dong-Ya Zhu, and Qi-Gang Zhou. Sucrose preference test for measurement of stress-induced anhedonia in mice. *Nature Protocols*, 13(7):1686–1698, 7 2018.

[57] Melloni N Cook, Martha Crounse, and Lorraine Flaherty. Anxiety in the elevated zero-maze is augmented in mice after repeated daily exposure. *Behavior genetics*, 32(2):113–8, 3 2002.

[58] Oksana Kaidanovich-Beilin, Tatiana Lipina, Igor Vukobradovic, John Roder, and James R Woodgett. Assessment of social interaction behaviors. *Journal of visualized experiments : JoVE*, 0(48), 2 2011.

[59] Roni Yankelevitch-Yahav, Motty Franko, Avrham Huly, and Ravid Doron. The forced swim test as a model of depressive-like behavior. *Journal of visualized experiments : JoVE*, 0(97), 3 2015.

[60] M R Foy, M E Stanton, S Levine, and R F Thompson. Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and neural biology*, 48(1):138–49, 7 1987.

[61] J A Rosenkranz, E R Venheim, and M Padival. Chronic stress causes amygdala hyperexcitability in rodents. *Biol Psychiatry*, 67(12):1128–1136, 2010.

[62] E H Chang, S A Frattini, S Robbiati, and P T Huerta. Construction of microdrive arrays for chronic neural recordings in awake behaving mice. *J Vis Exp*, 0(77):e50470, 2013.

[63] Sam A Golden, Herbert E Covington, Olivier Berton, and Scott J Russo. A standardized protocol for repeated social defeat stress in mice. *Nature Protocols*, 6(8):1183–1191, 8 2011.

[64] T Goto and A Toyoda. A Mouse Model of Subchronic and Mild Social Defeat Stress for Understanding Stress-induced Behavioral and Physiological Deficits. *J Vis Exp*, 0(105), 2015.

[65] S D Iniguez, Lace M Riggs, Steven J Nieto, Genesis Dayrit, Norma N Zamora, Kristi L Shawhan, Bryan Cruz, Brandon L Warren, Sergio D Iñiguez, Lace M Riggs, Steven J Nieto, Genesis Dayrit, Norma N Zamora, Kristi L Shawhan, Bryan Cruz, Brandon L Warren, S D Iniguez, Lace M Riggs, Steven J Nieto, Genesis Dayrit, Norma N Zamora, Kristi L Shawhan, Bryan Cruz, Brandon L Warren, Sergio D Iñiguez, Lace M Riggs, Steven J Nieto, Genesis Dayrit, Norma N Zamora, Kristi L Shawhan, Bryan Cruz, and Brandon L Warren. Social defeat stress induces a depression-like phenotype in adolescent male c57BL/6 mice. *Stress*, 17(3):247–255, 2014.

[66] Omar K Sial, Brandon L Warren, Lyonna F Alcantara, Eric M Parise, and Carlos A Bolaños-Guzmán. Vicarious social defeat stress: Bridging the gap between physical and emotional stress. *Journal of neuroscience methods*, 258:94–103, 1 2016.

[67] Brandon L. Warren, Vincent F. Vialou, Sergio D. Iñiguez, Lyonna F. Alcantara, Katherine N. Wright, Jiang Feng, Pamela J. Kennedy, Quincey LaPlant, Li Shen, Eric J. Nestler, and Carlos A. Bolaños-Guzmán. Neurobiological Sequelae of Witnessing Stressful Events in Adult Mice. *Biological Psychiatry*, 73(1):7–14, 1 2013.

[68] S E Cooper, M Kechner, D Caraballo-Pérez, S Kaska, A J Robison, and M S Mazei-Robison. Comparison of chronic physical and emotional social defeat stress effects on mesocorticolimbic circuit activation and voluntary consumption of morphine. *Scientific reports*, 7(1):8445, 8 2017.

[69] Man Li, Hang Xu, and Weiwen Wang. An Improved Model of Physical and Emotional Social Defeat: Different Effects on Social Behavior and Body Weight of Adolescent Mice by Interaction With Social Support. *Frontiers in Psychiatry*, 9, 12 2018.

[70] R J Blanchard, D C Blanchard, J Rodgers, and S M Weiss. The characterization and modelling of antipredator defensive behavior. *Neuroscience and biobehavioral reviews*, 14(4):463–72, 1990.

[71] Raimund Apfelbach, Caroline D Blanchard, Robert J Blanchard, R Andrew Hayes, and Iain S McGregor. The effects of predator odors in mammalian prey species: a review of field and laboratory studies. *Neuroscience and biobehavioral reviews*, 29(8):1123–44, 2005.

[72] Jeffrey B. Rosen. The Neurobiology of Conditioned and Unconditioned Fear: A Neurobehavioral System Analysis of the Amygdala. *Behavioral and Cognitive Neuroscience Reviews*, 3(1):23–41, 3 2004.

[73] Hagit Cohen, Zeev Kaplan, Michael A Matar, Uri Loewenthal, Nitsan Kozlovsky, and Joseph Zohar. Anisomycin, a protein synthesis inhibitor, disrupts traumatic memory consolidation and attenuates posttraumatic stress response in rats. *Biological psychiatry*, 60(7):767–76, 10 2006.

[74] Sophie St-Cyr and Patrick O McGowan. Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor. *Frontiers in behavioral neuroscience*, 9:145, 2015.

[75] Hagit Cohen, Joseph Zohar, and Michael Matar. The relevance of differential response to trauma in an animal model of posttraumatic stress disorder. *Biological psychiatry*, 53(6):463–73, 3 2003.

[76] K G Schraut, S B Jakob, M T Weidner, A G Schmitt, C J Scholz, T Strekalova, N El Hajj, L M T Eijssen, K Domschke, A Reif, T Haaf, G Ortega, H W M Steinbusch, K P Lesch, and D L Van den Hove. Prenatal stress-induced programming of genome-wide promoter DNA methylation in 5-HTT-deficient mice. *Translational psychiatry*, 4(10):e473, 10 2014.

[77] Dag Yasui, Jacob Peedicayil, and Dennis R Grayson. *Neuropsychiatric disorders and epigenetics*. Academic Press, 2016.

[78] Jessica L Andrews and Francesca Fernandez-Enright. Genetic variants in Nogo receptor signaling pathways may be associated with early life adversity in schizophrenia susceptibility. *BBA clinical*, 3:36–43, 6 2015.

[79] H U Wittchen and F Jacobi. Size and burden of mental disorders in Europe–a critical review and appraisal of 27 studies. *Eur Neuropsychopharmacol*, 15(4):357–376, 2005.

[80] H U Wittchen, F Jacobi, J Rehm, A Gustavsson, M Svensson, B Jonsson, J Olesen, C Allgulander, J Alonso, C Faravelli, L Fratiglioni, P Jennum, R Lieb, A Maercker, J van Os, M Preisig, L Salvador-Carulla, R Simon, and H C Steinhausen. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*, 21(9):655–679, 2011.

[81] Edward Chesney, Guy M Goodwin, and Seena Fazel. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World psychiatry*, 13(2):153–160, 2014.

[82] N Sartorious. Comorbidity of mental and physical diseases: a main challenge for medicine of the 21st century. *Shanghai Arch Psychiatry*, 25(2):68–69, 2013.

[83] T Klengel and E B Binder. Epigenetics of Stress-Related Psychiatric Disorders and Gene x Environment Interactions. *Neuron*, 86(6):1343–1357, 2015.

[84] N Bhore, B J Wang, Y W Chen, and Y F Liao. Critical Roles of Dual-Specificity Phosphatases in Neuronal Proteostasis and Neurological Diseases. *Int J Mol Sci*, 18(9), 2017.

[85] O M Seternes, A M Kidger, and S M Keyse. Dual-specificity MAP kinase phosphatases in health and disease. *Biochim Biophys Acta Mol Cell Res*, 1866(1):124–143, 2019.

[86] Kate I Patterson, Tilman Brummer, Philippa M O'Brien, and Roger J Daly. Dual-specificity phosphatases: critical regulators with diverse cellular targets. *Biochemical Journal*, 418(3):475–489, 4 2009.

[87] A Carracedo and P P Pandolfi. The PTEN-PI3K pathway: of feedbacks and cross-talks. *Oncogene*, 27(41):5527–5541, 2008.

[88] R Perez-Sen, M J Queipo, J C Gil-Redondo, Felipe Ortega, Rosa Gomez-Villafuertes, M T Miras-Portugal, Esmerilda G Delicado, Raquel Pérez-Sen, María José Queipo García, Gil-Redondo, Felipe Ortega, Rosa Gomez-Villafuertes, M T Miras-Portugal, and Esmerilda G Delicado. Dual-Specificity Phosphatase Regulation in Neurons and Glial Cells. *International Journal of Molecular Sciences*, 20(8):1999, 4 2019.

[89] O Bermudez, G Pages, and C Gimond. The dual-specificity MAP kinase phosphatases: critical roles in development and cancer. *Am J Physiol Cell Physiol*, 299(2):C189–202, 2010.

[90] H B Low and Y Zhang. Regulatory Roles of MAPK Phosphatases in Cancer. *Immune Netw*, 16(2):85–98, 2016.

[91] P Rios, C E Nunes-Xavier, L Tabernero, M Kohn, and R Pulido. Dual-specificity phosphatases as molecular targets for inhibition in human disease. *Antioxid Redox Signal*, 20(14):2251–2273, 2014.

[92] R Lang, M Hammer, and J Mages. DUSP meet immunology: dual specificity MAPK phosphatases in control of the inflammatory response. *J Immunol*, 177(11):7497–7504, 2006.

[93] C Y Huang and T H Tan. DUSPs, to MAP kinases and beyond. *Cell Biosci*, 2(1):24, 2012.

[94] S K Jung, D G Jeong, T S Yoon, J H Kim, S E Ryu, and S J Kim. Crystal structure of human slingshot phosphatase 2. *Proteins-Structure Function and Bioinformatics*, 68(1):408–412, 2007.

[95] L S Minamide, A M Striegl, J A Boyle, P J Meberg, and J R Bamburg. Neurodegenerative stimuli induce persistent ADF/cofilin-actin rods that disrupt distal neurite function. *Nat Cell Biol*, 2(9):628–636, 2000.

[96] Y Ohta, K Kousaka, K Nagata-Ohashi, K Ohashi, A Muramoto, Y Shima, R Niwa, T Uemura, and K Mizuno. Differential activities, subcellular distribution and tissue expression patterns of three members of Slingshot family phosphatases that dephosphorylate cofilin. *Genes Cells*, 8(10):811–824, 2003.

[97] D Barford, A K Das, and M P Egloff. The structure and mechanism of protein phosphatases: insights into catalysis and regulation. *Annu Rev Biophys Biomol Struct*, 27:133–164, 1998.

[98] R Niwa, K Nagata-Ohashi, M Takeichi, K Mizuno, and T Uemura. Control of actin reorganization by Slingshot, a family of phosphatases that dephosphorylate ADF/cofilin. *Cell*, 108(2):233–246, 2002.

[99] M Uhlen, P Oksvold, L Fagerberg, E Lundberg, K Jonasson, M Forsberg, M Zwahlen, C Kampf, K Wester, S Hober, H Wernerus, L Bjorling, and F Ponten. Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol*, 28(12):1248–1250, 2010.

[100] E Barone, S Mosser, and P C Fraering. Inactivation of brain Cofilin-1 by age, Alzheimer's disease and gamma-secretase. *Biochim Biophys Acta*, 1842(12 Pt A):2500–2509, 2014.

[101] S Zafar, N Younas, N Sheikh, W Tahir, M Shafiq, M Schmitz, I Ferrer, O Andreoletti, and I Zerr. Cytoskeleton-Associated Risk Modifiers Involved in Early and Rapid Progression of Sporadic Creutzfeldt-Jakob Disease. *Mol Neurobiol*, 2017.

[102] K Kligys, J N Claiborne, P J DeBiase, S B Hopkinson, Y Wu, K Mizuno, and J C Jones. The slingshot family of phosphatases mediates Rac1 regulation of cofilin phosphorylation, laminin-332 organization, and motility behavior of keratinocytes. *J Biol Chem*, 282(44):32520–32528, 2007.

[103] M Endo, K Ohashi, and K Mizuno. LIM kinase and slingshot are critical for neurite extension. *Journal of Biological Chemistry*, 282(18):13692–13702, 2007.

[104] M Endo, K Ohashi, Y Sasaki, Y Goshima, R Niwa, T Uemura, and K Mizuno. Control of growth cone motility and morphology by LIM kinase and Slingshot via phosphorylation and dephosphorylation of cofilin. *J Neurosci*, 23(7):2527–2537, 2003.

[105] J S Kim, T Y Huang, and G M Bokoch. Reactive oxygen species regulate a slingshot-cofilin activation pathway. *Mol Biol Cell*, 20(11):2650–2660, 2009.

[106] Y Wang, F Shibasaki, and K Mizuno. Calcium signal-induced cofilin dephosphorylation is mediated by Slingshot via calcineurin. *J Biol Chem*, 280(13):12683–12689, 2005.

[107] J Soosairajah, S Maiti, O Wiggan, P Sarmiere, N Moussi, B Sarcevic, R Sampath, J R Bamburg, and O Bernard. Interplay between components of a novel LIM kinase-slingshot phosphatase complex regulates cofilin. *EMBO J*, 24(3):473–486, 2005.

[108] P J Meberg, S Ono, L S Minamide, M Takahashi, and J R Bamburg. Actin depolymerizing factor and cofilin phosphorylation dynamics: response to signals that regulate neurite extension. *Cell Motil Cytoskeleton*, 39(2):172–190, 1998.

[109] K Ohashi. Roles of cofilin in development and its mechanisms of regulation. *Dev Growth Differ*, 57(4):275–290, 2015.

[110] Z Wen, L Han, J R Bamburg, S Shim, G L Ming, and J Q Zheng. BMP gradients steer nerve growth cones by a balancing act of LIM kinase and Slingshot phosphatase on ADF/cofilin. *J Cell Biol*, 178(1):107–119, 2007.

[111] S H Hsieh, G B Ferraro, and A E Fournier. Myelin-associated inhibitors regulate cofilin phosphorylation and neuronal inhibition through LIM kinase and Slingshot phosphatase. *J Neurosci*, 26(3):1006–1015, 2006.

[112] N Sparrow, M E Manetti, M Bott, T Fabianac, A Petrilli, M L Bates, M B Bunge, S Lambert, and C Fernandez-Valle. The actin-severing protein cofilin is downstream of neuregulin signaling and is essential for Schwann cell myelination. *J Neurosci*, 32(15):5284–5297, 2012.

[113] S Tielens, S Huysseune, J D Godin, A Chariot, B Malgrange, and L Nguyen. Elongator controls cortical interneuron migration by regulating actomyosin dynamics. *Cell Res*, 26(10):1131–1148, 2016.

[114] E Y Yuen, W Liu, T Kafri, H van Praag, and Z Yan. Regulation of AMPA receptor channels and synaptic plasticity by cofilin phosphatase Slingshot in cortical neurons. *J Physiol*, 588(Pt 13):2361–2371, 2010.

[115] M Wei, K V Korotkov, and J S Blackburn. Targeting phosphatases of regenerating liver (PRLs) in cancer. *Pharmacol Ther*, 190:128–138, 2018.

[116] A M Campbell and Z Y Zhang. Phosphatase of regenerating liver: a novel target for cancer therapy. *Expert Opin Ther Targets*, 18(5):555–569, 2014.

[117] P Rios, X Li, and M Kohn. Molecular mechanisms of the PRL phosphatases. *FEBS J*, 280(2):505–524, 2013.

[118] C M Dumaual, G E Sandusky, P L Crowell, and S K Randall. Cellular localization of PRL-1 and PRL-2 gene expression in normal adult human tissues. *J Histochem Cytochem*, 54(12):1401–1412, 2006.

[119] William F Matter, Thomas Estridge, Chen Zhang, Rama Belagaje, Louis Stancato, Jeff Dixon, Brian Johnson, Laura Bloem, Todd Pickard, and Mary Donaghue. Role of PRL-3, a human muscle-specific tyrosine phosphatase, in angiotensin-II signaling. *Biochemical and biophysical research communications*, 283(5):1061–1068, 2001.

[120] Qi Zeng, Wanjin Hong, and Y H Tan. Mouse PRL-2 and PRL-3, two potentially prenylated protein tyrosine phosphatases homologous to PRL-1. *Biochemical and biophysical research communications*, 244(2):421–427, 1998.

[121] Y Luo, F Liang, and Z Y Zhang. PRL1 promotes cell migration and invasion by increasing MMP2 and MMP9 expression through Src and ERK1/2 pathways. *Biochemistry*, 48(8):1838–1846, 2009.

[122] L Peng, X Xing, W Li, L Qu, L Meng, S Lian, B Jiang, J Wu, and C Shou. PRL-3 promotes the motility, invasion, and metastasis of LoVo colon cancer cells through PRL-3-integrin beta1-ERK1/2 and-MMP2 signaling. *Mol Cancer*, 8:110, 2009.

[123] Z Ye, A Q Al-Aidaroos, J E Park, H F Yuen, S D Zhang, A Gupta, Y Lin, H M Shen, and Q Zeng. PRL-3 activates mTORC1 in Cancer Progression. *Sci Rep*, 5:17046, 2015.

[124] Y Zhang, Z Li, X Fan, J Xiong, G Zhang, X Luo, K Li, Z Jie, Y Cao, Z Huang, F Wu, L Xiao, G Duan, and H Chen. PRL-3 promotes gastric cancer peritoneal metastasis via the PI3K/AKT signaling pathway in vitro and in vivo. *Oncol Lett*, 15(6):9069–9074, 2018.

[125] Dawn M Clifford, Chun-Ti Chen, Rachel H Roberts, Anna Feoktistova, Benjamin A Wolfe, Jun-Song Chen, Dannel McCollum, and Kathleen L Gould. The role of Cdc14 phosphatases in the control of cell division. *Biochem Soc Trans.*, 36(3):436–438, 2008.

[126] Susanne Trautmann and Dannel McCollum. Cell cycle: new functions for Cdc14 family phosphatases. *Current biology*, 12(21):R733–R735, 2002.

[127] S C Bremmer, H Hall, J S Martinez, C L Eissler, T H Hinrichsen, S Rossie, L L Parker, M C Hall, and H Charbonneau. Cdc14 phosphatases preferentially dephosphorylate a subset of cyclin-dependent kinase (Cdk) sites containing phosphoserine. *J Biol Chem*, 287(3):1662–1669, 2012.

[128] L Rosso, A C Marques, M Weier, N Lambert, M A Lambot, P Vanderhaeghen, and H Kaessmann. Birth and rapid subcellular adaptation of a hominoid-specific CDC14 protein. *PLoS Biol*, 6(6):e140, 2008.

[129] A Mocciaro and E Schiebel. Cdc14: a highly conserved family of phosphatases with non-conserved functions? *J Cell Sci*, 123(Pt 17):2867–2876, 2010.

[130] C H Gray, V M Good, N K Tonks, and D Barford. The structure of the cell cycle protein Cdc14 reveals a proline-directed protein phosphatase. *EMBO J*, 22(14):3524–3535, 2003.

[131] N Mailand, C Lukas, B K Kaiser, P K Jackson, J Bartek, and J Lukas. Deregulated human Cdc14A phosphatase disrupts centrosome separation and chromosome segregation. *Nat Cell Biol*, 4(4):317–322, 2002.

[132] F Stegmeier and A Amon. Closing mitosis: the functions of the Cdc14 phosphatase and its regulation. *Annu Rev Genet*, 38:203–232, 2004.

[133] D Govender and R Chetty. Gene of the month: PTEN. *J Clin Pathol*, 65(7):601–603, 2012.

[134] S Knafo and J A Esteban. PTEN: Local and Global Modulation of Neuronal Function in Health and Disease. *Trends Neurosci*, 40(2):83–91, 2017.

[135] H Liang, X Chen, Q Yin, D Ruan, X Zhao, C Zhang, M A McNutt, and Y Yin. PTENbeta is an alternatively translated isoform of PTEN that regulates rDNA transcription. *Nat Commun*, 8:14771, 2017.

[136] Benjamin D Hopkins, Cindy Hodakoski, Douglas Barrows, Sarah M Mense, and Ramon E Parsons. PTEN function: the long and the short of it. *Trends in biochemical sciences*, 39(4):183–190, 2014.

[137] Carolyn A Worby and Jack E Dixon. Pten. *Annu Rev Biochem*, 83:641–669, 2014.

[138] J O Lee, H Yang, M M Georgescu, A Di Cristofano, T Maehama, Y Shi, J E Dixon, P Pandolfi, and N P Pavletich. Crystal structure of the PTEN tumor suppressor: implications for its phosphoinositide phosphatase activity and membrane association. *Cell*, 99(3):323–334, 1999.

[139] Hui Liang, Shiming He, Jingyi Yang, Xinying Jia, Pan Wang, Xi Chen, Zhong Zhang, Xiajuan Zou, Michael A McNutt, Wen Hong Shen, and Yuxin Yin. PTENα is a PTEN isoform Translated through Alternative Initiation and Regulates Mitochondrial Function. *Cell metabolism*, 19(5):836–848, 2014.

[140] P Kreis, G Leondaritis, I Lieberam, and B J Eickholt. Subcellular targeting and dynamic regulation of PTEN: implications for neuronal cells and neurological disorders. *Front Mol Neurosci*, 7:23, 2014.

[141] C L LaSarge, R Y Pun, M B Muntifering, and S C Danzer. Disrupted hippocampal network physiology following PTEN deletion from newborn dentate granule cells. *Neurobiol Dis*, 96:105–114, 2016.

[142] Matthias Ebert, Guo Fei, Pedro Herrera, Helmut Friess, Markus Buechler, and Peter Malfertheiner. Over-expression of transforming growth factor beta-1 (TGF-B1) is associated with reduced pten expression in pancreatic fibrosis and cancer. *Gastroenterology*, 118(4):A650, 2000.

[143] Q Y Cai, X S Chen, S C Zhong, X Luo, and Z X Yao. Differential expression of PTEN in normal adult rat brain and upregulation of PTEN and p-Akt in the ischemic cerebral cortex. *Anat Rec (Hoboken)*, 292(4):498–512, 2009.

[144] M Bermudez Brito, E Goulielmaki, and E A Papakonstanti. Focus on PTEN Regulation. *Front Oncol*, 5:166, 2015.

[145] N R Leslie and C P Downes. PTEN: The down side of PI 3-kinase signalling. *Cell Signal*, 14(4):285–295, 2002.

[146] B Ye, L L Jiang, H T Xu, D W Zhou, and Z S Li. Expression of PI3K/AKT pathway in gastric cancer and its blockade suppresses tumor growth and metastasis. *Int J Immunopathol Pharmacol*, 25(3):627–636, 2012.

[147] Y Ohtake, U Hayat, and S Li. PTEN inhibition and axon regeneration and neural repair. *Neural Regen Res*, 10(9):1363–1368, 2015.

[148] W H Shen, A S Balajee, J Wang, H Wu, C Eng, P P Pandolfi, and Y Yin. Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell*, 128(1):157–170, 2007.

[149] M A Raess, S Friant, B S Cowling, and J Laporte. WANTED - Dead or alive: Myotubularins, a large disease-associated protein family. *Adv Biol Regul*, 63:49–58, 2017.

[150] Michael J Begley and Jack E Dixon. The structure and regulation of myotubularin phosphatases. *Current opinion in structural biology*, 15(6):614–620, 2005.

[151] J Laporte, F Blondeau, A Gansmuller, Y Lutz, J L Vonesch, and J L Mandel. The PtdIns3P phosphatase myotubularin is a cytoplasmic protein that also localizes to Rac1-inducible plasma membrane ruffles. *J Cell Sci*, 115(Pt 15):3105–3117, 2002.

[152] K Hnia, I Vaccari, A Bolino, and J Laporte. Myotubularin phosphoinositide phosphatases: cellular functions and disease pathophysiology. *Trends Mol Med*, 18(6):317–327, 2012.

[153] S C Previtali, B Zerega, D L Sherman, P J Brophy, G Dina, R H King, M M Salih, L Feltri, A Quattrini, R Ravazzolo, L Wrabetz, A P Monaco, and A Bolino. Myotubularin-related 2 protein phosphatase and neurofilament light chain protein, both mutated in CMT neuropathies, interact in peripheral nerve. *Hum Mol Genet*, 12(14):1713–1723, 2003.

[154] A Bolis, S Coviello, I Visigalli, C Taveggia, A Bachi, A H Chishti, T Hanada, A Quattrini, S C Previtali, A Biffi, and A Bolino. Dlg1, Sec8, and Mtmr2 regulate membrane homeostasis in Schwann cell myelination. *J Neurosci*, 29(27):8858–8870, 2009.

[155] A Bolino, M Muglia, F L Conforti, E LeGuern, M A Salih, D M Georgiou, K Christodoulou, I Hausmanowa-Petrusewicz, P Mandich, A Schenone, A Gambardella, F Bono, A Quattrone, M Devoto, and A P Monaco. Charcot-Marie-Tooth type 4B is caused by mutations in the gene encoding myotubularin-related protein-2. *Nat Genet*, 25(1):17–19, 2000.

[156] K Kondoh and E Nishida. Regulation of MAP kinases by MAP kinase phosphatases. *Biochim Biophys Acta*, 1773(8):1227–1237, 2007.

[157] C J Caunt and S M Keyse. Dual-specificity MAP kinase phosphatases (MKPs): shaping the outcome of MAP kinase signalling. *FEBS J*, 280(2):489–504, 2013.

[158] Y Dwivedi, H S Rizavi, R C Roberts, R C Conley, C A Tamminga, and G N Pandey. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J Neurochem*, 77(3):916–928, 2001.

[159] E K Kim and E J Choi. Compromised MAPK signaling in human diseases: an update. *Arch Toxicol*, 89(6):867–882, 2015.

[160] P Yuan, R Zhou, Y Wang, X Li, J Li, G Chen, X Guitart, and H K Manji. Altered levels of extracellular signal-regulated kinase signaling proteins in postmortem frontal cortex of individuals with mood disorders and schizophrenia. *J Affect Disord*, 124(1-2):164–169, 2010.

[161] D M Owens and S M Keyse. Differential regulation of MAP kinase signalling by dual-specificity protein phosphatases. *Oncogene*, 26(22):3203–3213, 2007.

[162] Erica L Cain and Alexander Beeser. Emerging Roles of Atypical Dual Specificity Phosphatases in Cancer. *Oncogene and Cancer-From Bench to Clinic*, 93, 2013.

[163] Yolanda Bayón and Andrés Alonso. Atypical DUSPs: 19 phosphatases in search of a role. *Emerging Signaling Pathways in Tumor Biology*, pages 185–208, 2010.

[164] Graham Thornicroft, Somnath Chatterji, Sara Evans-Lacko, Michael Gruber, Nancy Sampson, Sergio Aguilar-Gaxiola, Ali Al-Hamzawi, Jordi Alonso, Laura Andrade, and Guilherme Borges. Undertreatment of people with major depressive disorder in 21 countries. *The British Journal of Psychiatry*, 210(2):119–124, 2017.

[165] Paul Willner, Jørgen Scheel-Krüger, and Catherine Belzung. The neurobiology of depression and antidepressant action. *Neuroscience & Biobehavioral Reviews*, 37(10):2331–2371, 2013.

[166] L J Liu, C Zhu, H J Tian, T S Zheng, M J Ye, and H Li. Correlations of PTEN genetic polymorphisms with the risk of depression and depressive symptoms in a Chinese population. *Gene*, 595(1):77–82, 2016.

[167] F Karege, N Perroud, S Burkhardt, R Fernandez, E Ballmann, R La Harpe, and A Malafosse. Alterations in phosphatidylinositol 3-kinase activity and PTEN phosphatase in the prefrontal cortex of depressed suicide victims. *Neuropsychobiology*, 63(4):224–231, 2011.

[168] Zhifang Deng, Cheng Yuan, Jian Yang, Yan Peng, Wei Wang, Yan Wang, and Wenqi Gao. Behavioral defects induced by chronic social defeat stress are protected by Momordica charantia polysaccharides via attenuation of JNK3/PI3K/AKT neuroinflammatory pathway. *Annals of translational medicine*, 7(1), 2019.

[169] Zuotian Wu, Gaohua Wang, Yanyan Wei, Ling Xiao, and Huiling Wang. PI3K/AKT/GSK3β/CRMP-2-mediated neuroplasticity in depression induced by stress. *Neuroreport*, 29(15):1256–1263, 2018.

[170] M P Cunha, J Budni, F K Ludka, F L Pazini, J M Rosa, A Oliveira, M W Lopes, C I Tasca, R B Leal, and A L S Rodrigues. Involvement of PI3K/Akt Signaling Pathway and Its Downstream Intracellular Targets in the Antidepressant-Like Effect of Creatine. *Mol Neurobiol*, 53(5):2954–2968, 2016.

[171] Fabiana Kalyne Ludka, Leandra Celso Constantino, Tharine Dal-Cim, Luisa Bandeira Binder, Andréa Zomkowski, Ana Lúcia S Rodrigues, and Carla Inês Tasca. Involvement of PI3K/Akt/GSK-3β and mTOR in the antidepressant-like effect of atorvastatin in mice. *Journal of psychiatric research*, 82:50–57, 2016.

[172] C Pittenger and R S Duman. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*, 33(1):88–109, 2008.

[173] S Akbarian and R J Davis. Keep the 'phospho' on MAPK, be happy. *Nat Med*, 16(11):1187–1188, 2010.

[174] V Duric, M Banasr, P Licznerski, H D Schmidt, C A Stockmeier, A A Simen, S S Newton, and R S Duman. A negative regulator of MAP kinase causes depressive behavior. *Nat Med*, 16(11):1328–1332, 2010.

[175] Y Dwivedi, H S Rizavi, R R Conley, R C Roberts, C A Tamminga, and G N Pandey. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry*, 60(8):804–815, 2003.

[176] Y Dwivedi, H S Rizavi, R R Conley, and G N Pandey. ERK MAP kinase signaling in post-mortem brain of suicide subjects: differential regulation of upstream Raf kinases Raf-1 and B-Raf. *Mol Psychiatry*, 11(1):86–98, 2006.

[177] Wataru Iio, Noriko Matsukawa, Takamitsu Tsukahara, Daisuke Kohari, and Atsushi Toyoda. Effects of chronic social defeat stress on MAP kinase cascade. *Neurosci Lett*, 504(3):281–284, 10 2011.

[178] Yan Zhao, Shuang Wang, Zheng Chu, Yonghui Dang, Juanxia Zhu, and Xingli Su. MicroRNA-101 in the ventrolateral orbital cortex (VLO) modulates depressive-like behaviors in rats and targets dual-specificity phosphatase 1 (DUSP1). *Brain Research*, 1669:55–62, 2017.

[179] F Llorens, M Banez-Coronel, L Pantano, J A del Rio, I Ferrer, X Estivill, and E Marti. A highly expressed miR-101 isomiR is a functional silencing small RNA. *BMC Genomics*, 14:104, 2013.

[180] Q Y Zhu, Q Liu, J X Chen, K Lan, and B X Ge. MicroRNA-101 targets MAPK phosphatase-1 to regulate the activation of MAPKs in macrophages. *J Immunol*, 185(12):7435–7442, 2010.

[181] E Vilardo, C Barbato, M Ciotti, C Cogoni, and F Ruberti. MicroRNA-101 regulates amyloid precursor protein expression in hippocampal neurons. *J Biol Chem*, 285(24):18344–18351, 2010.

[182] M Kodama, D S Russell, and R S Duman. Electroconvulsive seizures increase the expression of MAP kinase phosphatases in limbic regions of rat brain. *Neuropsychopharmacology*, 30(2):360–371, 2005.

[183] B Labonte, O Engmann, I Purushothaman, C Menard, J Wang, C Tan, J R Scarpa, G Moy, Y E Loh, M Cahill, Z S Lorsch, P J Hamilton, E S Calipari, G E Hodes, O Issler, H Kronman, M Pfau, A L J Obradovic, Y Dong, R L Neve, S Russo, A Kazarskis, C Tamminga, N Mechawar, G Turecki, B Zhang, L Shen, and E J Nestler. Sex-specific transcriptional signatures in human depression. *Nat Med*, 23(9):1102–1111, 2017.

[184] Bogusława Budziszewska, M Szymanska, M Leskiewicz, Agnieszka Basta-Kaim, L Jaworska-Feil, Marta Kubera, Danuta Jantas, W Lason, Magdalena Szymańska, M Leskiewicz, Agnieszka Basta-Kaim, L Jaworska-Feil, Marta Kubera, Danuta Jantas, Władysław Lasoń, M Szymanska, M Leskiewicz, Agnieszka Basta-Kaim, L Jaworska-Feil, Marta Kubera, Danuta Jantas, and W Lason. The decrease in JNK- and p38-MAP kinase activity is accompanied by the enhancement of PP2A phosphate level in the brain of prenatally stressed rats. *J Physiol Pharmacol*, 61(2):207–215, 4 2010.

[185] P Feng, Z Guan, X Yang, and J Fang. Impairments of ERK signal transduction in the brain in a rat model of depression induced by neonatal exposure of clomipramine. *Brain Res*, 991(1-2):195–205, 2003.

[186] Paul J Harrison, John R Geddes, and Elizabeth M Tunbridge. The emerging neurobiology of bipolar disorder. *Trends in neurosciences*, 41(1):18–30, 2018.

[187] Tobias A Rowland and Steven Marwaha. Epidemiology and risk factors for bipolar disorder. *Therapeutic advances in psychopharmacology*, 8(9):251–269, 2018.

[188] Ekaterina Sigitova, Zdeněk Fišar, Jana Hroudová, Tereza Cikánková, and Jiří Raboch. Biological hypotheses and biomarkers of bipolar disorder. *Psychiatry and clinical neurosciences*, 71(2):77–103, 2017.

[189] Izabela Guimarães Barbosa, Natália Pessoa Rocha, Frankcinéia Assis, Érica Leandro Marciano Vieira, Jair C Soares, Moises Evandro Bauer, and Antônio Lúcio Teixeira. Monocyte and lymphocyte activation in bipolar disorder: a new piece in the puzzle of immune dysfunction in mood disorders. *International Journal of Neuropsychopharmacology*, 18(1), 2015.

[190] Joel Jakobsson, Maria Bjerke, Sara Sahebi, Anniella Isgren, Carl Johan Ekman, Carl Sellgren, Bob Olsson, Henrik Zetterberg, Kaj Blennow, and Erik Pålsson. Monocyte and microglial activation in patients with mood-stabilized bipolar disorder. *Journal of psychiatry & neuroscience: JPN*, 40(4):250, 2015.

[191] R C Drexhage, L van der Heul-Nieuwenhuijsen, R C Padmos, N van Beveren, D Cohen, M A Versnel, W A Nolen, and H A Drexhage. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients. *Int J Neuropsychopharmacol*, 13(10):1369–1381, 2010.

[192] R C Padmos, M H Hillegers, E M Knijff, R Vonk, A Bouvy, F J Staal, D de Ridder, R W Kupka, W A Nolen, and H A Drexhage. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry*, 65(4):395–407, 2008.

[193] S H Kim, S Y Shin, K Y Lee, E J Joo, J Y Song, Y M Ahn, Y H Lee, and Y S Kim. The genetic association of DUSP6 with bipolar disorder and its effect on ERK activity. *Prog Neuropsychopharmacol Biol Psychiatry*, 37(1):41–49, 2012.

[194] K Y Lee, Y M Ahn, E J Joo, J S Chang, and Y S Kim. The association of DUSP6 gene with schizophrenia and bipolar disorder: its possible role in the development of bipolar disorder. *Mol Psychiatry*, 11(5):425–426, 2006.

[195] Jan Struyf, Seth Dobrin, and David Page. Combining gene expression, demographic and clinical data in modeling disease: a case study of bipolar disorder and schizophrenia. *Bmc Genomics*, 9(1):531, 2008.

[196] M J McCarthy, H Wei, D Landgraf, M J Le Roux, and D K Welsh. Disinhibition of the extracellular-signal-regulated kinase restores the amplification of circadian rhythms by lithium in cells from bipolar disorder patients. *Eur Neuropsychopharmacol*, 26(8):1310–1319, 2016.

[197] Jakob Grove, Stephan Ripke, Thomas D Als, Manuel Mattheisen, Raymond K Walters, Hyejung Won, Jonatan Pallesen, Esben Agerbo, Ole A Andreassen, and Richard Anney. Identification of common genetic risk variants for autism spectrum disorder. *Nature genetics*, 51(3):431–444, 2019.

[198] Pauline Chaste and Marion Leboyer. Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues in clinical neuroscience*, 14(3):281, 2012.

[199] M G Butler, M J Dasouki, X P Zhou, Z Talebizadeh, M Brown, T N Takahashi, J H Miles, C H Wang, R Stratton, R Pilarski, and C Eng. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet*, 42(4):318–321, 2005.

[200] J D Buxbaum, G Cai, P Chaste, G Nygren, J Goldsmith, J Reichert, H Anckarsater, M Rastam, C J Smith, J M Silverman, E Hollander, M Leboyer, C Gillberg, A Verloes, and C Betancur. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am J Med Genet B Neuropsychiatr Genet*, 144B(4):484–491, 2007.

[201] G E Herman, E Butter, B Enrile, M Pastore, T W Prior, and A Sommer. Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly. *Am J Med Genet A*, 143A(6):589–593, 2007.

[202] T W Frazier, R Embacher, A K Tilot, K Koenig, J Mester, and C Eng. Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism. *Mol Psychiatry*, 20(9):1132–1138, 2015.

[203] A K Tilot, T W Frazier 2nd, and C Eng. Balancing Proliferation and Connectivity in PTEN-associated Autism Spectrum Disorder. *Neurotherapeutics*, 12(3):609–619, 2015.

[204] A Amiri, W Cho, J Zhou, S G Birnbaum, C M Sinton, R M McKay, and L F Parada. Pten deletion in adult hippocampal neural stem/progenitor cells causes cellular abnormalities and alters neurogenesis. *J Neurosci*, 32(17):5880–5890, 2012.

[205] Amanda K Tilot, Gurkan Bebek, Farshad Niazi, J B Altemus, Todd Romigh, Thomas W Frazier, and Charis Eng. Neural transcriptome of constitutional Pten dysfunction in mice and its relevance to human idiopathic autism spectrum disorder. *Molecular psychiatry*, 21(1):118–125, 2016.

[206] Y Tian, L Wang, M Jia, T Lu, Y Ruan, Z Wu, L Wang, J Liu, and D Zhang. Association of oligodendrocytes differentiation regulator gene DUSP15 with autism. *World J Biol Psychiatry*, 18(2):143–150, 2017.

[207] Benjamin M Neale, Yan Kou, Li Liu, Avi Ma'Ayan, Kaitlin E Samocha, Aniko Sabo, Chiao-Feng Lin, Christine Stevens, Li-San Wang, and Vladimir Makarov. Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*, 485(7397):242–245, 2012.

[208] Kim T. Mueser and Susan R. McGurk. Schizophrenia. *Lancet (London, England)*, 363(9426):2063–2072, 6 2004.

[209] J van Os, G Kenis, and B P Rutten. The environment and schizophrenia. *Nature*, 468(7321):203–212, 2010.

[210] Nancy C Andreasen and Scott Olsen. Negative v positive schizophrenia: Definition and validation. *Archives of general psychiatry*, 39(7):789–794, 1982.

[211] Michael J Owen, Akira Sawa, and Preben B Mortensen. Schizophrenia. *Lancet*, 388(10039):86–97, 7 2016.

[212] S V Kyosseva, A D Elbein, W S Griffin, R E Mrak, M Lyon, and C N Karson. Mitogen-activated protein kinases in schizophrenia. *Biol Psychiatry*, 46(5):689–696, 1999.

[213] M Hirayama-Kurogi, Y Takizawa, Y Kunii, J Matsumoto, A Wada, M Hino, H Akatsu, Y Hashizume, S Yamamoto, T Kondo, S Ito, M Tachikawa, S I Niwa, H Yabe, T Terasaki, M Setou, and S Ohtsuki. Downregulation of GNA13-ERK network in prefrontal cortex of schizophrenia brain identified by combined focused and targeted quantitative proteomics. *J Proteomics*, 2017.

[214] M P Boks, L C Houtepen, Z Xu, Y He, G Ursini, A X Maihofer, P Rajarajan, Q Yu, H Xu, Y Wu, S Wang, J P Shi, H E Hulshoff Pol, E Strengman, B P F Rutten, A E Jaffe, J E Kleinman, D G Baker, E M Hol, S Akbarian, C M Nievergelt, L D De Witte, C H Vinkers, D R Weinberger, J Yu, and R S Kahn. Genetic vulnerability to DUSP22 promoter hypermethylation is involved in the relation between in utero famine exposure and schizophrenia. *NPJ Schizophr*, 4(1):16, 2018.

[215] N A Bowden, J Weidenhofer, R J Scott, U Schall, J Todd, P T Michie, and P A Tooney. Preliminary investigation of gene expression profiles in peripheral blood lymphocytes in schizophrenia. *Schizophr Res*, 82(2-3):175–183, 2006.

[216] A Schmitt, F Leonardi-Essmann, P F Durrenberger, S P Wichert, R Spanagel, T Arzberger, H Kretzschmar, M Zink, M Herrera-Marschitz, R Reynolds, M J Rossner, P Falkai, and P J Gebicke-Haerter. Structural synaptic elements are differentially regulated in superior temporal cortex of schizophrenia patients. *Eur Arch Psychiatry Clin Neurosci*, 262(7):565–577, 2012.

[217] D Mehta and E B Binder. Gene x environment vulnerability factors for PTSD: the HPA-axis. *Neuropharmacology*, 62(2):654–662, 2012.

[218] Rachel Yehuda, Charles W Hoge, Alexander C McFarlane, Eric Vermetten, Ruth A Lanius, Caroline M Nievergelt, Stevan E Hobfoll, Karestan C Koenen, Thomas C Neylan, and Steven E Hyman. Post-traumatic stress disorder. *Nature Reviews Disease Primers*, 1(1):1–22, 2015.

[219] P Watson. PTSD as a Public Mental Health Priority. *Curr Psychiatry Rep*, 21(7):61, 2019.

[220] M J Friedman and N C Bernardy. Considering future pharmacotherapy for PTSD. *Neurosci Lett*, 649:181–185, 2017.

[221] S R Horn, D S Charney, and A Feder. Understanding resilience: New approaches for preventing and treating PTSD. *Exp Neurol*, 284(Pt B):119–132, 2016.

[222] M M Steenkamp, B T Litz, C W Hoge, and C R Marmar. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*, 314(5):489–500, 2015.

[223] A J Lang. Mindfulness in PTSD treatment. *Curr Opin Psychol*, 14:40–43, 2017.

[224] P Scheltens, K Blennow, M M Breteler, B de Strooper, G B Frisoni, S Salloway, and W M Van der Flier. Alzheimer's disease. *Lancet*, 388(10043):505–517, 2016.

[225] Dhamidhu Eratne, Samantha M Loi, Sarah Farrand, Wendy Kelso, Dennis Velakoulis, and Jeffrey C L Looi. Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. *Australasian Psychiatry*, 26(4):347–357, 2018.

[226] Colin L Masters, Randall Bateman, Kaj Blennow, Christopher C Rowe, Reisa A Sperling, and Jeffrey L Cummings. Alzheimer's disease. *Nature reviews. Disease primers*, 1:15056, 2015.

[227] M S Rafii. Update on Alzheimer's disease therapeutics. *Rev Recent Clin Trials*, 8(2):110–118, 2013.

[228] Yexiang Yehong Du, Yexiang Yehong Du, Yun Zhang, Zhilin Huang, Min Fu, Junjie Li, Yayan Pang, Peng Lei, Yu Tian Wang, and Weihong Song. MKP-1 reduces Aβ generation and alleviates cognitive impairments in Alzheimer's disease models. *Signal transduction and targeted therapy*, 4(1):1–12, 2019.

[229] Yue Gu, Lian-Jun Ma, Xiao-Xue Bai, Jing Jie, Xiu-Fang Zhang, Dong Chen, and Xiao-Ping Li. Mitogen-activated protein kinase phosphatase 1 protects PC12 cells from amyloid beta-induced neurotoxicity. *Neural regeneration research*, 13(10):1842, 2018.

[230] S Jung, J Nah, J Han, S G Choi, H Kim, J Park, H K Pyo, and Y K Jung. Dual-specificity phosphatase 26 (DUSP26) stimulates Abeta42 generation by promoting amyloid precursor protein axonal transport during hypoxia. *J Neurochem*, 137(5):770–781, 2016.

[231] Yaping Wang and Zhiyun Wang. Identification of dysregulated genes and pathways of different brain regions in Alzheimer's disease. *International Journal of Neuroscience*, pages 1–13, 2020.

[232] D E Kang, S E Roh, J A Woo, T Liu, J H Bu, A R Jung, and Y Lim. The Interface between Cytoskeletal Aberrations and Mitochondrial Dysfunction in Alzheimer's Disease and Related Disorders. *Exp Neurobiol*, 20(2):67–80, 2011.

[233] J V Sanchez-Mut, E Aso, H Heyn, T Matsuda, C Bock, I Ferrer, and M Esteller. Promoter hypermethylation of the phosphatase DUSP22 mediates PKA-dependent TAU phosphorylation and CREB activation in Alzheimer's disease. *Hippocampus*, 24(4):363–368, 2014.

[234] A Rickle, N Bogdanovic, I Volkmann, X Zhou, J J Pei, B Winblad, and R F Cowburn. PTEN levels in Alzheimer's disease medial temporal cortex. *Neurochem Int*, 48(2):114–123, 2006.

[235] R J Griffin, A Moloney, M Kelliher, J A Johnston, R Ravid, P Dockery, R O'Connor, and C O'Neill. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. *J Neurochem*, 93(1):105–117, 2005.

[236] Y Sonoda, H Mukai, K Matsuo, M Takahashi, Y Ono, K Maeda, H Akiyama, and T Kawamata. Accumulation of tumor-suppressor PTEN in Alzheimer neurofibrillary tangles. *Neurosci Lett*, 471(1):20–24, 2010.

[237] X Zhang, F Li, A Bulloj, Y W Zhang, G Tong, Z Zhang, F F Liao, and H Xu. Tumor-suppressor PTEN affects tau phosphorylation, aggregation, and binding to microtubules. *FASEB J*, 20(8):1272–1274, 2006.

[238] S Frere and I Slutsky. Targeting PTEN interactions for Alzheimer's disease. *Nat Neurosci*, 19(3):416–418, 2016.

[239] S Knafo, C Sanchez-Puelles, E Palomer, I Delgado, J E Draffin, J Mingo, T Wahle, K Kaleka, L Mou, I Pereda-Perez, E Klosi, E B Faber, H M Chapman, L Lozano-Montes, A Ortega-Molina, L Ordonez-Gutierrez, F Wandosell, J Vina, C G Dotti, R A Hall, R Pulido, N Z Gerges, A M Chan, M R Spaller, M Serrano, C Venero, and J A Esteban. PTEN recruitment controls synaptic and cognitive function in Alzheimer's models. *Nat Neurosci*, 19(3):443–453, 2016.

[240] F Kerr, A Rickle, N Nayeem, S Brandner, R F Cowburn, and S Lovestone. PTEN, a negative regulator of PI3 kinase signalling, alters tau phosphorylation in cells by mechanisms independent of GSK-3. *FEBS Lett*, 580(13):3121–3128, 2006.

[241] N Nayeem, F Kerr, H Naumann, J Linehan, S Lovestone, and S Brandner. Hyperphosphorylation of tau and neurofilaments and activation of CDK5 and ERK1/2 in PTEN-deficient cerebella. *Mol Cell Neurosci*, 34(3):400–408, 2007.

[242] Z Chen, B Chen, W F Xu, R F Liu, J Yang, and C X Yu. Effects of PTEN inhibition on regulation of tau phosphorylation in an okadaic acid-induced neurodegeneration model. *Int J Dev Neurosci*, 30(6):411–419, 2012.

[243] S Sveinbjornsdottir. The clinical symptoms of Parkinson's disease. *J Neurochem*, 139 Suppl:318–324, 2016.

[244] Antonina Kouli, Kelli M Torsney, and Wei-Li Kuan. Parkinson's disease: etiology, neuropathology, and pathogenesis. *Exon Publications*, pages 3–26, 2018.

[245] O B Tysnes and A Storstein. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna)*, 124(8):901–905, 2017.

[246] M Waragai, K Sekiyama, A Sekigawa, Y Takamatsu, M Fujita, and M Hashimoto. alpha-Synuclein and DJ-1 as potential biological fluid biomarkers for Parkinson's Disease. *Int J Mol Sci*, 11(11):4257–4266, 2010.

[247] L Parnetti, A Castrioto, D Chiasserini, E Persichetti, N Tambasco, O El-Agnaf, and P Calabresi. Cerebrospinal fluid biomarkers in Parkinson disease. *Nat Rev Neurol*, 9(3):131–140, 2013.

[248] Sathiya Sekar and Changiz Taghibiglou. Elevated nuclear phosphatase and tensin homolog (PTEN) and altered insulin signaling in substantia nigral region of patients with Parkinson's disease. *Neuroscience letters*, 666:139–143, 2018.

[249] Y Zhu, P Hoell, B Ahlemeyer, U Sure, H Bertalanffy, and J Krieglstein. Implication of PTEN in production of reactive oxygen species and neuronal death in in vitro models of stroke and Parkinson's disease. *Neurochem Int*, 50(3):507–516, 2007.

[250] A Domanskyi, C Geissler, I A Vinnikov, H Alter, A Schober, M A Vogt, P Gass, R Parlato, and G Schutz. Pten ablation in adult dopaminergic neurons is neuroprotective in Parkinson's disease models. *FASEB J*, 25(9):2898–2910, 2011.

[251] M Ogino, M Ichimura, N Nakano, A Minami, Y Kitagishi, and S Matsuda. Roles of PTEN with DNA Repair in Parkinson's Disease. *Int J Mol Sci*, 17(6), 2016.

[252] S Sepe, C Milanese, S Gabriels, K W Derks, C Payan-Gomez, IJcken W F Van, Y M Rijksen, A L Nigg, S Moreno, S Cerri, F Blandini, J H Hoeijmakers, and P G Mastroberardino. Inefficient DNA Repair Is an Aging-Related Modifier of Parkinson's Disease. *Cell Rep*, 15(9):1866–1875, 2016.

[253] Alan Edward Mayo Renton. *Gene expression and genetic analyses in Parkinson's disease with and without dementia*. PhD thesis, UCL (University College London), 2010.

[254] S Crotty, P Fitzgerald, E Tuohy, D M Harris, A Fisher, A Mandel, A E Bolton, A M Sullivan, and Y Nolan. Neuroprotective effects of novel phosphatidylglycerol-based phospholipids in the 6-hydroxydopamine model of Parkinson's disease. *Eur J Neurosci*, 27(2):294–300, 2008.

[255] S Walsh, D P Finn, and E Dowd. Time-course of nigrostriatal neurodegeneration and neuroinflammation in the 6-hydroxydopamine-induced axonal and terminal lesion models of Parkinson's disease in the rat. *Neuroscience*, 175:251–261, 2011.

[256] E J Ryu, J M Angelastro, and L A Greene. Analysis of gene expression changes in a cellular model of Parkinson disease. *Neurobiol Dis*, 18(1):54–74, 2005.

[257] L M Collins, A M Gavin, S Walsh, A M Sullivan, S L Wyatt, G W O'Keeffe, Y M Nolan, and A Toulouse. Expression of endogenous Mkp1 in 6-OHDA rat models of Parkinson's disease. *Springerplus*, 3:205, 2014.

[258] J D Berke, R F Paletzki, G J Aronson, S E Hyman, and C R Gerfen. A complex program of striatal gene expression induced by dopaminergic stimulation. *J Neurosci*, 18(14):5301–5310, 1998.

[259] Louise M Collins, Gerard W O'Keeffe, Caitriona M Long-Smith, Sean L Wyatt, Aideen M Sullivan, André Toulouse, and Yvonne M Nolan. Mitogen-activated protein kinase phosphatase (MKP)-1 as a neuroprotective agent: promotion of the morphological development of midbrain dopaminergic neurons. *Neuromolecular Med*, 15(2):435–446, 2013.

[260] C L Julien, J C Thompson, S Wild, P Yardumian, J S Snowden, G Turner, and D Craufurd. Psychiatric disorders in preclinical Huntington's disease. *J Neurol Neurosurg Psychiatry*, 78(9):939–943, 2007.

[261] D Bano, F Zanetti, Y Mende, and P Nicotera. Neurodegenerative processes in Huntington's disease. *Cell Death Dis*, 2:e228, 2011.

[262] J Schulte and J T Littleton. The biological function of the Huntingtin protein and its relevance to Huntington's Disease pathology. *Curr Trends Neurol*, 5:65–78, 2011.

[263] Stefano Patassini, Paul Begley, Jingshu Xu, Stephanie J Church, Nina Kureishy, Suzanne J Reid, Henry J Waldvogel, Richard L M Faull, Russell G Snell, and Richard D Unwin. Cerebral Vitamin B5 (D-Pantothenic Acid) Deficiency as a Potential Cause of Metabolic Perturbation and Neurodegeneration in Huntington's Disease. *Metabolites*, 9(6):113, 2019.

[264] Peter S Harper. The epidemiology of Huntington's disease. *Human genetics*, 89(4):365–376, 1992.

[265] M J Novak and S J Tabrizi. Huntington's disease: clinical presentation and treatment. *Int Rev Neurobiol*, 98:297–323, 2011.

[266] A Reiner, I Dragatsis, and P Dietrich. Genetics and neuropathology of Huntington's disease. *Int Rev Neurobiol*, 98:325–372, 2011.

[267] L Menalled and D Brunner. Animal models of Huntington's disease for translation to the clinic: best practices. *Mov Disord*, 29(11):1375–1390, 2014.

[268] Louise M Collins, Eric J Downer, André Toulouse, and Yvonne M Nolan. Mitogen-Activated Protein Kinase Phosphatase (MKP)-1 in Nervous System Development and Disease. *Mol Neurobiol*, 51(3):1158–1167, 2015.

[269] D M Taylor, R Moser, E Regulier, L Breuillaud, M Dixon, A A Beesen, L Elliston, F Silva Santos Mde, J Kim, L Jones, D R Goldstein, R J Ferrante, and R Luthi-Carter. MAP kinase phosphatase 1 (MKP-1/DUSP1) is neuroprotective in Huntington's disease via additive effects of JNK and p38 inhibition. *J Neurosci*, 33(6):2313–2325, 2013.

[270] J L Plotkin and D J Surmeier. Impaired striatal function in Huntington's disease is due to aberrant p75NTR signaling. *Rare Dis*, 2(1):e968482, 2014.

[271] J L Plotkin, M Day, J D Peterson, Z Xie, G J Kress, I Rafalovich, J Kondapalli, T S Gertler, M Flajolet, P Greengard, M Stavarache, M G Kaplitt, J Rosinski, C S Chan, and D J Surmeier. Impaired TrkB receptor signaling underlies corticostriatal dysfunction in Huntington's disease. *Neuron*, 83(1):178–188, 2014.

[272] G Kreiner, H Bierhoff, M Armentano, J Rodriguez-Parkitna, K Sowodniok, J R Naranjo, L Bonfanti, B Liss, G Schutz, I Grummt, and R Parlato. A neuroprotective phase precedes striatal degeneration upon nucleolar stress. *Cell Death Differ*, 20(11):1455–1464, 2013.

[273] R Parlato and G Kreiner. Nucleolar activity in neurodegenerative diseases: a missing piece of the puzzle? *J Mol Med (Berl)*, 91(5):541–547, 2013.

[274] E Beghi. Addressing the burden of epilepsy: Many unmet needs. *Pharmacol Res*, 107:79–84, 2016.

[275] A Singh and S Trevick. The Epidemiology of Global Epilepsy. *Neurol Clin*, 34(4):837–847, 2016.

[276] Dipan C Patel, Bhanu P Tewari, Lata Chaunsali, and Harald Sontheimer. Neuron–glia interactions in the pathophysiology of epilepsy. *Nature Reviews Neuroscience*, 20(5):282–297, 2019.

[277] Gerald Liu, Nicole Slater, and Allen Perkins. Epilepsy: treatment options. *American family physician*, 96(2):87–96, 2017.

[278] J Duran and J J Guinovart. Brain glycogen in health and disease. *Mol Aspects Med*, 46:70–77, 2015.

[279] M Kecmanovic, M Keckarevic-Markovic, D Keckarevic, G Stevanovic, N Jovic, and S Romac. Genetics of Lafora progressive myoclonic epilepsy: current perspectives. *Appl Clin Genet*, 9:49–53, 2016.

[280] P J Roach. Glycogen phosphorylation and Lafora disease. *Mol Aspects Med*, 46:78–84, 2015.

[281] P V de Souza, W B de Rezende Pinto, and A J Santos. Metastatic breast cancer in a man with nonprogressive ataxia and epilepsy. *Neurology*, 85(13):1183–1184, 2015.

[282] V Schick, M Majores, G Engels, S Spitoni, A Koch, C E Elger, M Simon, C Knobbe, I Blumcke, and A J Becker. Activation of Akt independent of PTEN and CTMP tumor-suppressor gene mutations in epilepsy-associated Taylor-type focal cortical dysplasias. *Acta Neuropathol*, 112(6):715–725, 2006.

[283] Yuichi Ueno, Takashi Enokizono, Hiroko Fukushima, Tatsuyuki Ohto, Kazuo Imagawa, Mai Tanaka, Aiko Sakai, Hisato Suzuki, Tomoko Uehara, and Toshiki Takenouchi. A novel missense PTEN mutation identified in a patient with macrocephaly and developmental delay. *Human genome variation*, 6(1):1–4, 2019.

[284] P Yang, T Liang, C Zhang, J Cai, W Zhang, B Chen, X Qiu, K Yao, G Li, H Wang, C Jiang, G You, and T Jiang. Clinicopathological factors predictive of postoperative seizures in patients with gliomas. *Seizure*, 35:93–99, 2016.

[285] M Elia, C Amato, M Bottitta, L Grillo, G Calabrese, M Esposito, and M Carotenuto. An atypical patient with Cowden syndrome and PTEN gene mutation presenting with cortical malformation and focal epilepsy. *Brain Dev*, 34(10):873–876, 2012.

[286] V Grande, G Manassero, and A Vercelli. Neuroprotective and anti-inflammatory roles of the phosphatase and tensin homolog deleted on chromosome Ten (PTEN) Inhibition in a Mouse Model of Temporal Lobe Epilepsy. *PLoS One*, 9(12):e114554, 2014.

[287] P Gass, A Eckhardt, H Schroder, R Bravo, and T Herdegen. Transient expression of the mitogen-activated protein kinase phosphatase MKP-1 (3CH134/ERP1) in the rat brain after limbic epilepsy. *Brain Res Mol Brain Res*, 41(1-2):74–80, 1996.

[288] Tina Y Tai, Lindsay N Warner, Terrance D Jones, Sangwook Jung, Francis A Concepcion, David W Skyrud, Jason Fender, Yusha Liu, Aaron D Williams, and John F Neumaier. Antiepileptic action of c-Jun N-terminal kinase (JNK) inhibition in an animal model of temporal lobe epilepsy. *Neuroscience*, 349:35–47, 2017.

[289] Motohiro Kurosawa. Phosphorylation and dephosphorylation of protein in regulating cellular function. *Journal of pharmacological and toxicological methods*, 31(3):135–139, 1994.

[290] H G Bernstein, E Jauch, H Dobrowolny, C Mawrin, J Steiner, and B Bogerts. Increased density of DISC1-immunoreactive oligodendroglial cells in fronto-parietal white matter of patients with paranoid schizophrenia. *Eur Arch Psychiatry Clin Neurosci*, 266(6):495–504, 2016.

[291] R. Delgado-Morales and M. Esteller. Opening up the DNA methylome of dementia. *Molecular psychiatry*, 22(4):485–496, 4 2017.

[292] Leonidas Chouliaras, Roy Lardenoije, Gunter Kenis, Diego Mastroeni, Patrick R Hof, Jim Van Os, Harry W M Steinbusch, Fred W Van Leeuwen, Bart P F Rutten, and Daniel L A Van Den Hove. Age-related

Disturbances in DNA (hydroxy) methylation in APP/PS1 Mice. *Translational neuroscience*, 9(1):190–202, 2018.

[293] L Chouliaras, D L A Van den Hove, G Kenis, J Dela Cruz, M A M Lemmens, J Van Os, H W M Steinbusch, C Schmitz, and B P F Rutten. Caloric restriction attenuates age-related changes of DNA methyltransferase 3a in mouse hippocampus. *Brain, behavior, and immunity*, 25(4):616–623, 2011.

[294] A J Chen, G Zhou, T Juan, S M Colicos, J P Cannon, M Cabriera-Hansen, C F Meyer, R Jurecic, N G Copeland, D J Gilbert, N A Jenkins, F Fletcher, T H Tan, and J W Belmont. The dual specificity JKAP specifically activates the c-Jun N-terminal kinase pathway. *J Biol Chem*, 277(39):36592–36601, 2002.

[295] N Hamada, M Mizuno, H Tomita, I Iwamoto, A Hara, and K I Nagata. Expression analyses of Dusp22 (Dual-specificity phosphatase 22) in mouse tissues. *Med Mol Morphol*, 51(2):111–117, 2018.

[296] M Uhlen, L Fagerberg, B M Hallstrom, C Lindskog, P Oksvold, A Mardinoglu, A Sivertsson, C Kampf, E Sjostedt, A Asplund, I Olsson, K Edlund, E Lundberg, S Navani, C A Szigyarto, J Odeberg, D Djureinovic, J O Takanen, S Hober, T Alm, P H Edqvist, H Berling, H Tegel, J Mulder, J Rockberg, P Nilsson, J M Schwenk, M Hamsten, K von Feilitzen, M Forsberg, L Persson, F Johansson, M Zwahlen, G von Heijne, J Nielsen, and F Ponten. Proteomics. Tissue-based map of the human proteome. *Science*, 347(6220):1260419, 2015.

[297] J P Li, Y N Fu, Y R Chen, and T H Tan. JNK pathway-associated phosphatase dephosphorylates focal adhesion kinase and suppresses cell migration. *J Biol Chem*, 285(8):5472–5478, 2010.

[298] Diek W Wheeler, Charise M White, Christopher L Rees, Alexander O Komendantov, David J Hamilton, and Giorgio A Ascoli. Hippocampome. org: a knowledge base of neuron types in the rodent hippocampus. *Elife*, 4:e09960, 2015.

[299] J P Li, C Y Yang, H C Chuang, J L Lan, D Y Chen, Y M Chen, X Wang, A J Chen, J W Belmont, and T H Tan. The phosphatase JKAP/DUSP22 inhibits T-cell receptor signalling and autoimmunity by inactivating Lck. *Nat Commun*, 5:3618, 2014.

[300] Charles R Gerfen, Michael N Economo, and Jayaram Chandrashekar. Long distance projections of cortical pyramidal neurons. *Journal of neuroscience research*, 96(9):1467–1475, 2018.

[301] David G Amaral, Helen E Scharfman, and Pierre Lavenex. The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Progress in brain research*, 163:3–790, 2007.

[302] Mikio Hoshino. Neuronal subtype specification in the cerebellum and dorsal hindbrain. *Development, growth & differentiation*, 54(3):317–326, 2012.

[303] D G Jeong, Y H Cho, T S Yoon, J H Kim, J H Son, S E Ryu, and S J Kim. Structure of human DSP18, a member of the dual-specificity protein tyrosine phosphatase family. *Acta Crystallogr D Biol Crystallogr*, 62(Pt 6):582–588, 2006.

[304] M P Boks, H C Mierlo, B P Rutten, T R Radstake, L De Witte, and E Geuze. Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. *Psychoneuroendocrinology*, 51:506–512, 2014.

[305] Leonidas Chouliaras, Diego Mastroeni, Elaine Delvaux, Andrew Grover, Gunter Kenis, Patrick R Hof, Harry W M Steinbusch, Paul D Coleman, Bart P F Rutten, and Daniel L A van den Hove. Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. *Neurobiology of aging*, 34(9):2091–2099, 2013.

[306] Deana M Apple, Rene Solano Fonseca, and Erzsebet Kokovay. The role of adult neurogenesis in psychiatric and cognitive disorders. *Brain Research*, 1655:270–276, 2017.

[307] Emily M Jobe and Xinyu Zhao. DNA Methylation and Adult Neurogenesis. *Brain Plasticity*, 3:5–26, 2017.

[308] Marie-France Marin, Catherine Lord, Julie Andrews, Robert-Paul Juster, Shireen Sindi, Geneviève Arsenault-Lapierre, Alexandra J Fiocco, and Sonia J Lupien. Chronic stress, cognitive functioning and mental health. *Neurobiology of learning and memory*, 96(4):583–595, 2011.

[309] B S McEwen. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci*, 1032:1–7, 2004.

[310] Christine Mohr, Silke Braun, René Bridler, Florian Chmetz, Juan P Delfino, Viktoria J Kluckner, Petra Lott, Yann Schrag, Erich Seifritz, and Hans H Stassen. Insufficient coping behavior under chronic stress and vulnerability to psychiatric disorders. *Psychopathology*, 47(4):235–243, 2014.

[311] José Javier Miguel-Hidalgo. Brain structural and functional changes in adolescents with psychiatric disorders. *International journal of adolescent medicine and health*, 25(3):245–256, 2013.

[312] Benedikt L Amann, E J Canales-Rodríguez, M Madre, J Radua, G Monte, S Alonso-Lana, R Landin-Romero, A Moreno-Alcázar, C M Bonnin, and S Sarró. Brain structural changes in schizoaffective disorder compared to schizophrenia and bipolar disorder. *Acta Psychiatrica Scandinavica*, 133(1):23–33, 2016.

[313] David L Perez, Benjamin Williams, Nassim Matin, W Curt LaFrance, Victor Costumero-Ramos, Gregory L Fricchione, Jorge Sepulcre, Matcheri S Keshavan, and Bradford C Dickerson. Corticolimbic structural alterations linked to health status and trait anxiety in functional neurological disorder. *Journal of Neurology, Neurosurgery & Psychiatry*, 88(12):1052–1059, 2017.

[314] Andrew Baum. Stress, intrusive imagery, and chronic distress. *Health psychology*, 9(6):653, 1990.

[315] Rajita Sinha. Chronic Stress, Drug Use, and Vulnerability to Addiction. *Annals of the New York Academy of Sciences*, 1141:105–130, 2008.

[316] Virginia Hughes. Stress: The roots of resilience. *Nature News*, 490(7419):165, 2012.

[317] Ilia N Karatsoreos and Bruce S McEwen. Resilience and vulnerability: a neurobiological perspective. *F1000prime reports*, 5, 2013.

[318] Brunno R Levone, John F Cryan, and Olivia F O'Leary. Role of adult hippocampal neurogenesis in stress resilience. *Neurobiology of stress*, 1:147–155, 2015.

[319] Lenita Lindgren, Jan Bergdahl, and Lars Nyberg. Longitudinal evidence for smaller hippocampus volume as a vulnerability factor for perceived stress. *Cerebral Cortex*, 26(8):3527–3533, 2016.

[320] Christoph Anacker, Victor M Luna, Gregory S Stevens, Amira Millette, Ryan Shores, Jessica C Jimenez, Briana Chen, and René Hen. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. *Nature*, 559(7712):98–102, 2018.

[321] Anders Bergström, M N Jayatissa, A Mørk, and O Wiborg. Stress sensitivity and resilience in the chronic mild stress rat model of depression; an in situ hybridization study. *Brain research*, 1196:41–52, 2008.

[322] Sundari Chetty, Aaron R Friedman, Kereshmeh Taravosh-Lahn, Elizabeth D Kirby, Christian Mirescu, Fuzheng Guo, Danna Krupik, Andrea Nicholas, A C Geraghty, and Amrita Krishnamurthy. Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Molecular psychiatry*, 19(12):1275–1283, 2014.

[323] Tian Rui Zhang, Amanda Larosa, Marie-Eve Di Raddo, Vanessa Wong, Alice S Wong, and Tak Pan Wong. Negative memory engrams in the hippocampus enhance the susceptibility to chronic social defeat stress. *Journal of Neuroscience*, 39(38):7576–7590, 2019.

[324] Stefan A Mann, Beatrix Versmold, Romy Marx, Sabine Stahlhofen, Irmgard D Dietzel, Rolf Heumann, and Richard Berger. Corticosteroids reverse cytokine-induced block of survival and differentiation of oligodendrocyte progenitor cells from rats. *Journal of Neuroinflammation*, 5(1):1–17, 2008.

[325] Frank Désarnaud, Sanjay Bidichandani, Pragna I Patel, Etienne-Emile Baulieu, and Michael Schumacher. Glucocorticosteroids stimulate the activity of the promoters of peripheral myelin protein-22 and protein zero genes in Schwann cells. *Brain research*, 865(1):12–16, 2000.

[326] T L Jernigan and Christine Fennema-Notestine. White matter mapping is needed. *Neurobiology of aging*, 25(1):37–39, 2004.

[327] Lei Li, Du Lei, Lingjiang Li, Xiaoqi Huang, Xueling Suo, Fenglai Xiao, Weihong Kuang, Jin Li, Feng Bi, and Su Lui. White matter abnormalities in post-traumatic stress disorder following a specific traumatic event. *EBioMedicine*, 4:176–183, 2016.

[328] Klaus-Armin Nave. Myelination and support of axonal integrity by glia. *Nature*, 468(7321):244–252, 2010.

[329] Bruce S McEwen, Carla Nasca, and Jason D Gray. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*, 41(1):3–23, 2016.

[330] Kuti Baruch, Gilad Silberberg, Alex Aviv, Eyal Shamir, Ulli Bening-Abu-Shach, Yehuda Baruch, Ariel Darvasi, and Ruth Navon. Association between golli-MBP and schizophrenia in the Jewish Ashkenazi population: are regulatory regions involved? *The The International Journal of Neuropsychopharmacology*, 12(7):885–894, 2009.

[331] Xiangyou Hu, Caitlin W Hicks, Wanxia He, Philip Wong, Wendy B Macklin, Bruce D Trapp, and Riqiang Yan. Bace1 modulates myelination in the central and peripheral nervous system. *Nature neuroscience*, 9(12):1520–1525, 2006.

[332] Vanessa Kiyomi Ota, Cristiano Noto, Marcos Leite Santoro, Leticia Maria Spindola, Eduardo Sauerbronn Gouvea, Carolina Muniz Carvalho, Camila Mauricio Santos, Gabriela Xavier, Cinthia Hiroko Higuchi, and Camila Yonamine. Increased expression of NDEL1 and MBP genes in the peripheral blood of antipsychotic-naïve patients with first-episode psychosis. *European Neuropsychopharmacology*, 25(12):2416–2425, 2015.

[333] Dmitri Tkachev, Michael L Mimmack, Margaret M Ryan, Matt Wayland, Tom Freeman, Peter B Jones, Michael Starkey, Maree J Webster, Robert H Yolken, and Sabine Bahn. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *The Lancet*, 362(9386):798–805, 2003.

[334] Stephen J Glatt, William S Stone, Nadine Nossova, Choong-Chin Liew, Larry J Seidman, and Ming T Tsuang. Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 156(8):869–887, 2011.

[335] Alexander B Niculescu and Helen Le-Niculescu. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. *Neuropsychopharmacology*, 35(1):355, 2010.

[336] D M Bannerman, M Grubb, R M J Deacon, B K Yee, J Feldon, and J N P Rawlins. Ventral hippocampal lesions affect anxiety but not spatial learning. *Behavioural brain research*, 139(1-2):197–213, 2003.

[337] Elisa Barbarese, Christopher Barry, Chi-Hsin Jen Chou, David J Goldstein, Grace A Nakos, Robin Hyde-DeRuyscher, Kathy Scheld, and John H Carson. Expression and localization of myelin basic protein in oligodendrocytes and transfected fibroblasts. *Journal of neurochemistry*, 51(6):1737–1745, 1988.

[338] Vítor Pinto, J C Costa, Pedro Morgado, C Mota, A Miranda, F V Bravo, Tiago Gil Oliveira, J J Cerqueira, and Nuno Sousa. Differential impact of chronic stress along the hippocampal dorsal–ventral axis. *Brain Structure and Function*, 220(2):1205–1212, 2015.

[339] S B McHugh, R M J Deacon, J N P Rawlins, and David M Bannerman. Amygdala and ventral hippocampus contribute differentially to mechanisms of fear and anxiety. *Behavioral neuroscience*, 118(1):63, 2004.

[340] Michael S Fanselow and Hong-Wei Dong. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, 65(1):7–19, 2010.

[341] Chiyo Shiota, Masayuki Miura, and Katsuhiko Mikoshiba. Developmental profile and differential localization of mRNAs of myelin proteins (MBP and PLP) in oligodendrocytes in the brain and in culture. *Developmental Brain Research*, 45(1):83–94, 1989.

[342] Viktoria Stelzhammer, Sureyya Ozcan, Michael G Gottschalk, Hannah Steeb, Georgia E Hodes, Paul C Guest, Hassan Rahmoune, Erik H F Wong, Scott J Russo, and Sabine Bahn. Central and peripheral changes underlying susceptibility and resistance to social defeat stress–A proteomic profiling study. *Diagnostics in Neuropsychiatry*, 1(1-4):1–7, 2015.

[343] M G Gottschalk, P Mortas, M Haman, SÜREYYA Ozcan, B Biemans, and S Bahn. Fluoxetine, not donepezil, reverses anhedonia, cognitive dysfunctions and hippocampal proteome changes during repeated social defeat exposure. *European Neuropsychopharmacology*, 28(1):195–210, 2018.

[344] Michael L Lehmann, Thaddeus K Weigel, Abdel G Elkahloun, and Miles Herkenham. Chronic social defeat reduces myelination in the mouse medial prefrontal cortex. *Scientific reports*, 7(1):1–13, 2017.

[345] Takefumi Kikusui, Yasushi Kiyokawa, and Yuji Mori. Deprivation of mother–pup interaction by early weaning alters myelin formation in male, but not female, ICR mice. *Brain research*, 1133:115–122, 2007.

[346] Greer A Bennett, Hannah K Palliser, Julia C Shaw, David Walker, and Jonathan J Hirst. Prenatal stress alters hippocampal neuroglia and increases anxiety in childhood. *Developmental neuroscience*, 37(6):533–545, 2015.

[347] Shingo Miyata, Yoshihisa Koyama, Kana Takemoto, Keiko Yoshikawa, Toshiko Ishikawa, Manabu Taniguchi, Kiyoshi Inoue, Miwa Aoki, Osamu Hori, and Taiichi Katayama. Plasma corticosterone activates SGK1 and induces morphological changes in oligodendrocytes in corpus callosum. *PloS one*, 6(5):e19859, 2011.

[348] Syuichi Tsuneishi, Satoshi Takada, Toshiyuki Motoike, Tamaki Ohashi, Kimihiko Sano, and Hajime Nakamura. Effects of dexamethasone on the expression of myelin basic protein, proteolipid protein, and glial fibrillary acidic protein genes in developing rat brain. *Developmental brain research*, 61(1):117–123, 1991.

[349] Eleni Parlapani, Andrea Schmitt, Andrea Erdmann, Hans-Gert Bernstein, Barbara Breunig, Oliver Gruber, Georg Petroianu, Martina von Wilmsdorff, Thomas Schneider-Axmann, and William Honer. Association between myelin basic protein expression and left entorhinal cortex pre-alpha cell layer disorganization in schizophrenia. *Brain research*, 1301:126–134, 2009.

[350] R Rimon, A Ahokas, J Ruutiainen, and P Halonen. Myelin basic protein antibodies in catatonic schizophrenia. *The Journal of clinical psychiatry*, 47(1):26–28, 1986.

[351] Fares Zeidán-Chuliá, Ben-Hur Neves de Oliveira, Manuel F Casanova, Emily L Casanova, Mami Noda, Alla B Salmina, and Alexei Verkhratsky. Up-regulation of oligodendrocyte lineage markers in the cerebellum of autistic patients: evidence from network analysis of gene expression. *Molecular neurobiology*, 53(6):4019–4025, 2016.

[352] Jia Liu, Jeffrey L Dupree, Mar Gacias, Rebecca Frawley, Tamjeed Sikder, Payal Naik, and Patrizia Casaccia. Clemastine enhances myelination in the prefrontal cortex and rescues behavioral changes in socially isolated mice. *Journal of Neuroscience*, 36(3):957–962, 2016.

[353] Shingo Miyata, Tsuyoshi Hattori, Shoko Shimizu, Akira Ito, and Masaya Tohyama. Disturbance of oligodendrocyte function plays a key role in the pathogenesis of schizophrenia and major depressive disorder. *BioMed research international*, 2015, 2015.

[354] Yumiko Matsusue, Noriko Horii-Hayashi, Tadaaki Kirita, and Mayumi Nishi. Distribution of corticosteroid receptors in mature oligodendrocytes and oligodendrocyte progenitors of the adult mouse brain. *Journal of Histochemistry & Cytochemistry*, 62(3):211–226, 2014.

[355] Jin G Kim, Regina C Armstrong, Denes v Agoston, Alexandra Robinsky, Claudia Wiese, James Nagle, and Lynn D Hudson. Myelin transcription factor 1 (Myt1) of the oligodendrocyte lineage, along with a closely related CCHC zinc finger, is expressed in developing neurons in the mammalian central nervous system. *Journal of neuroscience research*, 50(2):272–290, 1997.

[356] Youhang Jiang, C Yu Victor, Frank Buchholz, Shawn O'Connell, Simon J Rhodes, Carlos Candeloro, Yu-Rong Xia, Aldons J Lusis, and Michael G Rosenfeld. A Novel Family of Cys-Cys, His-Cys Zinc Finger Transcription Factors Expressed in Developing Nervous System and Pituitary Gland. *Journal of Biological Chemistry*, 271(18):10723–10730, 1996.

[357] Matteo Cassandri, Artem Smirnov, Flavia Novelli, Consuelo Pitolli, Massimiliano Agostini, Michal Malewicz, Gerry Melino, and Giuseppe Raschellà. Zinc-finger proteins in health and disease. *Cell Death Discovery*, 3(1):17071, 2017.

[358] Moritz Mall, Michael S Kareta, Soham Chanda, Henrik Ahlenius, Nicholas Perotti, Bo Zhou, Sarah D Grieder, Xuecai Ge, Sienna Drake, and Cheen Euong Ang. Myt1l safeguards neuronal identity by actively repressing many non-neuronal fates. *Nature*, 544(7649):245–249, 2017.

[359] Arkadi Manukyan, Izabela Kowalczyk, Tiffany A Melhuish, Agata Lemiesz, and David Wotton. Analysis of transcriptional activity by the Myt1 and Myt1l transcription factors. *Journal of cellular biochemistry*, 119(6):4644–4655, 2018.

[360] Joshua A Weiner and Jerold Chun. Png-1, a nervous system-specific zinc finger gene, identifies regions containing postmitotic neurons during mammalian embryonic development. *Journal of Comparative Neurology*, 381(2):130–142, 1997.

[361] Akitake Mukasa, Keisuke Ueki, Xijin Ge, Shumpei Ishikawa, Takafumi Ide, Takamitsu Fujimaki, Ryo Nishikawa, Akio Asai, Takaaki Kirino, and Hiroyuki Aburatani. Selective expression of a subset of neuronal genes in oligodendroglioma with chromosome 1p loss. *Brain pathology*, 14(1):34–42, 2004.

[362] Eric J Bellefroid, Catherine Bourguignon, Thomas Hollemann, Qiufu Ma, David J Anderson, Chris Kintner, and Tomas Pieler. X-MyT1, a Xenopus C2HC-type zinc finger protein with a regulatory function in neuronal differentiation. *Cell*, 87(7):1191–1202, 1996.

[363] Patricia Blanchet, Martina Bebin, Shaam Bruet, Gregory M Cooper, Michelle L Thompson, Benedicte Duban-Bedu, Benedicte Gerard, Amelie Piton, Sylvie Suckno, and Charu Deshpande. MYT1L mutations cause intellectual disability and variable obesity by dysregulating gene expression and development of the neuroendocrine hypothalamus. *PLoS genetics*, 13(8):e1006957, 2017.

[364] Fumio Matsushita, Toshiki Kameyama, Yuzo Kadokawa, and Tohru Marunouchi. Spatiotemporal expression pattern of Myt/NZF family zinc finger transcription factors during mouse nervous system development. *Developmental Dynamics*, 243(4):588–600, 2014.

[365] Agnieszka Kępa. Functional characterisation of MYT1L, a brain-specific transcriptional regulator, 2014.

[366] Elena Romm, Joseph A Nielsen, Jin G Kim, and Lynn D Hudson. Myt1 family recruits histone deacetylase to regulate neural transcription. *Journal of neurochemistry*, 93(6):1444–1453, 2005.

[367] Yanqing Shi, Qi Shao, Zhenghao Li, Ginez A Gonzalez, Fengfeng Lu, Dan Wang, Yingyan Pu, Aijun Huang, Chao Zhao, and Cheng He. Myt1L promotes differentiation of oligodendrocyte precursor cells and is necessary for remyelination after lysolecithin-induced demyelination. *Neuroscience bulletin*, 34(2):247–260, 2018.

[368] Nicole Baumann and Danielle Pham-Dinh. Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological reviews*, 2001.

[369] Cornelia Cudrici, Teodora Niculescu, Florin Niculescu, Moon L Shin, and Horea Rus. Oligodendrocyte cell death in pathogenesis of multiple sclerosis: Protection of oligodendrocytes from apoptosis by complement. *Journal of rehabilitation research and development*, 43(1):123, 2006.

[370] Pierre-Antoine Gourraud, Michael Sdika, Pouya Khankhanian, Roland G Henry, Azadeh Beheshtian, Paul M Matthews, Stephen L Hauser, Jorge R Oksenberg, Daniel Pelletier, and Sergio E Baranzini. A genome-wide association study of brain lesion distribution in multiple sclerosis. *Brain*, 136(4):1012–1024, 2013.

[371] Yohan Lee, Anand Mattai, Robert Long, Judith L Rapoport, Nitin Gogtay, and Anjené M Addington. Microduplications disrupting the MYT1L gene (2p25. 3) are associated with schizophrenia. *Psychiatric genetics*, 22(4):206, 2012.

[372] W Li, X Wang, J Zhao, J Lin, X-Q Song, Y Yang, C Jiang, B Xiao, G Yang, and H-X Zhang. Association study of myelin transcription factor 1-like polymorphisms with schizophrenia in Han Chinese population. *Genes, Brain and Behavior*, 11(1):87–93, 2012.

[373] Ruth Pidsley, Joana Viana, Eilis Hannon, Helen Spiers, Claire Troakes, Safa Al-Saraj, Naguib Mechawar, Gustavo Turecki, Leonard C Schalkwyk, and Nicholas J Bray. Methylomic profiling of human brain tissue supports a neurodevelopmental origin for schizophrenia. *Genome biology*, 15(10):1–11, 2014.

[374] Brien Riley, Dawn Thiselton, Brion S Maher, Tim Bigdeli, Brandon Wormley, G Omari McMichael, Ayman H Fanous, Vladimir Vladimirov, F Anthony O'Neill, and Dermot Walsh. Replication of association between schizophrenia and ZNF804A in the Irish case–control study of schizophrenia sample. *Molecular psychiatry*, 15(1):29–37, 2010.

[375] Terry Vrijenhoek, Jacobine E Buizer-Voskamp, Inge van der Stelt, Eric Strengman, Genetic Risk, Chiara Sabatti, Ad Geurts van Kessel, Han G Brunner, Roel A Ophoff, and Joris A Veltman. Recurrent CNVs disrupt three candidate genes in schizophrenia patients. *The American Journal of Human Genetics*, 83(4):504–510, 2008.

[376] Ti Wang, Zhen Zeng, Tao Li, Jie Liu, Junyan Li, You Li, Qian Zhao, Zhiyun Wei, Yang Wang, and Baojie Li. Common SNPs in myelin transcription factor 1-like (MYT1L): association with major depressive disorder in the Chinese Han population. *PloS one*, 5(10):e13662, 2010.

[377] Servi J C Stevens, Conny M A van Ravenswaaij-Arts, Jannie W H Janssen, Jolien S Klein Wassink-Ruiter, Anthonie J van Essen, Trijnie Dijkhuizen, Jeroen van Rheenen, Regina Heuts-Vijgen, Alexander P A Stegmann, and Eric EJGL Smeets. MYT1L is a candidate gene for intellectual disability in patients with 2p25. 3 (2pter) deletions. *American Journal of Medical Genetics Part A*, 155(11):2739–2745, 2011.

[378] Nina De Rocker, Sarah Vergult, David Koolen, Eva Jacobs, Alexander Hoischen, Susan Zeesman, Birgitte Bang, Frédérique Béna, Nele Bockaert, and Ernie M Bongers. Refinement of the critical 2p25. 3 deletion region: the role of MYT1L in intellectual disability and obesity. *Genetics in Medicine*, 17(6):460–466, 2015.

[379] Sonia Mayo, Mónica Roselló, Sandra Monfort, Silvestre Oltra, Carmen Orellana, and Francisco Martínez. Haploinsufficiency of the MYT1L gene causes intellectual disability frequently associated with behavioral disorder. *Genetics in Medicine*, 17(8):683–684, 2015.

[380] Kacie J Meyer, Michael S Axelsen, Val C Sheffield, Shivanand R Patil, and Thomas H Wassink. Germline mosaic transmission of a novel duplication of PXDN and MYT1L to two male half-siblings with autism. *Psychiatric genetics*, 22(3):137, 2012.

[381] Beth Wilmot, Rebecca Fry, Lisa Smeester, Erica D Musser, Jonathan Mill, and Joel T Nigg. Methylomic analysis of salivary DNA in childhood ADHD identifies altered DNA methylation in VIPR 2. *Journal of Child Psychology and Psychiatry*, 57(2):152–160, 2016.

[382] Danique R M Vlaskamp, Petra M C Callenbach, Patrick Rump, Lucia A A Giannini, Trijnie Dijkhuizen, Oebele F Brouwer, and Conny M A van Ravenswaaij-Arts. Copy number variation in a hospital-based cohort of children with epilepsy. *Epilepsia open*, 2(2):244–254, 2017.

[383] A Kepa, L Martinez Medina, S Erk, D P Srivastava, A Fernandes, R Toro, S Levi, B Ruggeri, C Fernandes, F Degenhardt, S H Witt, A Meyer-Lindenberg, J C Poncer, J L Martinot, M L Paillere Martinot, C P Muller, A Heinz, H Walter, G Schumann, and S Desrivieres. Associations of the Intellectual Disability Gene MYT1L with Helix-Loop-Helix Gene Expression, Hippocampus Volume and Hippocampus Activation During Memory Retrieval. *Neuropsychopharmacology*, 42(13):2516–2526, 2017.

[384] Judith K Daniels and Eric Vermetten. Odor-induced recall of emotional memories in PTSD–Review and new paradigm for research. *Experimental neurology*, 284:168–180, 2016.

[385] Eric Vermetten, Christian Schmahl, Steven M Southwick, and J Douglas Bremner. A positron tomographic emission study of olfactory induced emotional recall in veterans with and without combat-related posttraumatic stress disorder. *Psychopharmacology bulletin*, 40(1):8, 2007.

[386] Masayo Omura and Peter Mombaerts. Trpc2-Expressing Sensory Neurons in the Main Olfactory Epithelium of the Mouse. *Cell Reports*, 8(2):583–595, 2014.

[387] Lorey K Takahashi. Olfactory systems and neural circuits that modulate predator odor fear. *Frontiers in behavioral neuroscience*, 8:72, 2014.

[388] Huimeng Lei, Richard Mooney, and Lawrence C Katz. Synaptic integration of olfactory information in mouse anterior olfactory nucleus. *Journal of Neuroscience*, 26(46):12023–12032, 2006.

[389] Kazunari Miyamichi, Fernando Amat, Farshid Moussavi, Chen Wang, Ian Wickersham, Nicholas R Wall, Hiroki Taniguchi, Bosiljka Tasic, Z Josh Huang, and Zhigang He. Cortical representations of olfactory input by trans-synaptic tracing. *Nature*, 472(7342):191–196, 2011.

[390] Peter C Brunjes, Kurt R Illig, and Elizabeth A Meyer. A field guide to the anterior olfactory nucleus (cortex). *Brain research reviews*, 50(2):305–335, 2005.

[391] Rainer W Friedrich. Olfactory neuroscience: Beyond the bulb. *Current Biology*, 21(11):R438–R440, 2011.

[392] Lewis B Haberly. Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. *Chemical senses*, 26(5):551–576, 2001.

[393] Pierre-Marie Lledo, Gilles Gheusi, and Jean-Didier Vincent. Information processing in the mammalian olfactory system. *Physiological reviews*, 85(1):281–317, 2005.

[394] Afif J Aqrabawi and Jun Chul Kim. Topographic organization of hippocampal inputs to the anterior olfactory nucleus. *Frontiers in neuroanatomy*, 12:12, 2018.

[395] Afif J Aqrabawi and Jun Chul Kim. Hippocampal projections to the anterior olfactory nucleus differentially convey spatiotemporal information during episodic odour memory. *Nature communications*, 9(1):1–10, 2018.

[396] Afif J Aqrabawi, Caleb J Browne, Zahra Dargaei, Danielle Garand, C Sahara Khademullah, Melanie A Woodin, and Jun Chul Kim. Top-down modulation of olfactory-guided behaviours by the anterior olfactory nucleus pars medialis and ventral hippocampus. *Nature communications*, 7(1):1–9, 2016.

[397] Rachel B Kay and Peter C Brunjes. Diversity among principal and GABAergic neurons of the anterior olfactory nucleus. *Frontiers in cellular neuroscience*, 8:111, 2014.

[398] Kurt R Illig and Jennifer D Eudy. Contralateral projections of the rat anterior olfactory nucleus. *Journal of Comparative Neurology*, 512(1):115–123, 2009.

[399] Rachel B Kay, Elizabeth Amory Meyer, Kurt R Illig, and Peter C Brunjes. Spatial distribution of neural activity in the anterior olfactory nucleus evoked by odor and electrical stimulation. *Journal of Comparative Neurology*, 519(2):277–289, 2011.

[400] Shu Kikuta, Kenichiro Sato, Hideki Kashiwadani, Koichi Tsunoda, Tatsuya Yamasoba, and Kensaku Mori. Neurons in the anterior olfactory nucleus pars externa detect right or left localization of odor sources. *Proceedings of the National Academy of Sciences*, 107(27):12363 LP – 12368, 7 2010.

[401] Matthew J McGinley and Gary L Westbrook. Membrane and synaptic properties of pyramidal neurons in the anterior olfactory nucleus. *Journal of neurophysiology*, 105(4):1444–1453, 2011.

[402] Jessica L Brown and Peter C Brunjes. Development of the anterior olfactory nucleus in normal and unilaterally odor deprived rats. *Journal of comparative neurology*, 301(1):15–22, 1990.

[403] M V Barbado, J G Briñón, E Weruaga, A Porteros, R Arévalo, J Aijón, and J R Alonso. Changes in immunoreactivity to calcium-binding proteins in the anterior olfactory nucleus of the rat after neonatal olfactory deprivation. *Experimental neurology*, 177(1):133–150, 2002.

[404] M V Barbado, J G Briñón, E Weruaga, A Porteros, R Arévalo, J Aijón, and J R Alonso. Volumetric changes in the anterior olfactory nucleus of the rat after neonatal olfactory deprivation. *Experimental neurology*, 171(2):379–390, 2001.

[405] Renata Medinaceli Quintela, Jennifer Bauer, Lutz Wallhorn, Kim Le, Daniela Brunert, and Markus Rothermel. Dynamic impairment of olfactory behavior and signaling mediated by an olfactory corticofugal system. *Journal of Neuroscience*, 40(38):7269–7285, 2020.

[406] Lauren Gai Staples, I S McGregor, R Apfelbach, and G E Hunt. Cat odor, but not trimethylthiazoline (fox odor), activates accessory olfactory and defense-related brain regions in rats. *Neuroscience*, 151(4):937–947, 2008.

[407] Douglas W Wacker, Vicky A Tobin, Julia Noack, Valerie R Bishop, Adrian J Duszkiewicz, Mario Engelmann, Simone L Meddle, and Mike Ludwig. Expression of early growth response protein 1 in vasopressin neurones of the rat anterior olfactory nucleus following social odour exposure. *The Journal of physiology*, 588(23):4705–4717, 2010.

[408] Robert A Dielenberg, Glenn E Hunt, and Iain S McGregor. 'When a rat smells a cat': the distribution of Fos immunoreactivity in rat brain following exposure to a predatory odor. *Neuroscience*, 104(4):1085–1097, 2001.

[409] Iain S McGregor, Garth A Hargreaves, Raimund Apfelbach, and Glenn E Hunt. Neural correlates of cat odor-induced anxiety in rats: region-specific effects of the benzodiazepine midazolam. *Journal of Neuroscience*, 24(17):4134–4144, 2004.

[410] Lauren G Staples, Glenn E Hunt, Petra S van Nieuwenhuijzen, and Iain S McGregor. Rats discriminate individual cats by their odor: possible involvement of the accessory olfactory system. *Neuroscience & Biobehavioral Reviews*, 32(7):1209–1217, 2008.

[411] Doug Funk and Shimon Amir. Circadian modulation of fos responses to odor of the red fox, a rodent predator, in the rat olfactory system. *Brain research*, 866(1-2):262–267, 2000.

[412] D Dopfel, P D Perez, A Verbitsky, H Bravo-Rivera, Y Ma, G J Quirk, and N Zhang. Individual variability in behavior and functional networks predicts vulnerability using an animal model of PTSD. *Nat Commun*, 10(1):2372, 2019.

[413] Douglas W Wacker, Mario Engelmann, Vicky A Tobin, Simone L Meddle, and Mike Ludwig. Vasopressin and social odor processing in the olfactory bulb and anterior olfactory nucleus. *Annals of the New York Academy of Sciences*, 1220(1):106–116, 2011.

[414] John H McLean and Michael T Shipley. Serotonergic afferents to the rat olfactory bulb: I. Origins and laminar specificity of serotonergic inputs in the adult rat. *Journal of Neuroscience*, 7(10):3016–3028, 1987.

[415] A Hardy, B Palouzier-Paulignan, A Duchamp, J-P Royet, and P Duchamp-Viret. 5-Hydroxytryptamine action in the rat olfactory bulb: in vitro electrophysiological patch-clamp recordings of juxtaglomerular and mitral cells. *Neuroscience*, 131(3):717–731, 2005.

[416] Gabor C Petzold, Akari Hagiwara, and Venkatesh N Murthy. Serotonergic modulation of odor input to the mammalian olfactory bulb. *Nature neuroscience*, 12(6):784–791, 2009.

[417] Aude Muzerelle, Sophie Scotto-Lomassese, Jean François Bernard, Mariano Soiza-Reilly, and Patricia Gaspar. Conditional anterograde tracing reveals distinct targeting of individual serotonin cell groups (B5–B9) to the forebrain and brainstem. *Brain Structure and Function*, 221(1):535–561, 2016.

[418] Lucas Albrechet-Souza and Nicholas W Gilpin. The predator odor avoidance model of post-traumatic stress disorder in rats. *Behavioural pharmacology*, 30(2 and 3-Spec Issue):105–114, 4 2019.

[419] Y Wang, L Cao, C Y Lee, T Matsuo, K Wu, G Asher, L Tang, T Saitoh, J Russell, D Klewe-Nebenius, L Wang, S Soya, E Hasegawa, Y Cherasse, J Zhou, Y Li, T Wang, X Zhan, C Miyoshi, Y Irukayama, J Cao, J P Meeks, L Gautron, Z Wang, K Sakurai, H Funato, T Sakurai, M Yanagisawa, H Nagase, R Kobayakawa, K Kobayakawa, B Beutler, and Q Liu. Large-scale forward genetics screening identifies Trpa1 as a chemosensor for predator odor-evoked innate fear behaviors. *Nat Commun*, 9(1):2041, 2018.

[420] Markus Rothermel, Ryan M Carey, Adam Puche, Michael T Shipley, and Matt Wachowiak. Cholinergic inputs from Basal forebrain add an excitatory bias to odor coding in the olfactory bulb. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 34(13):4654–4664, 3 2014.

[421] Antonina Govic and Antonio G Paolini. In vivo electrophysiological recordings in amygdala subnuclei reveal selective and distinct responses to a behaviorally identified predator odor. *Journal of neurophysiology*, 113(5):1423–1436, 3 2015.

[422] Giuliano Iurilli and Sandeep Robert Datta. Population Coding in an Innately Relevant Olfactory Area. *Neuron*, 93(5):1180–1197.e7, 3 2017.

[423] Tetsuya Fujimoto and Shuji Aou. Prenatal bisphenol A exposure is associated with medial amygdala neuron hyperresponsiveness to predator odor in rats. *The Journal of toxicological sciences*, 43(9):531–536, 2018.

[424] Lauren G Staples. Predator odor avoidance as a rodent model of anxiety: Learning-mediated consequences beyond the initial exposure. *Neurobiology of Learning and Memory*, 94(4):435–445, 2010.

[425] Yoram Ben-Shaul, Lawrence C Katz, Richard Mooney, and Catherine Dulac. In vivo vomeronasal stimulation reveals sensory encoding of conspecific and allospecific cues by the mouse accessory olfactory bulb. *Proceedings of the National Academy of Sciences*, 107(11):5172–5177, 2010.

[426] Robert A Dielenberg and Iain S McGregor. Habituation of the hiding response to cat odor in rats (Rattus norvegicus)., 1999.

[427] Lauren G Staples, Iain S McGregor, and Glenn E Hunt. Long-lasting FosB/ΔFosB immunoreactivity in the rat brain after repeated cat odor exposure. *Neuroscience Letters*, 462(2):157–161, 2009.

[428] Carl E Schoonover, Sarah N Ohashi, Richard Axel, and Andrew J P Fink. Representational drift in primary olfactory cortex. *Nature*, 594(7864):541–546, 2021.

[429] Robert J Blanchard, D.Caroline Blanchard, Scott M Weiss, and Scott Meyer. The effects of ethanol and diazepam on reactions to predatory odors. *Pharmacology Biochemistry and Behavior*, 35(4):775–780, 1990.

[430] Carl F Weems and Victor G Carrion. The association between PTSD symptoms and salivary cortisol in youth: The role of time since the trauma. *Journal of Traumatic Stress*, 20(5):903–907, 2007.

[431] L Shepherd and J Wild. Emotion regulation, physiological arousal and PTSD symptoms in trauma-exposed individuals. *J Behav Ther Exp Psychiatry*, 45(3):360–367, 2014.

[432] C Dela Cruz Fajarito and R G De Guzman. Understanding Combat-Related PTSD Symptom Expression Through Index Trauma and Military Culture: Case Studies of Filipino Soldiers. *Mil Med*, 182(5):e1665–e1671, 2017.

[433] J P Herman and W E Cullinan. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci*, 20(2):78–84, 1997.

[434] H L Cai, P Jiang, Q Y Tan, R L Dang, M M Tang, Y Xue, Y Deng, B K Zhang, P F Fang, P Xu, D X Xiang, H D Li, and J K Yao. Therapeutic efficacy of atypical antipsychotic drugs by targeting multiple stress-related metabolic pathways. *Transl Psychiatry*, 7(5):e1130, 2017.

[435] B S McEwen. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*, 87(3):873–904, 2007.

[436] K Van Looveren, M Van Boxelaere, Z Callaerts-Vegh, and C Libert. Cognitive dysfunction in mice lacking proper glucocorticoid receptor dimerization. *PLoS One*, 14(12):e0226753, 2019.

[437] J Douglas Bremner. Does stress damage the brain? *Biol Psychiatry*, 45(7):797–805, 1999.

[438] Yashmin J G Karten, Ana Olariu, and Heather A Cameron. Stress in early life inhibits neurogenesis in adulthood. *Trends in neurosciences*, 28(4):171–172, 2005.

[439] Gregory E Miller, Edith Chen, and Eric S Zhou. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychol Bull*, 133(1):25–45, 2007.

[440] S Schumacher, H Niemeyer, S Engel, J C Cwik, S Laufer, H Klusmann, and C Knaevelsrud. HPA axis regulation in posttraumatic stress disorder: A meta-analysis focusing on potential moderators. *Neurosci Biobehav Rev*, 100:35–57, 2019.

[441] Giovana Camila Macedo, Gleice Midori Morita, Liz Paola Domingues, Cristiane Aparecida Favoretto, Deborah Suchecki, and Isabel Marian Hartmann Quadros. Consequences of continuous social defeat stress on anxiety- and depressive-like behaviors and ethanol reward in mice. *Hormones and Behavior*, 2018.

[442] Brandon L Warren, Michelle Mazei-Robison, Alfred J Robison, and Sergio D Iñiguez. Can I get a witness? Using vicarious defeat stress to study mood-related illnesses in traditionally understudied populations. *Biological psychiatry*, 2020.

[443] Shinya Fujii, Mahesh K Kaushik, Xuzhao Zhou, Mustafa Korkutata, and Michael Lazarus. Acute social defeat stress increases sleep in mice. *Frontiers in neuroscience*, 13:322, 2019.

[444] Adam P Croft, Matthew J O'Callaghan, S G Shaw, Gerald Connolly, Catherine Jacquot, and Hilary J Little. Effects of minor laboratory procedures, adrenalectomy, social defeat or acute alcohol on regional brain concentrations of corticosterone. *Brain research*, 1238:12–22, 2008.

[445] A Ieraci, A Mallei, and M Popoli. Social Isolation Stress Induces Anxious-Depressive-Like Behavior and Alterations of Neuroplasticity-Related Genes in Adult Male Mice. *Neural Plast*, 2016:6212983, 2016.

[446] Rupshi Mitra and Robert M Sapolsky. Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. *Proceedings of the National Academy of Sciences*, 105(14):5573–5578, 2008.

[447] Anzela Niraula, Yufen Wang, Jonathan P Godbout, and John F Sheridan. Corticosterone production during repeated social defeat causes monocyte mobilization from the bone marrow, glucocorticoid resistance, and neurovascular adhesion molecule expression. *Journal of Neuroscience*, 38(9):2328–2340, 2018.

[448] Marloes J A G Henckens, Floris Klumpers, Daphne Everaerd, Sabine C Kooijman, Guido A Van Wingen, and Guillen Fernández. Interindividual differences in stress sensitivity: basal and stress-induced cortisol levels differentially predict neural vigilance processing under stress. *Social cognitive and affective neuroscience*, 11(4):663–673, 2016.

[449] G Russell and S Lightman. The human stress response. *Nat Rev Endocrinol*, 15(9):525–534, 2019.

[450] Michael Rutter. Resilience as a dynamic concept. *Development and psychopathology*, 24(2):335–344, 2012.

[451] Clara Snijders, Lotta-Katrin Pries, Noemi Sgammeglia, Ghazi Al Jowf, Nagy A Youssef, Laurence de Nijs, Sinan Guloksuz, and Bart P F Rutten. Resilience Against Traumatic Stress: Current Developments and Future Directions. *Frontiers in psychiatry*, 9:676, 2018.

[452] Ronald S Duman. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. *Neurobiology of Aging*, 26(1):88–93, 2005.

[453] S A Dugan, J T Bromberger, E Segawa, E Avery, and B Sternfeld. Association between physical activity and depressive symptoms: midlife women in SWAN. *Med Sci Sports Exerc*, 47(2):335–342, 2015.

[454] J Gourgouvelis, P Yielder, S T Clarke, H Behbahani, and B A Murphy. Exercise Leads to Better Clinical Outcomes in Those Receiving Medication Plus Cognitive Behavioral Therapy for Major Depressive Disorder. *Front Psychiatry*, 9:37, 2018.

[455] E Aylett, N Small, and P Bower. Exercise in the treatment of clinical anxiety in general practice - a systematic review and meta-analysis. *BMC Health Serv Res*, 18(1):559, 2018.

[456] P Salmon. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clinical psychology review*, 21(1):33–61, 2 2001.

[457] Andreas Ströhle. Physical activity, exercise, depression and anxiety disorders, 2009.

[458] Frederick Ka Wing Ho, Lobo Hung Tak Louie, Chun Bong Chow, Wilfred Hing Sang Wong, and Patrick Ip. Physical activity improves mental health through resilience in Hong Kong Chinese adolescents. *BMC Pediatrics*, 2015.

[459] S B Harvey, S Overland, S L Hatch, S Wessely, A Mykletun, and M Hotopf. Exercise and the Prevention of Depression: Results of the HUNT Cohort Study. *Am J Psychiatry*, 175(1):28–36, 2018.

[460] E E Bernstein and R J McNally. Exercise as a buffer against difficulties with emotion regulation: A pathway to emotional wellbeing. *Behav Res Ther*, 109:29–36, 2018.

[461] H Zheng, Y Liu, W Li, B Yang, D Chen, X Wang, Z Jiang, H Wang, Z Wang, G Cornelisson, and F Halberg. Beneficial effects of exercise and its molecular mechanisms on depression in rats. *Behav Brain Res*, 168(1):47–55, 2006.

[462] Tae Kyung Kim and Pyung Lim Han. Physical Exercise Counteracts Stress-induced Upregulation of Melanin-concentrating Hormone in the Brain and Stress-induced Persisting Anxiety-like Behaviors. *Exp Neurobiol*, 25(4):163–173, 2016.

[463] P D Loprinzi and E Frith. Protective and therapeutic effects of exercise on stress-induced memory impairment. *J Physiol Sci*, 69(1):1–12, 2019.

[464] Carl W Cotman and Nicole C Berchtold. Exercise: A behavioral intervention to enhance brain health and plasticity, 2002.

[465] Philip V Holmes. Trophic Mechanisms for Exercise-Induced Stress Resilience: Potential Role of Interactions between BDNF and Galanin. *Frontiers in Psychiatry*, 2014.

[466] Ilia N Karatsoreos and Bruce S McEwen. Psychobiological allostasis: Resistance, resilience and vulnerability, 2011.

[467] S G Kinsey, M T Bailey, J F Sheridan, D A Padgett, and R Avitsur. 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, 2007.

[468] E Elliott, G Ezra-Nevo, L Regev, A Neufeld-Cohen, and A Chen. Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. *Nat Neurosci*, 13(11):1351–1353, 2010.

[469] Natalya Bondar, Leonid Bryzgalov, Nikita Ershov, Fedor Gusev, Vasiliy Reshetnikov, Damira Avgustinovich, Mikhail Tenditnik, Evgeny Rogaev, and Tatiana Merkulova. Molecular Adaptations to Social Defeat Stress and Induced Depression in Mice. *Molecular Neurobiology*, 55(4):3394–3407, 2018.

[470] Joram D Mul. Voluntary exercise and depression-like behavior in rodents: are we running in the right direction? *Journal of molecular endocrinology*, 60(3):R77–R95, 4 2018.

[471] V Krishnan, M H Han, D L Graham, O Berton, W Renthal, S J Russo, Q Laplant, A Graham, M Lutter, D C Lagace, S Ghose, R Reister, P Tannous, T A Green, R L Neve, S Chakravarty, A Kumar, A J Eisch, D W Self, F S Lee, C A Tamminga, D C Cooper, H K Gershenfeld, and E J Nestler. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell*, 131(2):391–404, 2007.

[472] F Faul, E Erdfelder, A G Lang, and A Buchner. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, 39(2):175–191, 2007.

[473] A S Selya, J S Rose, L C Dierker, D Hedeker, and R J Mermelstein. A Practical Guide to Calculating Cohen's f(2), a Measure of Local Effect Size, from PROC MIXED. *Front Psychol*, 3:111, 2012.

[474] Alessandro Bartolomucci, Eberhard Fuchs, Jaap Koolhaas, and Frauke Ohl. Acute and Chronic Social Defeat: Stress Protocols and Behavioral Testing. In *Neuromethods*, volume 42, pages 261–275. Springer, 2009.

[475] Alline C Campos, Manoela V Fogaca, Daniele C Aguiar, and Francisco S Guimaraes. Animal models of anxiety disorders and stress. *Revista brasileira de psiquiatria*, 35:S101–S111, 2013.

[476] F T Pijlman, G Wolterink, and J M Van Ree. Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats. *Behav Brain Res*, 139(1-2):131–138, 2003.

[477] Maria Razzoli, Lucia Carboni, Michela Andreoli, Francesca Michielin, Alice Ballottari, and Roberto Arban. Strain-specific outcomes of repeated social defeat and chronic fluoxetine treatment in the mouse. *Pharmacology Biochemistry and Behavior*, 97(3):566–576, 2011.

[478] Maria Razzoli, Lucia Carboni, Michela Andreoli, Alice Ballottari, and Roberto Arban. Different susceptibility to social defeat stress of BalbC and C57BL6/J mice. *Behavioural Brain Research*, 216(1):100–108, 2011.

[479] S Pietropaolo, I Branchi, F Cirulli, F Chiarotti, L Aloe, and E Alleva. Long-term effects of the periadolescent environment on exploratory activity and aggressive behaviour in mice: social versus physical enrichment. *Physiol Behav*, 81(3):443–453, 2004.

[480] Wataru Iio, Haruyoshi Takagi, Yasuki Ogawa, Takamitsu Tsukahara, Shigeru Chohnan, and Atsushi Toyoda. Effects of chronic social defeat stress on peripheral leptin and its hypothalamic actions. *BMC Neuroscience*, 2014.

[481] Ryan J Keenan, Jacky Chan, Paul S Donnelly, Kevin J Barnham, and Laura H Jacobson. The social defeat/overcrowding murine psychosocial stress model results in a pharmacologically reversible body weight gain but not depression-related behaviours. *Neurobiology of stress*, 9:176–187, 2018.

[482] H M Savignac, B C Finger, R C Pizzo, O F O'Leary, T G Dinan, and J F Cryan. Increased sensitivity to the effects of chronic social defeat stress in an innately anxious mouse strain. *Neuroscience*, 192:524–536, 2011.

[483] Lotte van Doeselaar, Huanqing Yang, Joeri Bordes, Lea Brix, Clara Engelhardt, Fiona Tang, and Mathias V Schmidt. Chronic social defeat stress in female mice leads to sex-specific behavioral and neuroendocrine effects. *Stress*, 24(2):168–180, 2021.

[484] S D Iniguez, V Vialou, B L Warren, J L Cao, L F Alcantara, L C Davis, Z Manojlovic, R L Neve, S J Russo, M H Han, E J Nestler, and C A Bolanos-Guzman. Extracellular signal-regulated kinase-2 within the ventral tegmental area regulates responses to stress. *J Neurosci*, 30(22):7652–7663, 2010.

[485] Timothy J O'Neal, Danielle M Friend, Juen Guo, Kevin D Hall, and Alexxai V Kravitz. Increases in Physical Activity Result in Diminishing Increments in Daily Energy Expenditure in Mice. *Current Biology*, 2017.

[486] O Berton, C A McClung, R J Dileone, V Krishnan, W Renthal, S J Russo, D Graham, N M Tsankova, C A Bolanos, M Rios, L M Monteggia, D W Self, and E J Nestler. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science*, 311(5762):864–868, 2006.

[487] Aron M Henriques-Alves and Claudio M Queiroz. Ethological Evaluation of the Effects of Social Defeat Stress in Mice: Beyond the Social Interaction Ratio. *Frontiers in Behavioral Neuroscience*, 2016.

[488] Alexander Z Harris, Piray Atsak, Zachary H Bretton, Emma S Holt, Raisa Alam, Mitchell P Morton, Atheir I Abbas, E David Leonardo, Scott S Bolkan, and René Hen. A novel method for chronic social defeat stress in female mice. *Neuropsychopharmacology*, 43(6):1276–1283, 2018.

[489] Sergio D Iñiguez, Francisco J Flores-Ramirez, Lace M Riggs, Jason B Alipio, Israel Garcia-Carachure, Mirella A Hernandez, David O Sanchez, Mary Kay Lobo, Peter A Serrano, Stephen H Braren, and Samuel A Castillo. Vicarious Social Defeat Stress Induces Depression-Related Outcomes in Female Mice. *Biological Psychiatry*, 2018.

[490] Denis Matrov, Kadri K$˜oiv, Margus Kanarik, Krista Peet, Karita Raudkivi, and Jaanus Harro. Middle-range exploratory activity in adult rats suggests higher resilience to chronic social defeat. *Acta Neuropsychiatr*, 28:125–140, 2016.

[491] E Venzala, A L Garcia-Garcia, N Elizalde, P Delagrange, and R M Tordera. Chronic social defeat stress model: behavioral features, antidepressant action, and interaction with biological risk factors. *Psychopharmacology (Berl)*, 224(2):313–325, 2012.

[492] M T Foster, M B Solomon, K L Huhman, and T J Bartness. Social defeat increases food intake, body mass, and adiposity in Syrian hamsters. *Am J Physiol Regul Integr Comp Physiol*, 290(5):R1284–93, 2006.

[493] D F Avgustinovich, I L Kovalenko, and N N Kudryavtseva. A model of anxious depression: persistence of behavioral pathology. *Neurosci Behav Physiol*, 35(9):917–924, 2005.

[494] Chao Dong, Ji-chun Zhang, Wei Yao, Qian Ren, Min Ma, Chun Yang, Shigeyuki Chaki, and Kenji Hashimoto. Rapid and sustained antidepressant action of the mGlu2/3 receptor antagonist MGS0039 in the social defeat stress model: comparison with ketamine. *International Journal of Neuropsychopharmacology*, 20(3):228–236, 2017.

[495] A Keeney, D S Jessop, M S Harbuz, C A Marsden, S Hogg, and R E Blackburn-Munro. Differential effects of acute and chronic social defeat stress on hypothalamic-pituitary-adrenal axis function and hippocampal serotonin release in mice. *J Neuroendocrinol*, 18(5):330–338, 2006.

[496] Michael L Lehmann and Miles Herkenham. Environmental enrichment confers stress resiliency to social defeat through an infralimbic cortex-dependent neuroanatomical pathway. *Journal of Neuroscience*, 31(16):6159–6173, 2011.

[497] Qian Ren, Min Ma, Tamaki Ishima, Christophe Morisseau, Jun Yang, Karen M Wagner, Ji-chun Zhang, Chun Yang, Wei Yao, Chao Dong, Mei Han, Bruce D Hammock, and Kenji Hashimoto. Gene deficiency and pharmacological inhibition of soluble epoxide hydrolase confers resilience to repeated social defeat stress. *Proceedings of the National Academy of Sciences*, 113(13):E1944 LP – E1952, 3 2016.

[498] David A Slattery, Nicole Uschold, Mauro Magoni, Julia Bär, Maurizio Popoli, Inga D Neumann, and Stefan O Reber. Behavioural consequences of two chronic psychosocial stress paradigms: anxiety without depression. *Psychoneuroendocrinology*, 37(5):702–714, 2012.

[499] N Calvo, M Cecchi, M Kabbaj, S J Watson, and H Akil. Differential effects of social defeat in rats with high and low locomotor response to novelty. *Neuroscience*, 183:81–89, 2011.

[500] Marc L Molendijk and E Ronald de Kloet. Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology*, 62:389–391, 2015.

[501] Deseree M Eudave, McKenna N BeLow, and Elizabeth I Flandreau. Effects of high fat or high sucrose diet on behavioral-response to social defeat stress in mice. *Neurobiology of stress*, 9:1–8, 2018.

[502] Michael L Lehmann, Tomris Mustafa, Adrian M Eiden, Miles Herkenham, and Lee E Eiden. PACAP-deficient mice show attenuated corticosterone secretion and fail to develop depressive behavior during chronic social defeat stress. *Psychoneuroendocrinology*, 2013.

[503] E Venzala, A L Garcia-Garcia, N Elizalde, and R M Tordera. Social vs. environmental stress models of depression from a behavioural and neurochemical approach. *Eur Neuropsychopharmacol*, 23(7):697–708, 2013.

[504] S Hayashida, T Oka, T Mera, and S Tsuji. Repeated social defeat stress induces chronic hyperthermia in rats. *Physiol Behav*, 101(1):124–131, 2010.

[505] C S De Kloet, E Vermetten, E Geuze, AMAA Kavelaars, C J Heijnen, and H G M Westenberg. Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *Journal of psychiatric research*, 40(6):550–567, 2006.

[506] Timmy Jones and Mary D Moller. Implications of hypothalamic–pituitary–adrenal axis functioning in post-traumatic stress disorder. *Journal of the American Psychiatric Nurses Association*, 17(6):393–403, 2011.

[507] Sonya M Abraham, Toby Lawrence, Anna Kleiman, Paul Warden, Mino Medghalchi, Jan Tuckermann, Jeremy Saklatvala, and Andrew R Clark. Antiinflammatory effects of dexamethasone are partly dependent on induction of dual specificity phosphatase 1. *Journal of Experimental Medicine*, 203(8):1883–1889, 2006.

[508] Moisés E Bauer and Antonio L Teixeira. Inflammation in psychiatric disorders: what comes first? *Annals of the New York Academy of Sciences*, 1437(1):57–67, 2019.

[509] V Bonnefil, K Dietz, M Amatruda, M Wentling, A V Aubry, J L Dupree, G Temple, H J Park, N S Burghardt, P Casaccia, and J Liu. Region-specific myelin differences define behavioral consequences of chronic social defeat stress in mice. *Elife*, 8, 2019.

[510] T Isosaka, T Matsuo, T Yamaguchi, K Funabiki, S Nakanishi, R Kobayakawa, and K Kobayakawa. Htr2a-Expressing Cells in the Central Amygdala Control the Hierarchy between Innate and Learned Fear. *Cell*, 163(5):1153–1164, 2015.

[511] A M Kinn Rød, A M Milde, J Grønli, F K Jellestad, H Sundberg, and R Murison. Long-term effects of foot-shock and social defeat on anxiety-like behaviours in rats: relationships to pre-stressor plasma corticosterone concentration. *Stress*, 15(6):658–670, 2012.

[512] Wenyuan Yin, Natalie R Gallagher, Caroline M Sawicki, Daniel B McKim, Jonathan P Godbout, and John F Sheridan. Repeated social defeat in female mice induces anxiety-like behavior associated with enhanced myelopoiesis and increased monocyte accumulation in the brain. *Brain, behavior, and immunity*, 78:131–142, 2019.

[513] Fan Zhang, Sanna Yuan, Feng Shao, and Weiwen Wang. Adolescent social defeat induced alterations in social behavior and cognitive flexibility in adult mice: effects of developmental stage and social condition. *Frontiers in behavioral neuroscience*, 10:149, 2016.

[514] Maria Razzoli, Carolyn Pearson, Scott Crow, and Alessandro Bartolomucci. Stress, overeating, and obesity: Insights from human studies and preclinical models. *Neuroscience & Biobehavioral Reviews*, 76:154–162, 2017.

[515] Tatsuhiko Goto, Yoshifumi Kubota, Yuki Tanaka, Wataru Iio, Naoko Moriya, and Atsushi Toyoda. Subchronic and mild social defeat stress accelerates food intake and body weight gain with polydipsia-like features in mice. *Behavioural Brain Research*, 270:339–348, 2014.

[516] Bernadette von Dawans, Amalie Trueg, Clemens Kirschbaum, Urs Fischbacher, and Markus Heinrichs. Acute social and physical stress interact to influence social behavior: The role of social anxiety. *PloS one*, 13(10):e0204665, 2018.

[517] Patrick Nasrallah, Edwina Abou Haidar, Joseph S Stephan, Lauretta El Hayek, Nabil Karnib, Mohamad Khalifeh, Nour Barmo, Vanessa Jabre, Rouba Houbeika, and Anthony Ghanem. Branched-chain amino acids mediate resilience to chronic social defeat stress by activating BDNF/TRKB signaling. *Neurobiology of stress*, 11:100170, 2019.

[518] Y H C Yau and M N Potenza. Stress and eating behaviors. *Minerva endocrinologica*, 38(3):255–267, 9 2013.

[519] David M. Almeida, Susan T. Charles, Jacqueline Mogle, Johanna Drewelies, Carolyn M. Aldwin, Avron Spiro, and Denis Gerstorf. Charting adult development through (historically changing) daily stress processes. *American Psychologist*, 75(4):511–524, 5 2020.

[520] Jiayang Chen, Mary E Lambo, Xia Ge, Joshua T Dearborn, Yating Liu, Katherine B McCullough, Raylynn G Swift, Dora R Tabachnick, Lucy Tian, and Kevin Noguchi. A MYT1L syndrome mouse model recapitulates

patient phenotypes and reveals altered brain development due to disrupted neuronal maturation. *Neuron*, 109(23):3775–3792, 2021.

[521] K Kousaka, H Kiyonari, N Oshima, A Nagafuchi, Y Shima, O Chisaka, and T Uemura. Slingshot-3 dephosphorylates ADF/cofilin but is dispensable for mouse development. *Genesis*, 46(5):246–255, 2008.

[522] Johan H van Heerden, Ana Conesa, Dan J Stein, David Montaner, Vivienne Russell, and Nicola Illing. Parallel changes in gene expression in peripheral blood mononuclear cells and the brain after maternal separation in the mouse. *BMC research notes*, 2(1):1–10, 2009.

[523] Kenneth M McCullough, Nikolaos P Daskalakis, Georgette Gafford, Filomene G Morrison, and Kerry J Ressler. Cell-type-specific interrogation of CeA Drd2 neurons to identify targets for pharmacological modulation of fear extinction. *Translational psychiatry*, 8(1):1–16, 2018.

[524] M D Lin, H T Lee, S C Wang, H R Li, H L Hsien, K W Cheng, Y D Chang, M L Huang, J K Yu, and Y H Chen. Expression of phosphatase of regenerating liver family genes during embryogenesis: an evolutionary developmental analysis among Drosophila, amphioxus, and zebrafish. *BMC Dev Biol*, 13:18, 2013.

[525] A Sebollela, L Freitas-Correa, F F Oliveira, A C Paula-Lima, L M Saraiva, S M Martins, L D Mota, C Torres, S Alves-Leon, J M de Souza, D M Carraro, H Brentani, F G De Felice, and S T Ferreira. Amyloid-beta oligomers induce differential gene expression in adult human brain slices. *J Biol Chem*, 287(10):7436–7445, 2012.

[526] H Ujike, M Takaki, M Kodama, and S Kuroda. Gene expression related to synaptogenesis, neuritogenesis, and MAP kinase in behavioral sensitization to psychostimulants. *Ann N Y Acad Sci*, 965:55–67, 2002.

[527] Adrián Martín-Segura, Álvaro Casadomé-Perales, Pietro Fazzari, José Manuel Mas, Laura Artigas, Raquel Valls, Angel R Nebreda, and Carlos G Dotti. Aging increases hippocampal DUSP2 by a membrane cholesterol loss-mediated RTK/p38MAPK activation mechanism. *Frontiers in Neurology*, 10:675, 2019.

[528] Raman G Kutty, Gang Xin, David M Schauder, Stephanie M Cossette, Michelle Bordas, Weiguo Cui, and Ramani Ramchandran. Dual specificity phosphatase 5 is essential for T cell survival. *PLoS One*, 11(12):e0167246, 2016.

[529] M Seleman, H Chapy, S Cisternino, C Courtin, M Smirnova, J Schlatter, F Chiadmi, J M Scherrmann, F Noble, and C Marie-Claire. Impact of P-glycoprotein at the blood-brain barrier on the uptake of heroin and its main metabolites: behavioral effects and consequences on the transcriptional responses and reinforcing properties. *Psychopharmacology (Berl)*, 231(16):3139–3149, 2014.

[530] K L Kuntz-Melcavage, R M Brucklacher, P S Grigson, W M Freeman, and K E Vrana. Gene expression changes following extinction testing in a heroin behavioral incubation model. *BMC Neurosci*, 10:95, 2009.

[531] B P Sokolov, O O Polesskaya, and G R Uhl. Mouse brain gene expression changes after acute and chronic amphetamine. *J Neurochem*, 84(2):244–252, 2003.

[532] K J Martell, A F Seasholtz, S P Kwak, K K Clemens, and J E Dixon. hVH-5: a protein tyrosine phosphatase abundant in brain that inactivates mitogen-activated protein kinase. *J Neurochem*, 65(4):1823–1833, 1995.

[533] H W Lee, Y Kim, K Han, H Kim, and E Kim. The phosphoinositide 3-phosphatase MTMR2 interacts with PSD-95 and maintains excitatory synapses by modulating endosomal traffic. *J Neurosci*, 30(16):5508–5518, 2010.

[534] Anna E Mammel, Katherine C Delgado, Andrea L Chin, Alec F Condon, Jo Q Hill, Sue A Aicher, Yingming Wang, Lev M Fedorov, and Fred L Robinson. Distinct roles for the Charcot-Marie-Tooth disease-causing endosomal regulators Mtmr5 and Mtmr13 in axon radial sorting and Schwann cell myelination. *bioRxiv*, page 843219, 2019.

[535] Subramaniam Ganesh, Kishan Lal Agarwala, Kenji Amano, Toshimitsu Suzuki, Antonio V Delgado-Escueta, and Kazuhiro Yamakawa. Regional and developmental expression of Epm2a gene and its evolutionary conservation. *Biochemical and biophysical research communications*, 283(5):1046–1053, 2001.

[536] J Galvao, K Iwao, A Apara, Y Wang, M Ashouri, T N Shah, M Blackmore, N J Kunzevitzky, D L Moore, and J L Goldberg. The Kruppel-Like Factor Gene Target Dusp14 Regulates Axon Growth and Regeneration. *Invest Ophthalmol Vis Sci*, 59(7):2736–2747, 2018.

[537] J F Rodriguez-Molina, C Lopez-Anido, Ki H Ma, Chongyu Zhang, Tyler Olson, Katharina N Muth, Matthias Weider, John Svaren, José F Rodríguez-Molina, Camila Lopez-Anido, Ki H Ma, Chongyu Zhang, Tyler Olson, Katharina N Muth, Matthias Weider, and John Svaren. Dual specificity phosphatase 15 regulates Erk activation in Schwann cells. *J Neurochem*, 140(3):368–382, 2017.

[538] K N Muth, S Piefke, M Weider, E Sock, I Hermans-Borgmeyer, M Wegner, and M Kuspert. The Dual-specificity phosphatase Dusp15 is regulated by Sox10 and Myrf in Myelinating Oligodendrocytes. *Glia*, 64(12):2120–2132, 2016.

[539] Qihan Wu, Shaohua Gu, Jianfeng Jianliang Dai, Jianfeng Jianliang Dai, Liu Wang, Yao Li, Li Zeng, Jian Xu, Xin Ye, and Wei Zhao. Molecular cloning and characterization of a novel dual-specificity phosphatase18 gene from human fetal brain. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, 1625(3):296–304, 2003.

[540] N Mu, J Gu, N Liu, X Xue, Z Shu, K Zhang, T Huang, C Chu, W Zhang, L Gong, H Zhao, B Jia, D Gao, L Shang, W Zhang, and Q Guo. PRL-3 is a potential glioblastoma prognostic marker and promotes

glioblastoma progression by enhancing MMP7 through the ERK and JNK pathways. *Theranostics*, 8(6):1527–1539, 2018.

[541] L Wang, J Liu, Z Zhong, X Gong, W Liu, L Shi, and X Li. PTP4A3 is a target for inhibition of cell proliferatin, migration and invasion through Akt/mTOR signaling pathway in glioblastoma under the regulation of miR-137. *Brain Res*, 1646:441–450, 2016.

[542] J Su, H Zhou, Y Tao, Z Guo, S Zhang, Y Zhang, Y Huang, Y Tang, R Hu, and Q Dong. HCdc14A is involved in cell cycle regulation of human brain vascular endothelial cells following injury induced by high glucose, free fatty acids and hypoxia. *Cell Signal*, 27(1):47–60, 2015.

[543] M Guillamot, E Manchado, M Chiesa, G Gomez-Lopez, D G Pisano, M P Sacristan, and M Malumbres. Cdc14b regulates mammalian RNA polymerase II and represses cell cycle transcription. *Sci Rep*, 1:189, 2011.

[544] F Galeano, C Rossetti, S Tomaselli, Loredana Cifaldi, M Lezzerini, M Pezzullo, R Boldrini, L Massimi, C M Di Rocco, and F Locatelli. ADAR2-editing activity inhibits glioblastoma growth through the modulation of the CDC14B/Skp2/p21/p27 axis. *Oncogene*, 32(8):998–1009, 2013.

[545] C P Goh, U Putz, J Howitt, L H Low, J Gunnersen, N Bye, C Morganti-Kossmann, and S S Tan. Nuclear trafficking of Pten after brain injury leads to neuron survival not death. *Exp Neurol*, 252:37–46, 2014.

[546] Y Chen, W C Huang, J Sejourne, A E Clipperton-Allen, and D T Page. Pten Mutations Alter Brain Growth Trajectory and Allocation of Cell Types through Elevated beta-Catenin Signaling. *J Neurosci*, 35(28):10252–10267, 2015.

[547] A E Clipperton-Allen and D T Page. Pten haploinsufficient mice show broad brain overgrowth but selective impairments in autism-relevant behavioral tests. *Hum Mol Genet*, 23(13):3490–3505, 2014.

[548] M M Fraser, I T Bayazitov, S S Zakharenko, and S J Baker. Phosphatase and tensin homolog, deleted on chromosome 10 deficiency in brain causes defects in synaptic structure, transmission and plasticity, and myelination abnormalities. *Neuroscience*, 151(2):476–488, 2008.

[549] A Igarashi, K Itoh, T Yamada, Y Adachi, T Kato, D Murata, H Sesaki, and M Iijima. Nuclear PTEN deficiency causes microcephaly with decreased neuronal soma size and increased seizure susceptibility. *J Biol Chem*, 293(24):9292–9300, 2018.

[550] C H Kwon, B W Luikart, C M Powell, J Zhou, S A Matheny, W Zhang, Y Li, S J Baker, and L F Parada. Pten regulates neuronal arborization and social interaction in mice. *Neuron*, 50(3):377–388, 2006.

[551] Y Yang, N Shao, G Luo, L Li, L Zheng, P Nilsson-Ehle, and N Xu. Mutations of PTEN gene in gliomas correlate to tumor differentiation and short-term survival rate. *Anticancer Res*, 30(3):981–985, 2010.

[552] A Vanderver, D Tonduti, I Kahn, J Schmidt, L Medne, J Vento, K A Chapman, B Lanpher, P Pearl, A Gropman, C Lourenco, J S Bamforth, C Sharpe, M Pineda, J Schallner, O Bodamer, S Orcesi, S A Oberstein, E A Sistermans, H G Yntema, C Bonnemann, A T Waldman, and M S van der Knaap. Characteristic brain magnetic resonance imaging pattern in patients with macrocephaly and PTEN mutations. *Am J Med Genet A*, 164A(3):627–633, 2014.

[553] Freddy Jeanneteau, Katrin Deinhardt, Goichi Miyoshi, Anton M Bennett, and Moses V Chao. The MAP kinase phosphatase MKP-1 regulates BDNF-induced axon branching. *Nat Neurosci .*, 13(11):1373–1379, 2010.

[554] M Doi, S Cho, I Yujnovsky, J Hirayama, N Cermakian, A C Cato, and P Sassone-Corsi. Light-inducible and clock-controlled expression of MAP kinase phosphatase 1 in mouse central pacemaker neurons. *J Biol Rhythms*, 22(2):127–139, 2007.

[555] H Yu, J Park, J Lee, K Choi, and C Choi. Constitutive Expression of MAP Kinase Phosphatase-1 Confers Multi-drug Resistance in Human Glioblastoma Cells. *Cancer Res Treat*, 44(3):195–201, 2012.

[556] N Z Abdul Rahman, S M Greenwood, R R Brett, K Tossell, M A Ungless, R Plevin, and T J Bushell. Mitogen-Activated Protein Kinase Phosphatase-2 Deletion Impairs Synaptic Plasticity and Hippocampal-Dependent Memory. *J Neurosci*, 36(8):2348–2354, 2016.

[557] S Tripathi, R Kushwaha, J Mishra, M K Gupta, H Kumar, S Sanyal, D Singh, S Sanyal, A A Sahasrabuddhe, M Kamthan, M K Mudiam, and S Bandyopadhyay. Docosahexaenoic acid up-regulates both PI3K/AKT-dependent FABP7-PPARgamma interaction and MKP3 that enhance GFAP in developing rat brain astrocytes. *J Neurochem*, 140(1):96–113, 2017.

[558] N T Wickramasekera, D Gebremedhin, K A Carver, P Vakeel, R Ramchandran, A Schuett, and D R Harder. Role of dual-specificity protein phosphatase-5 in modulating the myogenic response in rat cerebral arteries. *J Appl Physiol (1985)*, 114(2):252–261, 2013.

[559] K Ueda, H Arakawa, and Y Nakamura. Dual-specificity phosphatase 5 (DUSP5) as a direct transcriptional target of tumor suppressor p53. *Oncogene*, 22(36):5586–5591, 2003.

[560] J E Ham, E K Oh, D H Kim, and S H Choi. Differential expression profiles and roles of inducible DUSPs and ERK1/2-specific constitutive DUSP6 and DUSP7 in microglia. *Biochem Biophys Res Commun*, 467(2):254–260, 2015.

[561] N Thiriet, N Humblot, C Burgun, D Aunis, and J Zwiller. Cocaine and fluoxetine induce the expression of the hVH-5 gene encoding a MAP kinase phosphatase. *Brain Res Mol Brain Res*, 62(2):150–157, 1998.

[562] D A Banks, A Dahal, A G McFarland, B M Flowers, C A Stephens, B Swack, A Gugssa, W A Anderson, and S D Hinton. MK-STYX Alters the Morphology of Primary Neurons, and Outgrowths in MK-STYX Overexpressing PC-12 Cells Develop a Neuronal Phenotype. *Front Mol Biosci*, 4:76, 2017.

[563] B M Flowers, L E Rusnak, K E Wong, D A Banks, M R Munyikwa, A G McFarland, and S D Hinton. The pseudophosphatase MK-STYX induces neurite-like outgrowths in PC12 cells. *PLoS One*, 9(12):e114535, 2014.

[564] M Isrie, M Zamani Esteki, H Peeters, T Voet, J Van Houdt, W Van Paesschen, and H Van Esch. Homozygous missense mutation in STYXL1 associated with moderate intellectual disability, epilepsy and behavioural complexities. *Eur J Med Genet*, 58(4):205–210, 2015.

[565] Jean-Philippe Guilloux, Sabrina Bassi, Ying Ding, Chris Walsh, Gustavo Turecki, George Tseng, Jill M Cyranowski, and Etienne Sibille. Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. *Neuropsychopharmacology*, 40(3):701–710, 2015.

[566] S Miyata, M Kurachi, Y Okano, N Sakurai, A Kobayashi, K Harada, H Yamagata, K Matsuo, K Takahashi, K Narita, M Fukuda, Y Ishizaki, and M Mikuni. Blood Transcriptomic Markers in Patients with Late-Onset Major Depressive Disorder. *PLoS One*, 11(2):e0150262, 2016.

[567] A Bolis, S Coviello, S Bussini, G Dina, C Pardini, S C Previtali, M Malaguti, P Morana, U Del Carro, M L Feltri, A Quattrini, L Wrabetz, and A Bolino. Loss of Mtmr2 phosphatase in Schwann cells but not in motor neurons causes Charcot-Marie-Tooth type 4B1 neuropathy with myelin outfoldings. *J Neurosci*, 25(37):8567–8577, 2005.

[568] T Abdalla-Moady, A Peleg, O Sadeh, K Badarneh, and F Fares. Whole-Exome Sequencing Identifies a Novel Homozygous Frameshift Mutation in the MTMR2 Gene as a Causative Mutation in a Patient with Charcot-Marie-Tooth Disease Type 4B1. *Mol Neurobiol*, 2017.

[569] A M Bourgonje, K Verrijp, J T Schepens, A C Navis, J A Piepers, C B Palmen, M van den Eijnden, R Hooft van Huijsduijnen, P Wesseling, W P Leenders, and W J Hendriks. Comprehensive protein tyrosine phosphatase mRNA profiling identifies new regulators in the progression of glioma. *Acta Neuropathol Commun*, 4(1):96, 2016.

[570] W J Buchser, T I Slepak, O Gutierrez-Arenas, J L Bixby, and V P Lemmon. Kinase/phosphatase overexpression reveals pathways regulating hippocampal neuron morphology. *Mol Syst Biol*, 6:391, 2010.

[571] A Manole, A Horga, J Gamez, N Raguer, M Salvado, B San Millan, C Navarro, A Pittmann, M M Reilly, and H Houlden. SBF1 mutations associated with autosomal recessive axonal neuropathy with cranial nerve involvement. *Neurogenetics*, 18(1):63–67, 2017.

[572] P Sanchez-Juan, M T Bishop, Y S Aulchenko, J P Brandel, F Rivadeneira, M Struchalin, J C Lambert, P Amouyel, O Combarros, J Sainz, A Carracedo, A G Uitterlinden, A Hofman, I Zerr, H A Kretzschmar, J L Laplanche, R S Knight, R G Will, and C M van Duijn. Genome-wide study links MTMR7 gene to variant Creutzfeldt-Jakob risk. *Neurobiol Aging*, 33(7):1487 e21–8, 2012.

[573] P W Hook, S A McClymont, G H Cannon, W D Law, A J Morton, L A Goff, and A S McCallion. Single-Cell RNA-Seq of Mouse Dopaminergic Neurons Informs Candidate Gene Selection for Sporadic Parkinson Disease. *Am J Hum Genet*, 102(3):427–446, 2018.

[574] M G Waugh. Chromosomal Instability and Phosphoinositide Pathway Gene Signatures in Glioblastoma Multiforme. *Mol Neurobiol*, 53(1):621–630, 2016.

[575] A Forsingdal, K Fejgin, V Nielsen, T Werge, and J Nielsen. 15q13.3 homozygous knockout mouse model display epilepsy-, autism- and schizophrenia-related phenotypes. *Transl Psychiatry*, 6(7):e860, 2016.

[576] J H Kogan, A K Gross, R E Featherstone, R Shin, Q Chen, C L Heusner, M Adachi, A Lin, N M Walton, S Miyoshi, S Miyake, K Tajinda, H Ito, S J Siegel, and M Matsumoto. Mouse Model of Chromosome 15q13.3 Microdeletion Syndrome Demonstrates Features Related to Autism Spectrum Disorder. *J Neurosci*, 35(49):16282–16294, 2015.

[577] S Valbonesi, C Magri, M Traversa, S V Faraone, A Cattaneo, E Milanesi, V Valenti, M Gennarelli, and C Scassellati. Copy number variants in attention-deficit hyperactive disorder: identification of the 15q13 deletion and its functional role. *Psychiatr Genet*, 25(2):59–70, 2015.

[578] K R Veeramah, L Johnstone, T M Karafet, D Wolf, R Sprissler, J Salogiannis, A Barth-Maron, M E Greenberg, T Stuhlmann, S Weinert, T J Jentsch, M Pazzi, L L Restifo, D Talwar, R P Erickson, and M F Hammer. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. *Epilepsia*, 54(7):1270–1281, 2013.

[579] Aubree A Ng, Anne M Logan, Eric J Schmidt, and Fred L Robinson. The CMT4B disease-causing phosphatases Mtmr2 and Mtmr13 localize to the Schwann cell cytoplasm and endomembrane compartments, where they depend upon each other to achieve wild-type levels of protein expression. *Human molecular genetics*, 22(8):1493–1506, 2013.

[580] F L Robinson, I R Niesman, K K Beiswenger, and J E Dixon. Loss of the inactive myotubularin-related phosphatase Mtmr13 leads to a Charcot-Marie-Tooth 4B2-like peripheral neuropathy in mice. *Proc Natl Acad Sci U S A*, 105(12):4916–4921, 2008.

[581] M Chen, J Wu, N Liang, L Tang, Y Chen, H Chen, W Wei, T Wei, H Huang, X Yi, and M Qi. Identification of a novel SBF2 frameshift mutation in charcot-marie-tooth disease type 4B2 using whole-exome sequencing. *Genomics Proteomics Bioinformatics*, 12(5):221–227, 2014.

[582] L Negrao, L Almendra, J Ribeiro, A Matos, A Geraldo, and J Pinto-Basto. Charcot-Marie-Tooth 4B2 caused by a novel mutation in the MTMR13/SBF2 gene in two related Portuguese families. *Acta Myol*, 33(3):144–148, 2014.

[583] J Gayarre, L Duran-Trio, O Criado Garcia, C Aguado, L Juana-Lopez, I Crespo, E Knecht, P Bovolenta, and S Rodriguez de Cordoba. The phosphatase activity of laforin is dispensable to rescue Epm2a-/- mice from Lafora disease. *Brain*, 137(Pt 3):806–818, 2014.

[584] M A Garcia-Gimeno, P N Rodilla-Ramirez, R Viana, X Salas-Puig, M K Brewer, M S Gentry, and P Sanz. A novel EPM2A mutation yields a slow progression form of Lafora disease. *Epilepsy Res*, 145:169–177, 2018.

[585] P Gomez-Garre, Y Sanz, S R Rodriguez De Cordoba, and J M Serratosa. Mutational spectrum of the EPM2A gene in progressive myoclonus epilepsy of Lafora: high degree of allelic heterogeneity and prevalence of deletions. *Eur J Hum Genet*, 8(12):946–954, 2000.

[586] M Kedmi and A Orr-Urtreger. Expression changes in mouse brains following nicotine-induced seizures: the modulation of transcription factor networks. *Physiol Genomics*, 30(3):242–252, 2007.

[587] K K Park, K Liu, Y Hu, J L Kanter, and Z He. PTEN/mTOR and axon regeneration. *Exp Neurol*, 223(1):45–50, 2010.

[588] C Marie-Claire, N Benturquia, A Lundqvist, C Courtin, and F Noble. Characteristics of dual specificity phosphatases mRNA regulation by 3,4-methylenedioxymethamphetamine acute treatment in mice striatum. *Brain Res*, 1239:42–48, 2008.

[589] R M Tordera, A L Garcia-Garcia, N Elizalde, V Segura, E Aso, E Venzala, M J Ramirez, and J Del Rio. Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. *Eur Neuropsychopharmacol*, 21(1):23–32, 2011.

[590] P Rao-Ruiz, J J Couey, I M Marcelo, C G Bouwkamp, D E Slump, M R Matos, R J van der Loo, G J Martins, M van den Hout, IJcken W F Van, R M Costa, M C van den Oever, and S A Kushner. Engram-specific transcriptome profiling of contextual memory consolidation. *Nat Commun*, 10(1):2232, 2019.

[591] M Geva, R Kusko, H Soares, K D Fowler, T Birnberg, S Barash, A M Wagner, T Fine, A Lysaght, B Weiner, Y Cha, S Kolitz, F Towfic, A Orbach, R Laufer, B Zeskind, I Grossman, and M R Hayden. Pridopidine activates neuroprotective pathways impaired in Huntington Disease. *Hum Mol Genet*, 25(18):3975–3987, 2016.

[592] S Y Kim, M Oh, K S Lee, W K Kim, K J Oh, S C Lee, K H Bae, and B S Han. Profiling analysis of protein tyrosine phosphatases during neuronal differentiation. *Neurosci Lett*, 612:219–224, 2016.

[593] H Caren, A Djos, M Nethander, R M Sjoberg, P Kogner, C Enstrom, S Nilsson, and T Martinsson. Identification of epigenetically regulated genes that predict patient outcome in neuroblastoma. *BMC Cancer*, 11:66, 2011.

[594] C H Yang, Y J Yeh, J Y Wang, Y W Liu, Y L R Chen, H W Cheng, C M Cheng, Y J Chuang, C H Yuh, and Y L R Chen. NEAP/DUSP26 suppresses receptor tyrosine kinases and regulates neuronal development in zebrafish. *Sci Rep*, 7(1):5241, 2017.

[595] Y Shi, I T Ma, R H Patel, X Shang, Z Chen, Y Zhao, J Cheng, Y Fan, Y Rojas, E Barbieri, Z Chen, Y Yu, J Jin, E S Kim, J M Shohet, S A Vasudevan, and J Yang. NSC-87877 inhibits DUSP26 function in neuroblastoma resulting in p53-mediated apoptosis. *Cell Death Dis*, 6:e1841, 2015.

[596] D A Nielsen, F Ji, V Yuferov, A Ho, C He, J Ott, and M J Kreek. Genome-wide association study identifies genes that may contribute to risk for developing heroin addiction. *Psychiatr Genet*, 20(5):207–214, 2010.

[597] R Ottman, J Levy, W E Grizzle, and R Chakrabarti. The other face of miR-17-92a cluster, exhibiting tumor suppressor effects in prostate cancer. *Oncotarget*, 7(45):73739–73753, 2016.

[598] Y Yamashiro, C L Papke, J Kim, L J Ringuette, Q J Zhang, Z P Liu, H Mirzaei, J E Wagenseil, E C Davis, and H Yanagisawa. Abnormal mechanosensing and cofilin activation promote the progression of ascending aortic aneurysms in mice. *Sci Signal*, 8(399):ra105, 2015.

[599] X Lu, U Boora, L Seabra, E M Rabai, J Fenton, A Reiman, Z Nagy, and E R Maher. Knockdown of Slingshot 2 (SSH2) serine phosphatase induces Caspase3 activation in human carcinoma cell lines with the loss of the Birt-Hogg-Dube tumour suppressor gene (FLCN). *Oncogene*, 33(8):956–965, 2014.

[600] R A Torres, D A Drake, V Solodushko, R Jadhav, E Smith, P Rocic, and D S Weber. Slingshot isoform-specific regulation of cofilin-mediated vascular smooth muscle cell migration and neointima formation. *Arterioscler Thromb Vasc Biol*, 31(11):2424–2431, 2011.

[601] X Xu, N Gera, H Li, M Yun, L Zhang, Y Wang, Q J Wang, and T Jin. GPCR-mediated PLCbetagamma/PKCbeta/PKD signaling pathway regulates the cofilin phosphatase slingshot 2 in neutrophil chemotaxis. *Mol Biol Cell*, 26(5):874–886, 2015.

[602] T Kanai, S Seki, J A Jenks, A Kohli, T Kawli, D P Martin, M Snyder, R Bacchetta, and K C Nadeau. Identification of STAT5A and STAT5B target genes in human T cells. *PLoS One*, 9(1):e86790, 2014.

[603] Y H Hu, Y X Lu, Z Y Zhang, J M Zhang, W J Zhang, L Zheng, W H Lin, W J Zhang, and X N Li. SSH3 facilitates colorectal cancer cell invasion and metastasis by affecting signaling cascades involving LIMK1/Rac1. *Am J Cancer Res*, 9(5):1061–1073, 2019.

[604] A K Muller, M Foll, B Heckelmann, S Kiefer, M Werner, O Schilling, M L Biniossek, C A Jilg, and V Drendel. Proteomic Characterization of Prostate Cancer to Distinguish Nonmetastasizing and Metastasizing Primary Tumors and Lymph Node Metastases. *Neoplasia*, 20(2):140–151, 2018.

[605] R H Diamond, C Peters, S P Jung, L E Greenbaum, B A Haber, D G Silberg, P G Traber, and R Taub. Expression of PRL-1 nuclear PTPase is associated with proliferation in liver but with differentiation in intestine. *Am J Physiol*, 271(1 Pt 1):G121–9, 1996.

[606] Y Bai, H M Zhou, L Zhang, Y Dong, Q Zeng, W Shou, and Z Y Zhang. Role of phosphatase of regenerating liver 1 (PRL1) in spermatogenesis. *Sci Rep*, 6:34211, 2016.

[607] S Shinmei, K Sentani, T Hayashi, N Sakamoto, K Goto, H Zarni Oo, Y Naito, J Teishima, A Matsubara, N Oue, H Kuniyasu, and W Yasui. Identification of PRL1 as a novel diagnostic and therapeutic target for castration-resistant prostate cancer by the Escherichia coli ampicillin secretion trap (CAST) method. *Urol Oncol*, 32(6):769–778, 2014.

[608] R Reich, S Hadar, and B Davidson. Expression and clinical role of protein of regenerating liver (PRL) phosphatases in ovarian carcinoma. *Int J Mol Sci*, 12(2):1133–1145, 2011.

[609] Y Wang and J S Lazo. Metastasis-associated phosphatase PRL-2 regulates tumor cell migration and invasion. *Oncogene*, 31(7):818–827, 2012.

[610] M Kobayashi, S C Nabinger, Y Bai, M Yoshimoto, R Gao, S Chen, C Yao, Y Dong, L Zhang, S Rodriguez, Y Yashiro-Ohtani, W S Pear, N Carlesso, M C Yoder, R Kapur, M H Kaplan, H Daniel Lacorazza, Z Y Zhang, and Y Liu. Protein Tyrosine Phosphatase PRL2 Mediates Notch and Kit Signals in Early T Cell Progenitors. *Stem Cells*, 35(4):1053–1064, 2017.

[611] Y Dong, L Zhang, S Zhang, Y Bai, H Chen, X Sun, W Yong, W Li, S C Colvin, S J Rhodes, W Shou, and Z Y Zhang. Phosphatase of regenerating liver 2 (PRL2) is essential for placental development by down-regulating PTEN (Phosphatase and Tensin Homologue Deleted on Chromosome 10) and activating Akt protein. *J Biol Chem*, 287(38):32172–32179, 2012.

[612] J Li, K Guo, V W Koh, J P Tang, B Q Gan, H Shi, H X Li, and Q Zeng. Generation of PRL-3- and PRL-1-specific monoclonal antibodies as potential diagnostic markers for cancer metastases. *Clin Cancer Res*, 11(6):2195–2204, 2005.

[613] M W Zimmerman, G E Homanics, and J S Lazo. Targeted deletion of the metastasis-associated phosphatase Ptp4a3 (PRL-3) suppresses murine colon cancer. *PLoS One*, 8(3):e58300, 2013.

[614] E N Vandsemb, H Bertilsson, P Abdollahi, O Storkersen, T K Vatsveen, M B Rye, T B Ro, M Borset, and T S Slordahl. Phosphatase of regenerating liver 3 (PRL-3) is overexpressed in human prostate cancer tissue and promotes growth and migration. *J Transl Med*, 14:71, 2016.

[615] M Foy, O Anezo, S Saule, and N Planque. PRL-3/PTP4A3 phosphatase regulates integrin beta1 in adhesion structures during migration of human ocular melanoma cells. *Exp Cell Res*, 353(2):88–99, 2017.

[616] N A Patel, P S Patel, and H H Vora. Role of PRL-3, Snail, Cytokeratin and Vimentin expression in epithelial mesenchymal transition in breast carcinoma. *Breast Dis*, 35(2):113–127, 2015.

[617] K Schindler and R M Schultz. The CDC14A phosphatase regulates oocyte maturation in mouse. *Cell Cycle*, 8(7):1090–1098, 2009.

[618] S Y Song, M R Kang, N J Yoo, and S H Lee. Mutational analysis of mononucleotide repeats in dual specificity tyrosine phosphatase genes in gastric and colon carcinomas with microsatellite instability. *APMIS*, 118(5):389–393, 2010.

[619] J Wu, H P Cho, D B Rhee, D K Johnson, J Dunlap, Y Liu, and Y Wang. Cdc14B depletion leads to centriole amplification, and its overexpression prevents unscheduled centriole duplication. *J Cell Biol*, 181(3):475–483, 2008.

[620] Hyekyung P Cho, Yie Liu, Marla Gomez, John Dunlap, Mike Tyers, and Yisong Wang. The dual-specificity phosphatase CDC14B bundles and stabilizes microtubules. *Molecular and cellular biology*, 25(11):4541–4551, 2005.

[621] S H Roy, J E Clayton, J Holmen, E Beltz, and R M Saito. Control of Cdc14 activity coordinates cell cycle and development in Caenorhabditis elegans. *Mech Dev*, 128(7-10):317–326, 2011.

[622] S Szmit, M Jank, H Maciejewski, M Grabowski, R Glowczynska, A Majewska, K J Filipiak, T Motyl, and G Opolski. Gene expression profiling in peripheral blood nuclear cells in patients with refractory ischaemic end-stage heart failure. *J Appl Genet*, 51(3):353–368, 2010.

[623] G L Mutter, M C Lin, J T Fitzgerald, J B Kum, J P Baak, J A Lees, L P Weng, and C Eng. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *J Natl Cancer Inst*, 92(11):924–930, 2000.

[624] M Frattini, P Saletti, E Romagnani, V Martin, F Molinari, M Ghisletta, A Camponovo, L L Etienne, F Cavalli, and L Mazzucchelli. PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. *Br J Cancer*, 97(8):1139–1145, 2007.

[625] Y Dong, L Sui, F Yamaguchi, K Kamitori, Y Hirata, A Hossain, C Noguchi, A Katagi, M Nishio, A Suzuki, X Lou, and M Tokuda. The expression of PTEN in the development of mouse cochlear lateral wall. *Neuroscience*, 258:263–269, 2014.

[626] M N Lague, J Detmar, M Paquet, A Boyer, J S Richards, S L Adamson, and D Boerboom. Decidual PTEN expression is required for trophoblast invasion in the mouse. *Am J Physiol Endocrinol Metab*, 299(6):E936–46, 2010.

[627] S T Reddy, J T Nguyen, V Grijalva, G Hough, S Hama, M Navab, and A M Fogelman. Potential role for mitogen-activated protein kinase phosphatase-1 in the development of atherosclerotic lesions in mouse models. *Arterioscler Thromb Vasc Biol*, 24(9):1676–1681, 2004.

[628] C C Franklin and A S Kraft. Conditional expression of the mitogen-activated protein kinase (MAPK) phosphatase MKP-1 preferentially inhibits p38 MAPK and stress-activated protein kinase in U937 cells. *J Biol Chem*, 272(27):16917–16923, 1997.

[629] A Lawan, L Zhang, F Gatzke, K Min, M J Jurczak, M Al-Mutairi, P Richter, J P Camporez, A Couvillon, D Pesta, R J Roth Flach, G I Shulman, and A M Bennett. Hepatic mitogen-activated protein kinase phosphatase 1 selectively regulates glucose metabolism and energy homeostasis. *Mol Cell Biol*, 35(1):26–40, 2015.

[630] T Zhang, X Lu, P Arnold, Y Liu, R Baliga, H Huang, J A Bauer, Y Liu, and Q Feng. Mitogen-activated protein kinase phosphatase-1 inhibits myocardial TNF-alpha expression and improves cardiac function during endotoxemia. *Cardiovasc Res*, 93(3):471–479, 2012.

[631] C Denkert, W D Schmitt, S Berger, A Reles, S Pest, A Siegert, W Lichtenegger, M Dietel, and S Hauptmann. Expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in primary human ovarian carcinoma. *Int J Cancer*, 102(5):507–513, 2002.

[632] Adelaida M Celaya, Isabel Sánchez-Pérez, Jose M Bermúdez-Muñoz, Lourdes Rodriguez-de la Rosa, Laura Pintado-Berninches, Rosario Perona, Silvia Murillo-Cuesta, and Isabel Varela-Nieto. Deficit of mitogen-activated protein kinase phosphatase 1 (DUSP1) accelerates progressive hearing loss. *Elife*, 8:e39159, 2019.

[633] Y Chu, P A Solski, R Khosravi-Far, C J Der, and K Kelly. The mitogen-activated protein kinase phosphatases PAC1, MKP-1, and MKP-2 have unique substrate specificities and reduced activity in vivo toward the ERK2 sevenmaker mutation. *J Biol Chem*, 271(11):6497–6501, 1996.

[634] A Misra-Press, C S Rim, H Yao, M S Roberson, and P J Stork. A novel mitogen-activated protein kinase phosphatase. Structure, expression, and regulation. *J Biol Chem*, 270(24):14587–14596, 1995.

[635] T T Cornell, A Fleszar, W McHugh, N B Blatt, A M Le Vine, and T P Shanley. Mitogen-activated protein kinase phosphatase 2, MKP-2, regulates early inflammation in acute lung injury. *Am J Physiol Lung Cell Mol Physiol*, 303(3):L251–8, 2012.

[636] A Barajas-Espinosa, A Basye, M G Angelos, and C A Chen. Modulation of p38 kinase by DUSP4 is important in regulating cardiovascular function under oxidative stress. *Free Radic Biol Med*, 89:170–181, 2015.

[637] M Muda, U Boschert, R Dickinson, J C Martinou, I Martinou, M Camps, W Schlegel, and S Arkinstall. MKP-3, a novel cytosolic protein-tyrosine phosphatase that exemplifies a new class of mitogen-activated protein kinase phosphatase. *J Biol Chem*, 271(8):4319–4326, 1996.

[638] C E Nunes-Xavier, C Tarrega, R Cejudo-Marin, J Frijhoff, A Sandin, A Ostman, and R Pulido. Differential up-regulation of MAP kinase phosphatases MKP3/DUSP6 and DUSP5 by Ets2 and c-Jun converge in the control of the growth arrest versus proliferation response of MCF-7 breast cancer cells to phorbol ester. *J Biol Chem*, 285(34):26417–26430, 2010.

[639] L Rossig, J Haendeler, C Hermann, P Malchow, C Urbich, A M Zeiher, and S Dimmeler. Nitric oxide down-regulates MKP-3 mRNA levels: involvement in endothelial cell protection from apoptosis. *J Biol Chem*, 275(33):25502–25507, 2000.

[640] C Li, D A Scott, E Hatch, X Tian, and S L Mansour. Dusp6 (Mkp3) is a negative feedback regulator of FGF-stimulated ERK signaling during mouse development. *Development*, 134(1):167–176, 2007.

[641] Marco Muda, Ursula Boschert, Anna Smith, Bruno Antonsson, Corine Gillieron, Christian Chabert, Montserrat Camps, Isabelle Martinou, Alan Ashworth, and Steve Arkinstall. Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP-4. *Journal of Biological Chemistry*, 272(8):5141–5151, 1997.

[642] B Emanuelli, D Eberle, R Suzuki, and C R Kahn. Overexpression of the dual-specificity phosphatase MKP-4/DUSP-9 protects against stress-induced insulin resistance. *Proc Natl Acad Sci U S A*, 105(9):3545–3550, 2008.

[643] G R Christie, D J Williams, F Macisaac, R J Dickinson, I Rosewell, and S M Keyse. The dual-specificity protein phosphatase DUSP9/MKP-4 is essential for placental function but is not required for normal embryonic development. *Mol Cell Biol*, 25(18):8323–8333, 2005.

[644] M Niedzielska, F A Raffi, J Tel, S Muench, K Jozefowski, N Alati, K Lahl, J Mages, U Billmeier, M Schiemann, U K Appelt, S Wirtz, T Sparwasser, H Hochrein, C G Figdor, S M Keyse, and R Lang. Selective Expression of the MAPK Phosphatase Dusp9/MKP-4 in Mouse Plasmacytoid Dendritic Cells and Regulation of IFN-beta Production. *J Immunol*, 195(4):1753–1762, 2015.

[645] T Tanoue, T Moriguchi, and E Nishida. Molecular cloning and characterization of a novel dual specificity phosphatase, MKP-5. *J Biol Chem*, 274(28):19949–19956, 1999.

[646] A Theodosiou, A Smith, C Gillieron, S Arkinstall, and A Ashworth. MKP5, a new member of the MAP kinase phosphatase family, which selectively dephosphorylates stress-activated kinases. *Oncogene*, 18(50):6981–6988, 1999.

[647] M Nomura, K Shiiba, C Katagiri, I Kasugai, K Masuda, I Sato, M Sato, Y Kakugawa, E Nomura, K Hayashi, Y Nakamura, T Nagata, T Otsuka, R Katakura, Y Yamashita, M Sato, N Tanuma, and H Shima. Novel function of MKP-5/DUSP10, a phosphatase of stress-activated kinases, on ERK-dependent gene expression, and upregulation of its gene expression in colon carcinomas. *Oncol Rep*, 28(3):931–936, 2012.

[648] Y Zhang, J N Blattman, N J Kennedy, J Duong, T Nguyen, Y Wang, R J Davis, P D Greenberg, R A Flavell, and C Dong. Regulation of innate and adaptive immune responses by MAP kinase phosphatase 5. *Nature*, 430(7001):793–797, 2004.

[649] R M Jones, V M Sloane, H Wu, L Luo, A Kumar, M V Kumar, A T Gewirtz, and A S Neish. Flagellin administration protects gut mucosal tissue from irradiation-induced apoptosis via MKP-7 activity. *Gut*, 60(5):648–657, 2011.

[650] K Masuda, H Shima, M Watanabe, and K Kikuchi. MKP-7, a novel mitogen-activated protein kinase phosphatase, functions as a shuttle protein. *J Biol Chem*, 276(42):39002–39011, 2001.

[651] Y Zhang, K C Nallaparaju, X Liu, H Jiao, J M Reynolds, Z X Wang, and C Dong. MAPK phosphatase 7 regulates T cell differentiation via inhibiting ERK-mediated IL-2 expression. *J Immunol*, 194(7):3088–3095, 2015.

[652] H Kanemaru, F Yamane, H Tanaka, K Maeda, T Satoh, and S Akira. BATF2 activates DUSP2 gene expression and up-regulates NF-kappaB activity via phospho-STAT3 dephosphorylation. *Int Immunol*, 30(6):255–265, 2018.

[653] G I Lancaster, M J Kraakman, H L Kammoun, K G Langley, E Estevez, A Banerjee, R J Grumont, M A Febbraio, and S Gerondakis. The dual-specificity phosphatase 2 (DUSP2) does not regulate obesity-associated inflammation or insulin resistance in mice. *PLoS One*, 9(11):e111524, 2014.

[654] W Dong, N Li, X Pei, and X Wu. Differential expression of DUSP2 in left- and right-sided colon cancer is associated with poor prognosis in colorectal cancer. *Oncol Lett*, 15(4):4207–4214, 2018.

[655] J S Habibian, M Jefic, R A Bagchi, R H Lane, R A McKnight, T A McKinsey, R F Morrison, and B S Ferguson. DUSP5 functions as a feedback regulator of TNFalpha-induced ERK1/2 dephosphorylation and inflammatory gene expression in adipocytes. *Sci Rep*, 7(1):12879, 2017.

[656] S Pourteymour, M Hjorth, S Lee, T Holen, T M Langleite, J Jensen, K I Birkeland, C A Drevon, and K Eckardt. Dual specificity phosphatase 5 and 6 are oppositely regulated in human skeletal muscle by acute exercise. *Physiol Rep*, 5(19), 2017.

[657] D Yu, Z Li, M Gan, H Zhang, X Yin, S Tang, L Wan, Y Tian, S Zhang, Y Zhu, M Lai, and D Zhang. Decreased expression of dual specificity phosphatase 22 in colorectal cancer and its potential prognostic relevance for stage IV CRC patients. *Tumour Biol*, 36(11):8531–8535, 2015.

[658] A Alonso, J J Merlo, S Na, N Kholod, L Jaroszewski, A Kharitonenkov, S Williams, A Godzik, J D Posada, and T Mustelin. Inhibition of T cell antigen receptor signaling by VHR-related MKPX (VHX), a new dual specificity phosphatase related to VH1 related (VHR). *J Biol Chem*, 277(7):5524–5528, 2002.

[659] T A Dayeh, A H Olsson, P Volkov, P Almgren, T Ronn, and C Ling. Identification of CpG-SNPs associated with type 2 diabetes and differential DNA methylation in human pancreatic islets. *Diabetologia*, 56(5):1036–1046, 2013.

[660] J Smeeton, P Dhir, D Hu, M M Feeney, L Chen, and N D Rosenblum. Integrin-linked Kinase Controls Renal Branching Morphogenesis via Dual Specificity Phosphatase 8. *J Am Soc Nephrol*, 27(5):1465–1477, 2016.

[661] B A Katchman, D Chowell, G Wallstrom, A F Vitonis, J LaBaer, D W Cramer, and K S Anderson. Autoantibody biomarkers for the detection of serous ovarian cancer. *Gynecol Oncol*, 146(1):129–136, 2017.

[662] N M Niemi, N J Lanning, J A Klomp, S W Tait, Y Xu, K J Dykema, L O Murphy, L A Gaither, H E Xu, K A Furge, D R Green, and J P MacKeigan. MK-STYX, a catalytically inactive phosphatase regulating mitochondrially dependent apoptosis. *Mol Cell Biol*, 31(7):1357–1368, 2011.

[663] Jocelyn Laporte, Ling Jia Hu, Christine Kretz, Jean-Louis Mandel, Petra Kioschis, Johannes F Coy, Sabine M Klauck, Annemarie Poustka, and Niklas Dahl. A gene mutated in X–linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. *Nature genetics*, 13(2):175–182, 1996.

[664] R Mansour, S Severin, J M Xuereb, M P Gratacap, J Laporte, A Buj-Bello, H Tronchere, and B Payrastre. Expression of myotubularins in blood platelets: Characterization and potential diagnostic of X-linked myotubular myopathy. *Biochem Biophys Res Commun*, 476(3):167–173, 2016.

[665] M Santoro, A Modoni, M Masciullo, T Gidaro, A Broccolini, E Ricci, P A Tonali, and G Silvestri. Analysis of MTMR1 expression and correlation with muscle pathological features in juvenile/adult onset myotonic dystrophy type 1 (DM1) and in myotonic dystrophy type 2 (DM2). *Exp Mol Pathol*, 89(2):158–168, 2010.

[666] T H Ho, D Bundman, D L Armstrong, and T A Cooper. Transgenic mice expressing CUG-BP1 reproduce splicing mis-regulation observed in myotonic dystrophy. *Hum Mol Genet*, 14(11):1539–1547, 2005.

[667] S A Kim, G S Taylor, K M Torgersen, and J E Dixon. Myotubularin and MTMR2, phosphatidylinositol 3-phosphatases mutated in myotubular myopathy and type 4B Charcot-Marie-Tooth disease. *J Biol Chem*, 277(6):4526–4531, 2002.

[668] A Bolino, V Marigo, F Ferrera, J Loader, L Romio, A Leoni, M Di Duca, R Cinti, C Cecchi, M L Feltri, L Wrabetz, R Ravazzolo, and A P Monaco. Molecular characterization and expression analysis of Mtmr2, mouse homologue of MTMR2, the Myotubularin-related 2 gene, mutated in CMT4B. *Gene*, 283(1-2):17–26, 2002.

[669] Y Z Kuo, Y H Tai, H I Lo, Y L Chen, H C Cheng, W Y Fang, S H Lin, C L Yang, S T Tsai, and L W Wu. MiR-99a exerts anti-metastasis through inhibiting myotubularin-related protein 3 expression in oral cancer. *Oral Dis*, 20(3):e65–75, 2014.

[670] A Lahiri, M Hedl, and C Abraham. MTMR3 risk allele enhances innate receptor-induced signaling and cytokines by decreasing autophagy and increasing caspase-1 activation. *Proc Natl Acad Sci U S A*, 112(33):10461–10466, 2015.

[671] Z Wang, M Zhang, R Shan, Y J Wang, J Chen, J Huang, L Q Sun, and W B Zhou. MTMR3 is upregulated in patients with breast cancer and regulates proliferation, cell cycle progression and autophagy in breast cancer cells. *Oncol Rep*, 42(5):1915–1923, 2019.

[672] M J Naughtin, D A Sheffield, P Rahman, W E Hughes, R Gurung, J L Stow, H H Nandurkar, J M Dyson, and C A Mitchell. The myotubularin phosphatase MTMR4 regulates sorting from early endosomes. *J Cell Sci*, 123(Pt 18):3071–3083, 2010.

[673] R Zhao, Y Qi, J Chen, and Z J Zhao. FYVE-DSP2, a FYVE domain-containing dual specificity protein phosphatase that dephosphorylates phosphotidylinositol 3-phosphate. *Exp Cell Res*, 265(2):329–338, 2001.

[674] O Lorenzo, S Urbe, and M J Clague. Systematic analysis of myotubularins: heteromeric interactions, subcellular localisation and endosome related functions. *J Cell Sci*, 119(Pt 14):2953–2959, 2006.

[675] B Jarzab, M Wiench, K Fujarewicz, K Simek, M Jarzab, M Oczko-Wojciechowska, J Wloch, A Czarniecka, E Chmielik, D Lange, A Pawlaczek, S Szpak, E Gubala, and A Swierniak. Gene expression profile of papillary thyroid cancer: sources of variability and diagnostic implications. *Cancer Res*, 65(4):1587–1597, 2005.

[676] R Firestein and M L Cleary. Pseudo-phosphatase Sbf1 contains an N-terminal GEF homology domain that modulates its growth regulatory properties. *J Cell Sci*, 114(Pt 16):2921–2927, 2001.

[677] A Kuzmin, K Jarvi, K Lo, L Spencer, G Y Chow, G Macleod, Q Wang, and S Varmuza. Identification of potentially damaging amino acid substitutions leading to human male infertility. *Biol Reprod*, 81(2):319–326, 2009.

[678] R Firestein, P L Nagy, M Daly, P Huie, M Conti, and M L Cleary. Male infertility, impaired spermatogenesis, and azoospermia in mice deficient for the pseudophosphatase Sbf1. *J Clin Invest*, 109(9):1165–1172, 2002.

[679] Y Mochizuki, R Ohashi, T Kawamura, H Iwanari, T Kodama, M Naito, and T Hamakubo. Phosphatidylinositol 3-phosphatase myotubularin-related protein 6 (MTMR6) is regulated by small GTPase Rab1B in the early secretory and autophagic pathways. *J Biol Chem*, 288(2):1009–1021, 2013.

[680] Y Mochizuki and P W Majerus. Characterization of myotubularin-related protein 7 and its binding partner, myotubularin-related protein 9. *Proc Natl Acad Sci U S A*, 100(17):9768–9773, 2003.

[681] Z Yuan, Y Chen, X Zhang, X Zhou, M Li, H Chen, M Wu, Y Zhang, and D Mo. Silencing myotubularin related protein 7 enhances proliferation and early differentiation of C2C12 myoblast. *Biochem Biophys Res Commun*, 484(3):592–597, 2017.

[682] P Weidner, M Sohn, T Gutting, T Friedrich, T Gaiser, J Magdeburg, P Kienle, H Ruh, C Hopf, H M Behrens, C Rocken, T Hanoch, R Seger, M P Ebert, and E Burgermeister. Myotubularin-related protein 7 inhibits insulin signaling in colorectal cancer. *Oncotarget*, 7(31):50490–50506, 2016.

[683] Silke Appel, Kathrin Reichwald, Wolfgang Zimmermann, André Reis, André Rosenthal, and Hans Christian Hennies. Identification and Localization of a New Human Myotubularin-Related Protein Gene, MTMR8, on 8p22–p23. *Genomics*, 75(1-3):6–8, 2001.

[684] J Mei, Z Li, and J F Gui. Cooperation of Mtmr8 with PI3K regulates actin filament modeling and muscle development in zebrafish. *PLoS One*, 4(3):e4979, 2009.

[685] J Mei, S Liu, Z Li, and J F Gui. Mtmr8 is essential for vasculature development in zebrafish embryos. *BMC Dev Biol*, 10:96, 2010.

[686] S Ali, K Ghosh, and S Shetty. Differential expression of genes involved in Bengal macrothrombocytopenia (BMTCP). *Blood Cells Mol Dis*, 55(4):410–414, 2015.

[687] L Tang, Y Tong, H Cao, S Xie, Q Yang, F Zhang, Q Zhu, L Huang, Q Lu, Y Yang, D Li, M Chen, C Yu, W Jin, Y Yuan, and N Tong. The MTMR9 rs2293855 polymorphism is associated with glucose tolerance, insulin secretion, insulin sensitivity and increased risk of prediabetes. *Gene*, 546(2):150–155, 2014.

[688] M von Deimling, R Hasler, V Steinbach, P M Holterhus, S von Spiczak, U Stephani, I Helbig, and H Muhle. Gene expression analysis in untreated absence epilepsy demonstrates an inconsistent pattern. *Epilepsy Res*, 132:84–90, 2017.

[689] J B Le Pichon, S Yu, N Kibiryeva, W D Graf, and D C Bittel. Genome-wide gene expression in a patient with 15q13.3 homozygous microdeletion syndrome. *Eur J Hum Genet*, 21(10):1093–1099, 2013.

[690] M A Lucci, R Orlandi, T Triulzi, E Tagliabue, A Balsari, and E Villa-Moruzzi. Expression profile of tyrosine phosphatases in HER2 breast cancer cells and tumors. *Cell Oncol*, 32(5-6):361–372, 2010.

[691] N N Kabir, L Ronnstrand, and J U Kazi. Deregulation of protein phosphatase expression in acute myeloid leukemia. *Med Oncol*, 30(2):517, 2013.

[692] D I Scheffer, J Shen, D P Corey, and Z Y Chen. Gene Expression by Mouse Inner Ear Hair Cells during Development. *J Neurosci*, 35(16):6366–6380, 2015.

[693] V A Gupta, K Hnia, L L Smith, S R Gundry, J E McIntire, J Shimazu, J R Bass, E A Talbot, L Amoasii, N E Goldman, J Laporte, and A H Beggs. Loss of catalytically inactive lipid phosphatase myotubularin-related protein 12 impairs myotubularin stability and promotes centronuclear myopathy in zebrafish. *PLoS Genet*, 9(6):e1003583, 2013.

[694] H Azzedine, A Bolino, T Taieb, N Birouk, M Di Duca, A Bouhouche, S Benamou, A Mrabet, T Hammadouche, T Chkili, R Gouider, R Ravazzolo, A Brice, J Laporte, and E LeGuern. Mutations in MTMR13, a new pseudophosphatase homologue of MTMR2 and Sbf1, in two families with an autosomal recessive demyelinating form of Charcot-Marie-Tooth disease associated with early-onset glaucoma. *Am J Hum Genet*, 72(5):1141–1153, 2003.

[695] J Senderek, C Bergmann, S Weber, U P Ketelsen, H Schorle, S Rudnik-Schoneborn, R Buttner, E Buchheim, and K Zerres. Mutation of the SBF2 gene, encoding a novel member of the myotubularin family, in Charcot-Marie-Tooth neuropathy type 4B2/11p15. *Hum Mol Genet*, 12(3):349–356, 2003.

[696] B A Minassian, J R Lee, J A Herbrick, J Huizenga, S Soder, A J Mungall, I Dunham, R Gardner, C Y Fong, S Carpenter, L Jardim, P Satishchandra, E Andermann, O C Snead 3rd, I Lopes-Cendes, L C Tsui, A V Delgado-Escueta, G A Rouleau, and S W Scherer. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet*, 20(2):171–174, 1998.

[697] J M Serratosa, P Gomez-Garre, M E Gallardo, B Anta, D B de Bernabe, D Lindhout, P B Augustijn, C A Tassinari, R M Malafosse, M Topcu, D Grid, C Dravet, S F Berkovic, and S R de Cordoba. A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). *Hum Mol Genet*, 8(2):345–352, 1999.

[698] D He, Z Ma, C Fang, J Ding, W Yang, P Chen, L Huang, C Wang, Y Yu, L Yang, Y Li, and Z Zhou. Pseudophosphatase STYX promotes tumor growth and metastasis by inhibiting FBXW7 function in colorectal cancer. *Cancer Lett*, 454:53–65, 2019.

[699] M J Wishart and J E Dixon. The archetype STYX/dead-phosphatase complexes with a spermatid mRNA-binding protein and is essential for normal sperm production. *Proc Natl Acad Sci U S A*, 99(4):2112–2117, 2002.

[700] V Reiterer, D Fey, W Kolch, B N Kholodenko, and H Farhan. Pseudophosphatase STYX modulates cell-fate decisions and cell migration by spatiotemporal regulation of ERK1/2. *Proc Natl Acad Sci U S A*, 110(31):E2934–43, 2013.

[701] M Amand, C Erpicum, K Bajou, F Cerignoli, S Blacher, M Martin, F Dequiedt, P Drion, P Singh, T Zurashvili, M Vandereyken, L Musumeci, T Mustelin, M Moutschen, C Gilles, A Noel, and S Rahmouni. DUSP3/VHR is a pro-angiogenic atypical dual-specificity phosphatase. *Mol Cancer*, 13:108, 2014.

[702] Y J Arnoldussen, P I Lorenzo, M E Pretorius, H Waehre, B Risberg, G M Maelandsmo, H E Danielsen, and F Saatcioglu. The mitogen-activated protein kinase phosphatase vaccinia H1-related protein inhibits apoptosis in prostate cancer cells and is overexpressed in prostate cancer. *Cancer Res*, 68(22):9255–9264, 2008.

[703] L Musumeci, M J Kuijpers, K Gilio, A Hego, E Theatre, L Maurissen, M Vandereyken, C V Diogo, C Lecut, W Guilmain, E V Bobkova, J A Eble, R Dahl, P Drion, J Rascon, Y Mostofi, H Yuan, E Sergienko, T D Chung, M Thiry, Y Senis, M Moutschen, T Mustelin, P Lancellotti, J W Heemskerk, L Tautz, C Oury, and S Rahmouni. Dual-specificity phosphatase 3 deficiency or inhibition limits platelet activation and arterial thrombosis. *Circulation*, 131(7):656–668, 2015.

[704] T H Kang and K T Kim. VRK3-mediated inactivation of ERK signaling in adult and embryonic rodent tissues. *Biochim Biophys Acta*, 1783(1):49–58, 2008.

[705] R Hasler, M Kerick, N Mah, C Hultschig, G Richter, F Bretz, C Sina, H Lehrach, W Nietfeld, S Schreiber, and P Rosenstiel. Alterations of pre-mRNA splicing in human inflammatory bowel disease. *Eur J Cell Biol*, 90(6-7):603–611, 2011.

[706] J M Burke, R P Kincaid, R M Nottingham, A M Lambowitz, and C S Sullivan. DUSP11 activity on triphosphorylated transcripts promotes Argonaute association with noncanonical viral microRNAs and regulates steady-state levels of cellular noncoding RNAs. *Genes Dev*, 30(18):2076–2092, 2016.

[707] G Caprara, R Zamponi, M Melixetian, and K Helin. Isolation and characterization of DUSP11, a novel p53 target gene. *J Cell Mol Med*, 13(8B):2158–2170, 2009.

[708] L F Monteiro and F L Forti. Network analysis of DUSP12 partners in the nucleus under genotoxic stress. *J Proteomics*, 197:42–52, 2019.

[709] Z Huang, L M Wu, J L Zhang, A Sabri, S J Wang, G J Qin, C Q Guo, H T Wen, B B Du, D H Zhang, L Y Kong, X Y Tian, R Yao, Y P Li, C Liang, P C Li, Z Wang, J Y Guo, L Li, J Z Dong, and Y Z Zhang. Dual

Specificity Phosphatase 12 Regulates Hepatic Lipid Metabolism Through Inhibition of the Lipogenesis and Apoptosis Signal-Regulating Kinase 1 Pathways. *Hepatology*, 70(4):1099–1118, 2019.

[710] H R Choi, W K Kim, A Park, H Jung, B S Han, S C Lee, and K H Bae. Protein tyrosine phosphatase profiling studies during brown adipogenic differentiation of mouse primary brown preadipocytes. *BMB Rep*, 46(11):539–543, 2013.

[711] H H Chen, R Luche, B Wei, and N K Tonks. Characterization of two distinct dual specificity phosphatases encoded in alternative open reading frames of a single gene located on human chromosome 10q22.2. *J Biol Chem*, 279(40):41404–41413, 2004.

[712] C Katagiri, K Masuda, M Nomura, K Tanoue, S Fujita, Y Yamashita, R Katakura, K Shiiba, E Nomura, M Sato, N Tanuma, and H Shima. DUSP13B/TMDP inhibits stress-activated MAPKs and suppresses AP-1-dependent gene expression. *Mol Cell Biochem*, 352(1-2):155–162, 2011.

[713] K Nakamura, H Shima, M Watanabe, T Haneji, and K Kikuchi. Molecular cloning and characterization of a novel dual-specificity protein phosphatase possibly involved in spermatogenesis. *Biochem J*, 344 Pt 3:819–825, 1999.

[714] L Hong, J Ai, and D Ma. Activation of Dusp14 protects against osteoclast generation and bone loss by regulating AMPKalpha-dependent manner. *Biochem Biophys Res Commun*, 519(3):445–452, 2019.

[715] C Y Li, Q Zhou, L C Yang, Y H Chen, J W Hou, K Guo, Y P Wang, and Y G Li. Dual-specificity phosphatase 14 protects the heart from aortic banding-induced cardiac hypertrophy and dysfunction through inactivation of TAK1-P38MAPK/-JNK1/2 signaling pathway. *Basic Res Cardiol*, 111(2):19, 2016.

[716] X Wang, W Mao, C Fang, S Tian, X Zhu, L Yang, Z Huang, and H Li. Dusp14 protects against hepatic ischaemia-reperfusion injury via Tak1 suppression. *J Hepatol*, 2017.

[717] M Hijikata, I Matsushita, N T Le Hang, P H Thuong, D B Tam, S Maeda, S Sakurada, V C Cuong, L T Lien, and N Keicho. Influence of the polymorphism of the DUSP14 gene on the expression of immune-related genes and development of pulmonary tuberculosis. *Genes Immun*, 17(4):207–212, 2016.

[718] A Alonso, S Narisawa, J Bogetz, L Tautz, R Hadzic, H Huynh, S Williams, A Gjorloff-Wingren, M C Bremer, L J Holsinger, J L Millan, and T Mustelin. VHY, a novel myristoylated testis-restricted dual specificity protein phosphatase related to VHX. *J Biol Chem*, 279(31):32586–32591, 2004.

[719] Q Wu, S Huang, Y Sun, S Gu, F Lu, J Dai, G Yin, L Sun, D Zheng, C Dou, C Feng, C Ji, Y Xie, and Y Mao. Dual specificity phosphotase 18, interacting with SAPK, dephosphorylates SAPK and inhibits SAPK/JNK signal pathway in vivo. *Front Biosci*, 11:2714–2724, 2006.

[720] Haipeng Cheng, Qi Gao, Min Jiang, Yushu Ma, Xiaohua Ni, Lingchen Guo, Wei Jin, Gentao Cao, Chaoneng Ji, and Kang Ying. Molecular cloning and characterization of a novel human protein phosphatase, LMW-DSP3. *The international journal of biochemistry & cell biology*, 35(2):226–234, 2003.

[721] T Zama, R Aoki, T Kamimoto, K Inoue, Y Ikeda, and M Hagiwara. A novel dual specificity phosphatase SKRP1 interacts with the MAPK kinase MKK7 and inactivates the JNK MAPK pathway. Implication for the precise regulation of the particular MAPK pathway. *J Biol Chem*, 277(26):23909–23918, 2002.

[722] Y Wang, Z Xu, J Wang, and S Xu. DUSP19, a downstream effector of leptin, inhibits chondrocyte apoptosis via dephosphorylating JNK during osteoarthritis pathogenesis. *Mol Biosyst*, 12(3):721–728, 2016.

[723] Q Deng, K Y Li, H Chen, J H Dai, Y Y Zhai, Q Wang, N Li, Y P Wang, and Z G Han. RNA interference against cancer/testis genes identifies dual specificity phosphatase 21 as a potential therapeutic target in human hepatocellular carcinoma. *Hepatology*, 59(2):518–530, 2014.

[724] N A Abdul Aziz, N M Mokhtar, R Harun, M M Mollah, I Mohamed Rose, I Sagap, A Mohd Tamil, W Z Wan Ngah, and R Jamal. A 19-Gene expression signature as a predictor of survival in colorectal cancer. *BMC Med Genomics*, 9(1):58, 2016.

[725] E Balada, L Felip, J Ordi-Ros, and M Vilardell-Tarres. DUSP23 is over-expressed and linked to the expression of DNMTs in CD4+ T cells from systemic lupus erythematosus patients. *Clin Exp Immunol*, 187(2):242–250, 2017.

[726] J P Tang, C P Tan, J Li, M M Siddique, K Guo, S W Chan, J E Park, W N Tay, Z Y Huang, W C Li, J Chen, and Q Zeng. VHZ is a novel centrosomal phosphatase associated with cell growth and human primary cancers. *Mol Cancer*, 9:128, 2010.

[727] K Takagaki, T Satoh, N Tanuma, K Masuda, M Takekawa, H Shima, and K Kikuchi. Characterization of a novel low-molecular-mass dual-specificity phosphatase-3 (LDP-3) that enhances activation of JNK and p38. *Biochem J*, 383(Pt. 3):447–455, 2004.

[728] P Ye, J Liu, W Xu, D Liu, X Ding, S Le, H Zhang, S Chen, M Chen, and J Xia. Dual-Specificity Phosphatase 26 Protects Against Nonalcoholic Fatty Liver Disease in Mice Through Transforming Growth Factor Beta-Activated Kinase 1 Suppression. *Hepatology*, 69(5):1946–1964, 2019.

[729] F Huang, X X Sheng, and H J Zhang. DUSP26 regulates podocyte oxidative stress and fibrosis in a mouse model with diabetic nephropathy through the mediation of ROS. *Biochem Biophys Res Commun*, 515(3):410–416, 2019.

[730] W Yu, I Imoto, J Inoue, M Onda, M Emi, and J Inazawa. A novel amplification target, DUSP26, promotes anaplastic thyroid cancer cell growth by inhibiting p38 MAPK activity. *Oncogene*, 26(8):1178–1187, 2007.

[731] K I Patterson, T Brummer, R J Daly, and P M O'Brien. DUSP26 negatively affects the proliferation of epithelial cells, an effect not mediated by dephosphorylation of MAPKs. *Biochim Biophys Acta*, 1803(9):1003–1012, 2010.

[732] Kandice Fero, Sadie A Bergeron, Eric J Horstick, Hiba Codore, Grace H Li, Fumihito Ono, James J Dowling, and Harold A Burgess. Impaired embryonic motility in dusp27 mutants reveals a developmental defect in myofibril structure. *Disease models & mechanisms*, 7(2):289–298, 2014.

[733] K Iio, Y Nagasawa, H Iwatani, R Yamamoto, A Horii, D Okuzaki, Y Furumatsu, H Inohara, H Nojima, E Imai, Y Isaka, and H Rakugi. Microarray analysis of tonsils in immunoglobulin A nephropathy patients. *Biochem Biophys Res Commun*, 393(4):565–570, 2010.

[734] I Friedberg, K Nika, L Tautz, K Saito, F Cerignoli, I Friedberg, A Godzik, and T Mustelin. Identification and characterization of DUSP27, a novel dual-specific protein phosphatase. *FEBS Lett*, 581(13):2527–2533, 2007.

[735] D C Bessette, D Qiu, and C J Pallen. PRL PTPs: mediators and markers of cancer progression. *Cancer Metastasis Rev*, 27(2):231–252, 2008.