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Review article

Cerebral consequences of environmental noise exposure

Omar Hahad [a,b,c,*,1], Maria Teresa Bayo Jimenez [a,1], Marin Kuntic [a], Katie Frenis [d], Sebastian Steven [a,b], Andreas Daiber [a,b], Thomas Münzel [a,b]

[a] Department of Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[b] German Center for Cardiovascular Research (DZHK), partner site Rhine-Main, Mainz, Germany
[c] Leibniz Institute for Resilience Research (LIR), Mainz, Germany
[d] Boston Children's Hospital and Harvard Medical School, Department of Hematology/Oncology, Boston, MA, USA

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ABSTRACT

The importance of noise exposure as a major environmental determinant of public health is being increasingly recognized. While in recent years a large body evidence has emerged linking environmental noise exposure mainly to cardiovascular disease, much less is known concerning the adverse health effects of noise on the brain and associated neuropsychiatric outcomes. Despite being a relatively new area of investigation, indeed, mounting research and conclusive evidence demonstrate that exposure to noise, primarily from traffic sources, may affect the central nervous system and brain, thereby contributing to an increased risk of neuropsychiatric disorders such as stroke, dementia and cognitive decline, neurodevelopmental disorders, depression, and anxiety disorder. On a mechanistic level, a significant number of studies suggest the involvement of reactive oxygen species/oxidative stress and inflammatory pathways, among others, to fundamentally drive the adverse brain health effects of noise exposure. This in-depth review on the cerebral consequences of environmental noise exposure aims to contribute to the associated research needs by evaluating current findings from human and animal studies. From a public health perspective, these findings may also help to reinforce efforts promoting adequate mitigation strategies and preventive measures to lower the societal consequences of unhealthy environments.

1. Brain-heart interactions in the context of noise exposure

Environmental risk factors such as noise or air pollution contribute significantly to the burden of cardiovascular disease (CVD) (Hahad et al., 2019; Hahad et al., 2021). During the last decades, more people have transitioned to living in large urban areas where modifiable risk factors, such as noise, are an integral part of the physical environment and may independently facilitate the development of CVD (Kalsch et al., 2014; Schmidt et al., 2015). The World Health Organization (WHO) estimates that at least 1.6 million healthy life years are lost every year in western European countries alone due to the environmental noise (Kempen et al., 2018). In an earlier publication from the (WHO, 2011), it was estimated that in western Europe, 61,000 disability adjusted life years (DALYs) were lost to noise-associated ischemic heart disease, 45,000 to cognitive impairment in children, 903,000 to sleep disturbance, 22,000 to tinnitus, and 587,000 to annoyance. It was also independently determined that noise could cause these negative health issues such as annoyance (Miedema and Oudshoorn, 2001), sleep disturbance (Muzet, 2007), and CVD (Sorensen et al., 2012; van Kempen and Babisch, 2012). It is also well established that annoyance and sleep disturbance have a profound impact on mental health (Freeman et al., 2020; Anderson and Bradley, 2013; Jensen et al., 2018; Beutel et al., 2020; Dzhambov and Lercher, 2019). Chronic exposure to noise might be the driver of the observed risk to mental and cardio-cerebrovascular health, as prolonged exposure to excessive noise levels is a major risk factor in epidemiological studies (Lan et al., 2020; Eze et al., 2017; Heritier et al., 2017). Additionally, short-term noise exposure has been shown to have an impact on the cardiovascular system and stress responses as well (Schmidt et al., 2013; Walker et al., 2016). Studies have also emphasized the effects of noise in the impairment of the central nervous system (CNS) via increased oxidative stress, imbalance in neurotransmitter levels, deterioration of the molecular functions,

* Corresponding author at: Department of Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany.
E-mail address: omar.hahad@unimedizin-mainz.de (O. Hahad).
[1] Both authors contributed equally and should be regarded as joint first authors.

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impaired cognition, and genetic modifications (Arjunan and Rajan, 2020; Kroller-Schon et al., 2018; Munzel et al., 2017; Munzel et al., 2020). Many questions remain unanswered, however, the most relevant is: to what extent is noise altering the molecular pathways of the brain and how can it disrupt neuronal function at the molecular level, leading to the development of CVD and neuronal disease? Since neuropsychiatric diseases reflect a major contributor the global burden of disease and public health costs, there is an urgent need to identify relevant risk factors and constellations, making environmental noise exposure a potential target of prevention strategies (Riedel, 2016). In the present review, we analyzed comprehensive evidence from human and animal studies on the cerebral consequences of environmental noise exposure affecting neuropsychiatric disease risk. We further report on central pathophysiological mechanism, which may act as a mechanistic link for

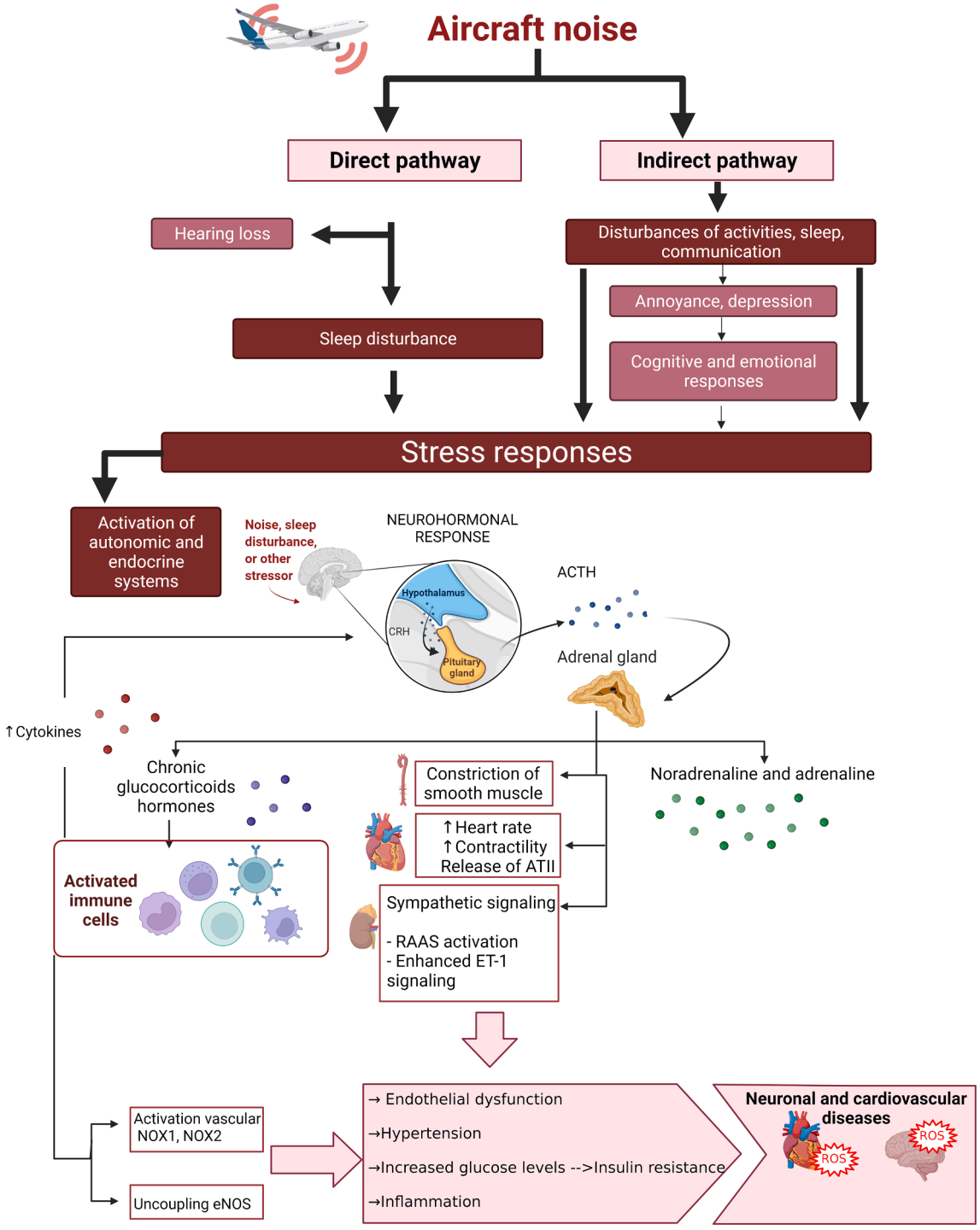

Fig. 1. Noise reaction scheme. Noise causes physiological responses through two separate pathways (direct and indirect) that intersect through the arousal of stress responses. Upon chronic activation of stress response pathways, cardiovascular risk factors can emerge or be exacerbated and lead to cardiovascular disease. After stress, the release of CRH starts in the brain. Upon CRH uptake in the pituitary gland, ACTH is released to stimulate the adrenal gland into release of neurotransmitters and glucocorticoids, which can cause direct effects on blood pressure and activate immune cells. Cytokines released by activated immune cells then feed back to the brain. CRH = corticotrophin-releasing hormone, ACTH = adrenocorticotropic hormone, RAAS = renin-angiotensin-aldosterone, ET-1 = endothelin-1. The scheme is adopted from (Munzel et al., 2021; Elenkov et al., 2000; Masi et al., 2019; Schlaich et al., 2009). Created with BioRender.com.

the observed clinical outcomes.

1.1. The direct and indirect pathways of noise exposure

In 2002, Babisch originated the idea that there could be two pathways through which noise could affect human physiology (Babisch, 2002). This original idea has been refined and a noise reaction scheme was developed involving both a direct and indirect pathway (Fig. 1). The first, a direct pathway, encompasses effects that emerge through high sound pressure levels; loud noise will damage the hair cells, sensory receptors of the auditory system, and disrupt sleep (Le et al., 2017) (Table 1 displays examples of noise levels in terms of exposure to common sources). Approximately 16% of disabling hearing loss in adults worldwide has been caused by the effects of high noise via this direct pathway (Nelson et al., 2005). The direct pathway can also disturb sleep, which is a well-accepted cardiovascular risk factor (Lechat et al., 2021; Coborn et al., 2019). On the other hand, the indirect pathway involves the cognitive and emotional response to a stimulus (i.e. feeling angry or annoyed) (Beutel et al., 2020; Beutel et al., 2016). Noise stimulates the limbic region of the brain to generate an emotional response (Spreng, 2000), leading to neuroendocrine arousal that affects the metabolic state (Henry, 1992). The altered metabolic state is responsible for many risk factors that are known to be implicated in cardio-cerebrovascular and neurodegenerative disease, such as changes in glucose metabolism (Mottillo et al., 2010; Frisardi et al., 2010), lipid dysregulation, and hemodynamic changes (Wong et al., 2017; Zhao et al., 2015; Sabayan et al., 2012; Zhang et al., 2014). The Gutenberg Health Study, which examined annoyance caused by noise of environmental origin, suggested for the first time that noise annoyance is associated with the common arrhythmia atrial fibrillation (Hahad et al., 2018) as a consequence of the activation of the indirect pathway by noise. Both pathways, direct and indirect, lead to physiological effects causing a stress response that activates the autonomic and endocrine systems. This response includes an increase in catecholamine, adrenocorticotropic hormone (ACTH) and cortisol secretion, disruption of the circadian rhythm, decreased melatonin production, decreased insulin sensitivity and leptin levels, increases in ghrelin and appetite, upregulation of inflammatory proteins such as tumor necrosis alpha (TNFα), interleukins (IL) (i.e. IL-1β or IL6), and C-reactive protein (CRP). Noise exposure also promotes an increase in the production of reactive oxygen species (ROS) thereby causing oxidative stress (Hahad et al., 2019; Daiber et al., 2019; Munzel et al., 2021).

Animal studies on the adverse health effects of noise cannot easily distinguish between the direct and the indirect pathways. The emotional agitation of laboratory animals is difficult to quantify in a manner that simulates the human experience of noise exposure (Kunc and Schmidt, 2019; Rabat, 2007), and as such, most experimental models focus on the direct pathways. In a recent study, we conducted audiometry measurements of hearing thresholds in mice exposed to noise at mean sound pressure levels of 72 dB(A) and peak sound levels of 85 dB(A) for 4 days to 4 weeks and found no impairment of the hearing threshold allowing to assign all observed adverse cardiovascular and cerebral health effects in these mice to the indirect effects of noise (Frenis et al., 2021).

Table 1
Examples of noise levels in terms of exposure to common sources.

Examples	Loudness
Threshold of hearing	0 dB
Rustling leaves	10 dB
Ticking of a watch	20 dB
Whisper	30 dB
Quiet living room	40 dB
Rain	50 dB
Conversation	60 dB
Passenger car	70 dB
Telephone ringing	80 dB
Truck	90 dB
Jackhammer	100 dB
Rock band	110 dB
Aircraft on take off	120 dB
Threshold of pain	130 dB

Examples were obtained from (Munzel et al., 2017). dB: Decibel.

1.2. Activation of autonomic and endocrine systems: Neurohormonal response

There is variance in the noise-reaction models in terms of sound pressure level, origin of noise, and experimental setup but all these models converge in causing stress reactions (Fig. 1) (Hahad et al., 2019; Turner et al., 2005; Westman and Walters, 1981). Stress reactions produce risk factors over time including vascular dysfunction that initiates the development of cardiovascular and neuronal diseases. Vascular tone, circulation of blood cells, inflammation, and platelet activity are some of the most essential functions regulated by the endothelium (Gonzalez and Selwyn, 2003; Lerman and Burnett, 1992). However, stress states in cardiovascular disease are characterized by impaired NO signaling and are associated with an increase in circulating stress hormones, cytokines, vasoconstrictors such as angiotensin II, and circulating or infiltrating immune cells (Gliozzi et al., 2019; Balligand et al., 2009), as well as, other free radicals such as superoxide, which ultimately leads to endothelial dysfunction. Noise-induced stress activates the sympathetic nervous system, hypothalamic–pituitaryadrenal axis, and endocrine systems to produce stress responses that, when sustained, result in increases in blood pressure, cardiac output, blood viscosity, glucose and blood coagulation, and changes in the lipid profile, all of which are risk factors for the development of CVD (Daiber et al., 2019; Munzel et al., 2018; Said and El-Gohary, 2016; Munzel et al., 2014). The initiating factor is the perception of noise, which causes either the hypothalamus–pituitaryadrenal (HPA) or by the activation of the sympathetic nervous system (SNS) with subsequent catecholamine formation, for instance adrenaline (A) and noradrenaline (NA). The hypothalamus causes to release corticotrophin-releasing hormone (CRH), which is the main element that drives the body's response to stress, the signal to the pituitary gland to secrete ACTH into the blood, which then stimulates the production of glucocorticoid hormones (cortisol in humans and corticosterone in mice) by the adrenal glands (Fig. 1). The adrenal glands are also responsible for the production of catecholamines (adrenaline and noradrenaline) (Jedema and Grace, 2004), these hormones are then responsible for activating secondary systems, such as the renin-angiotensin-aldosterone system (RAAS), which will increase oxidative stress and inflammation (Campos-Rodriguez et al., 2013). Both RAAS and the neurotransmitters have activating effects on immune cells that precipitate the production of ROS and inflammatory cytokines (Schlaich et al., 2005; Xiao et al., 2015; Daiber et al., 2020). Angiotensin II (and subsequently cortisol) then activates endothelial NADPH oxidase (Nox) via protein kinase C causing oxidative stress, which will directly scavenge nitric oxide ($^{\bullet}$NO) leading to the formation of the highly reactive intermediate, peroxynitrite (ONOO–) and subsequently to tetrahydrobiopterin (BH4 – cofactor of eNOS) oxidation to the trihydrobiopterin (BH3) radical and to increased endothelial nitric oxide synthase (eNOS) S-glutathionylation (Daiber et al., 2020; Li and Shah, 2003; Frenis et al., 2021), both reactions being associated with eNOS uncoupling (Daiber et al., 2014; Daiber et al., 2019). Since $^{\bullet}$NO is one of the most important signalling molecules for vasorelaxation, the uncoupling of the enzyme that produces it, eNOS, results in the direct impairment of the ability of the endothelium to regulate vascular tone.

The production of excess ROS can activate important signalling pathways, including phosphoinositide 3-kinases / Protein kinase B (PI3K/Akt) signalling, the forkhead box (FOXO) transcription factors, transforming growth factor beta 1 (TGF-b1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signalling as well as

the endothelin-1 (ET-1 – potent vasoconstrictor peptide) system (Wilcox et al., 2019), increasing the circulating levels of interleukin 6 (IL-6 – proinflammatory cytokine) and the expression of vascular adhesion molecules (Munzel et al., 2018; Munzel et al., 2017). ROS production by infiltrating immune cells (neutrophils, natural killer cells, and monocytes/macrophages) promotes oxidative damage, especially impairment of endothelial function (Daiber et al., 2017; Daiber and Chlopicki, 2020) as mentioned via eNOS uncoupling.

Endothelial $^{\bullet}$NO production is further reduced by glucocorticoids like cortisol, leading to impaired vasodilation and increased blood pressure (Munzel et al., 2017; Zielinska et al., 2016). Additionally, overproduction of catecholamines (NA, A) and ET-1 increases vasoconstriction and adversely affects vascular function, which is further enhanced by glucocorticoids. It was shown that increased blood glucose levels, insulin resistance (Morakinyo et al., 2019), obesity (Mavanji et al., 2013), hypertension (Steven et al., 2020), and atherosclerosis in noise-exposed mice were worsened by oxidative stress, vascular dysfunction, autonomic imbalance, inflammation, and metabolic abnormalities (Munzel et al., 2021; Munzel et al., 2018). Upon chronic activation of stress response pathways, cardiovascular risk factors can emerge or be exacerbated and lead to cardiovascular or neuronal diseases (explained in detail in Fig. 1) (Munzel et al., 2021; Sorensen and Pershagen, 2019).

Translational studies have further supported the hypothesis that stress responses resulting from noise exposure lead to the induction of inflammatory processes. This adverse effect was also observed to be attenuated by co-treatment with anti-inflammatory and antioxidant substances, supporting a fundamental mechanistical role of the redox changes and inflammatory responses caused by noise exposure (Baldwin and Bell, 2007). Noise exposure is associated with altered DNA methylation (Guo et al., 2017) and telomere length (Meillere et al., 2015), both "biomarkers" well-known to be sensitive to inflammation and oxidative stress and being capable to predict future cardiovascular disease and events in humans (Agha et al., 2019; Haycock et al., 2014). Previous studies with aircraft-noise exposed mice demonstrated that noise causes an increase in stress hormones, systolic and diastolic blood pressure associated with oxidative stress in the vasculature and brain. Likewise, the aortic endothelium was more infiltrated with inflammatory cells suggesting the increased oxidative stress was in part originating from phagocytic phagocytic NADPH oxidase (Nox2) (Kroller-Schon et al., 2018; Munzel et al., 2017). Additionally, in our recent study it was demonstrated a link between a pro-inflammatory phenotype of plasma, activation of circulating leukocytes, and microvascular dysfunction in mice exposed to aircraft noise (Eckrich et al., 2021).

Specifically in the brain, a neuroinflammatory phenotype was demonstrated resulting from acute noise exposure that was characterized by astrocyte and microglia activation, enhanced expression of inflammatory markers, and increases in oxidative stress (Frenis et al., 2021), which were worsened by the presence of pre-existing hypertension and only observed upon noise exposure during the sleep phase of the mice (Kroller-Schon et al., 2018; Steven et al., 2020). These deleterious effects were almost completely prevented in *Nox2* knockout mice, confirming a crucial role for these cells in the detrimental phenotype resulting from acute aircraft noise exposure (Kroller-Schon et al., 2018; Frenis et al., 2021).

2. Mechanistic insight on cerebral consequences of noise exposure and implications for neuropsychiatric outcomes

2.1. Vulnerability of the brain morphology to noise stress

There is increasing evidence that noise impairs higher and limbic structures (Arnsten and Goldman-Rakic, 1998; McEwen et al., 1968) via stress effects causing neuroanatomical changes in experimental animals. For instance, in 2002 it was demonstrated that impulse noise (198 or 202 dB) causes brain damage in female rats, upregulating the expression of proto-oncogenes c-Fos, c-Myc, and β-APP (Saljo et al., 2002). The first 3 weeks post-exposure were followed by focal ischemia in the rat anterior cortex, hippocampus, thalamus, and cerebellum. Additionally, some studies have shown that noise stress could result in impaired cognition and impairment of spatial memory. For instance, Chen et al. showed that noise exposure could cause structural and functional problems in the auditory cortex and hippocampus (Saljo et al., 2002). They used a murine noise exposure model wherein mice were exposed for 1 or 3 weeks to moderate noise (80 dB SPL, 2 h/day). They suggested that although the hippocampus (non-auditory system) and auditory cortex (auditory systems) were both affected by moderate noise exposure, the hippocampus may have been more vulnerable to environmental noise than the auditory cortex. Interestingly, it was shown that light/dark cycles and sex play a role in the impact of chronic traffic noise exposure on mouse brain structure–function, and they demonstrated the adverse effects of the chronic noise stress on behavior and brain structure such as reduced cortical thickness and shrunken brain volume (Jafari et al., 2018). Some studies associated the excess of dopamine levels in the brain with noise stress (Samson et al., 2005; Sundareswaran et al., 2017; Wankhar et al., 2017). These studies demonstrated that the excess of dopamine in the cytosol could be metabolized by monoamine oxidase to produce hydrogen peroxide thereby increasing ROS, which in turn initiates a cascade of ROS-mediated changes in the morphology of cerebellar Purkinje cells (Wankhar et al., 2017). Moreover, chronic stress has been associated with macroscopic changes in certain brain surfaces, leading to physical changes in neural networks (McEwen et al., 1968). According to some studies, the effects of stress in the prefrontal cortex (PFC) and the limbic system were characterized by a decrease in the volume of various structures and an alteration in neuronal plasticity through dendritic atrophy and reduced spinal density, suggesting that depressive disorders, commonly associated with chronic stress in humans, can also be caused by noise (Arnsten and Goldman-Rakic, 1998; Wright et al., 2014). Atrophy of the basal ganglia and a significant decrease of gray matter in certain areas of the prefrontal cortex have been observed in individuals affected by long-term stress (Lucassen et al., 2014; Manukyan, 2022).

2.2. The cognitive and emotional response to the noise stimulus: Preclinical outcomes in animals

Several studies have demonstrated that noise stress impairs cognition, motor coordination, changes of feeding behavior, fear, and anxiety due to the adverse effect of this stress that include metabolic and anatomical changes in neurons, reduced dendritic count, impaired memory, cognition, and locomotor activity (summarized in Fig. 2 and Table 2) (Jafari et al., 2018; Zhang et al., 2021). According to the Centers for Disease Control and Prevention, *"a healthy brain is one that can perform all the mental processes that are collectively known as cognition, including the ability to learn new things, intuition, judgment, language and remembering."* (Fink, 2017). Currently, impaired cognition is associated with a significant socioeconomic burden, compounding the public health imperative (Babulal et al., 2019). Many animal models showed that they could develop impaired cognition with noise exposure (Jafari et al., 2020). Moreover, repeated noise stress exposure has also been reported to alter stress hormones (Akyazi and Eraslan, 2014), produces metabolic and anatomical changes in neurons, reduced dendritic count, impaired memory, and cognition (Manikandan et al., 2006; Cui et al., 2009). For instance, Manikandan et al. demonstrated that long-term noise induced oxidative stress, increased acetylcholinesterase activity, reduced dendritic count in hippocampus, medial prefrontal cortex regions, and elevated plasma corticosterone level, and might have caused the impairment of spatial memory in rats (Manikandan et al., 2006). Additionally, the effects of varying degrees of stress on several motor and sensory tasks that are frequently used to assess functional recovery were studied after lesion-induced impairments in adult rats (Metz et al., 2001). The noise effect caused alterations in neurotransmitter release

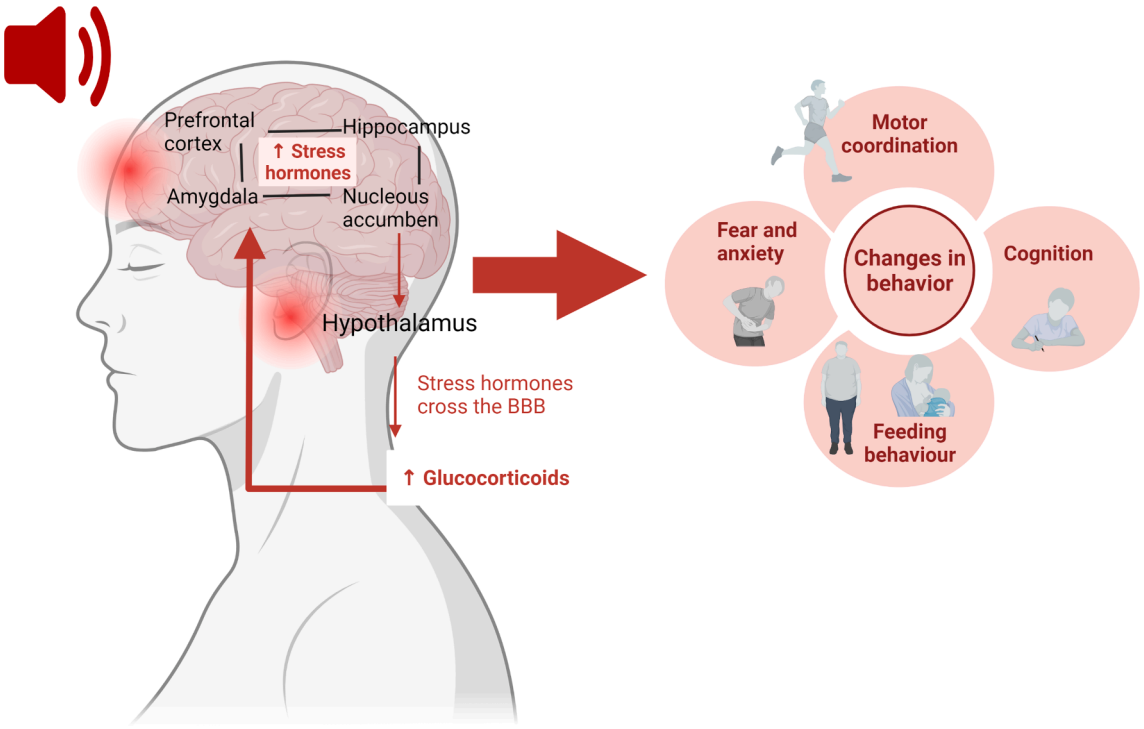

Fig. 2. View of the brain–body interaction in response to noise stress. Stressful stimuli modify the release of different neurotransmitters on the limbic surfaces of the brain (prefrontal cortex, hippocampus, amygdala, and nucleus accumbens), leading to the promotion and modulation of behavioral processes to deal with the stressor. Hypothalamic activation triggers the release of different hormones and peptides (dopamine, noradrenaline, acetylcholine, or glutamate) from the body that cross the blood–brain barrier (BBB) to feed back into the brain. Adapted from Francisco Mora et al. (Mora et al., 2012). Created with BioRender.com.

and induced changes in long-term potential as well as synaptic plasticity, leading to learning and memory impairment. In line with these findings, evidence also suggests that stress adversely affects motor function in humans (Maki and McIlroy, 1996). Furthermore, some translational studies have shown that chronic noise-induced oxidative stress caused the impairment of memory and reduction of the dendritic processes in the hippocampus (Cui et al., 2015; Jafari et al., 2019). Unfortunately, the neural mechanisms underlying the impacts of noise on non-auditory function are still unclear, particularly when it comes to learning and memory. However, recent animal studies have shown that exposure to loud noise, which causes temporary or permanent changes in hearing threshold, disrupts hippocampus histology, reduces neurogenesis in the hippocampus, and impairs hippocampus function associating with learning and memory abilities (Cui et al., 2009; Kraus et al., 2010; Uran et al., 2012; Barzegar et al., 2015; Hayes et al., 2019). On the other hand, it is known that the central nervous system controls motor coordination by the activation of the motor cortex, the cerebellum, and basal ganglia (Arjunan and Rajan, 2020). The activation of the basal ganglia promotes the secretion of dopamine as a major neurotransmitter involved in movement and locomotion. Moreover, noise increases dopamine that facilitates free radical damage in the cerebellum leading to impaired motor coordination (Wankhar et al., 2017). With respect to the permeability of blood–brain barrier (BBB), there is no direct evidence indicating that noise pollution increases its permeability, while substantial peripheral immune infiltration in the brains of noise exposed mice was recently observed (Frenis et al., 2021).

There is also evidence that noise stress impairs eating and lactation behavior (Jafari et al., 2017; Epel et al., 2001). Nevertheless, some studies determined that acute stress activates sympathetic arousal and glucocorticoids release supports behavioral, automatic, and endocrinological changes that promote energy mobilization such as increased cardiac output, blood pressure, gluconeogenesis, triglyceride levels, and redirection of blood flow to fuel the muscles, heart, and brain (Yau and Potenza, 2013). In addition, in both humans (Epel et al., 2001; Oliver et al., 2000; Zellner et al., 2006) and animals (Dallman et al., 2003; la Fleur et al., 2005; Pecoraro et al., 2004), a shift toward choosing more pleasurable and palatable foods is observed irrespective of caloric intake changes associated with stress. Taken together, these findings suggest that stress may promote irregular eating patterns and strengthen networks towards hedonic overeating; these effects may be exacerbated in overweight and obese individuals due to chronic exposures to stress that dysregulate the hypothalamic–pituitaryadrenal (HPA) axis, affecting energy metabolism and feeding behavior (Yau and Potenza, 2013).

Finally, research has demonstrated that noise increases anxiety-like behavior via downstream targets that mediate many of the behavioral, autonomic, and electrophysiological consequences (Lan et al., 2020; Standing and Stace, 1980; Edsell, 1976). Moreover, high levels of glucocorticoids increases the excitation of neurons in the amygdala by decreasing the gamma-aminobutyric acid, or GABA, level and increasing the cytosolic calcium, which triggers cytoarchitectural changes in basolateral amygdala neurons (Mora et al., 2012).

Studies have also reported that chronic exposure to noise deteriorates brain function and may lead to neurodegenerative disease. Exposure to continuous noise of 85–90 dB increased the oxidative stress and decreased the antioxidant level in various regions of the brain. Also, stress activates the HPA and secretion of glucocorticoids (corticosterone in rats and cortisol in humans) in adrenal glands, which crosses the blood–brain barrier and interacts with the neurons and neuroglia cells that alters the neuroanatomical and neurophysiological functions in brain (Mora et al., 2012; McEwen, 2007; McEwen, 2010). Then, the increase of acetylcholine and glutamate levels promotes neurochemical changes and morphological changes including reduced dendrite density and branches. Additionally, noise stress results in the damage to the hippocampus, which is involved in cognition and is involved in the conscious or voluntary memory (Belanoff et al., 2001).

Table 2
Overview of selected animal studies on emotional response to the noise stimulus: preclinical outcomes.

Study	Year	Species	Exposure	Major outcome	Ref.
Morvai et al.	1994	Rat	95 dBA, industrial noise, 6 h, 3w	Noise and alcohol modify the α-adrenergic effect of noradrenaline.	(Morvai et al., 1994)
Singewald et al.	2000	Rat	95 dB, unknown type, 3 minutes	Noise stress resulted in exaggerated glutaminergic responses in the amygdala of SHR versus Wistar-Kyoto rats.	(Singewald et al., 2000)
Saljo et al.	2002	Rat	Impulse noise of 198 or 202 dB	Impulse noise causes brain damage, the expression of c-Fos and c-Myc increased at 2 h after exposure in neurons of the cerebral cortex.	(Saljo et al., 2002)
Lenzi et al.	2003	Rat	100 dBA, white noise, 12 h	Increased catecholamine content in myocardium, DNA damage in cardiomyocytes, mitochondrial membrane swelling in right atrium.	(Lenzi et al., 2003)
Frenzilli et al.	2004	Rat	100 dBA, white noise, 12 h	DNA damage in the adrenal gland, possible redox involvement.	(Frenzilli et al., 2004)
Samson et al.	2005	Rat	Broadband white noise, 100 dB, 4 h/day, in acute: 1 day, subacute: 15d and chronic stress: 30d	The noise induced alterations in free radicals may be assumed to serve as a linkage between the environmental noise and the manifestation of multifactorial diseases.	(Samson et al., 2005)
Manikandan et al.	2006	Rat	100 dBA/4h per d for 30d	Elevated plasma corticosterone level which develops in long-term noise-stress exposed rats, might have caused the impairment of spatial memory.	(Manikandan et al., 2006)
Cui et al.	2009	Rat	100 dB white noise, 4 h/d	Chronic noise exposure might have caused the impairment of spatial learning and memory.	(Cui et al., 2009)
Gannouni et al.	2013	Rat	70 dB, 80 dB, unknown type, 6 h, 90d	Increased corticosterone levels, affected various parameters of the endocrine glands and cardiac function. Markers of oxidative stress (catalase, superoxide dismutase, and lipid peroxidation) were increased.	(Gannouni et al., 2013)
Akyazi et al.	2014	Rat	White noise stress in a period of 15d	White noise exposure caused a stress response characterized by an elevation of cortisol level.	(Akyazi and Eraslan, 2014)
Gannouni et al.	2014	Rat	70 dBA, unknown type, 6 h/d, 3/5 months	Structural alterations within the adrenal gland consistent with chronic stress. Signs of necrosis and inflammation in myocardium.	(Gannouni et al., 2014)
Cui et al.	2015	Rat	100 dB (4 h per d for 28d, from 8:00 to 12:00)	Lifelong environmental noise exposure may have cumulative effects on the onset and development of Alzheimer's disease.	(Cui et al., 2015)
Said et al.	2016	Rat	80–100 dB, chronic and intermittent, unknown type, 8 h, 20d	Increases in plasma levels of corticosterone, adrenaline, noradrenaline, endothelin-1, nitric oxide and malondialdehyde. Decreases in superoxide dismutase.	(Said and El-Gohary, 2016)
Konkle et al.	2017	Rat	87.3 dBA, unknown type, 15 minutes -1 h, 21d	Plasma ACTH, adrenal gland weight, IL-6, IL-1b levels were unchanged following noise exposure. Increases in TNFα and CRP were seen.	(Konkle et al., 2017)
Münzel et al.	2017	Mouse	72cdBA, intermittent aircraft, 4d	Endothelial dysfunction, blood pressure, and redox balance were disturbed following noise exposure	(Munzel et al., 2017)
Wankhar et al.	2017	Rat	Above 100 dB	Increased reactive free radical species can initiate lipid peroxidation mediated changes in the cerebellar Purkinje cells, which is responsible for initiating inhibitory motor response.	(Wankhar et al., 2017)
Jafari et al.	2017	Mouse	3000 Hz tone	Auditory stress caused an increase in anxiety-like behavior, reduced time spent exploring new object/environment, and reduced balance when compared to the physical stress and control groups.	(Jafari et al., 2017)
Jafari et al.	2018	Mouse	Traffic noise on either the light-cycle or dark-cycle for 30d	Traffic noise exposure caused the hypothalamic–pituitaryadrenal axis hyperactivity, anxiety-like behavior, impairments in learning and memory, dysfunction in balance and motor coordination.	(Jafari et al., 2018)
Zhang et al.	2021	Rat	~65 dB	Moderate-level noise with little effect on stress status can substantially impair hippocampus-related learning and memory.	(Zhang et al., 2021)

dB: Decibel, h: hours, w: weeks, d: days, SHR: spontaneously hypertensive rat, ACTH: adrenocorticotropic hormone, IL: interleukin, TNFα: tumor necrosis alpha, CRP: C-reactive protein.

2.3. Neurodegenerative implications of noise exposure

Neurodegenerative diseases like Alzheimer's disease are caused by dysregulation of neuronal signaling and neuron death arising from the accumulation of insoluble plaques in the CNS (Dugger and Dickson, 2017). Alzheimer's disease, and more broadly dementia, is known to be exacerbated by chronic inflammation and oxidative stress (Paul et al., 2019). Since noise was observed to induce both neuroinflammation and oxidative stress (Kroller-Schon et al., 2018), it is possible that excessive exposure to noise could accelerate the progression of neurodegenerative diseases. ROS, a hallmark feature in noise exposure models, is known to activate protein kinases such as PKC and PKA (Cosentino-Gomes et al., 2012), which can then hyperphosphorylate tau, one of the proteins responsible for the accumulation of plaques, and destabilize microtubules leading to progression of Alzheimer's disease (Alonso et al., 2018). Amyloid precursor protein (APP), the protein from which amyloid beta (Aβ) is cleaved, is a transmembrane protein with a cholesterol binding domain, and is sensitive to membrane fluidity and lipid composition (Hicks et al., 2012). Neuronal ROS can easily oxidize lipids and disturb the APP, leading to further progression of Alzheimer's disease (Kao et al., 2020). Because of the overlap in key mechanisms, it is tempting to make indirect associations that oxidative stress is caused by noise which could then potentially expedite the onset and progression of Alzheimer's disease.

Though only a few studies provide direct links between noise exposure and neurodegenerative diseases, these links have been explored by studies conducted in rodent models (Jafari et al., 2020). In one study, exposure of Wistar rats to 4 weeks of white noise showed that noise caused accumulation of $A\beta_{40}$ and $A\beta_{42}$ in the hippocampus, which persisted for up to two weeks after the noise exposure has ended. APP and its cleavage enzymes, β- and γ-secretase were also found to be elevated, together with TNF-α, glial fibrillary acidic protein and ionized calcium-binding adapter molecule 1, all pointing to a pro-Alzheimer's phenotype (Cui et al., 2015). Another study conducted in rats found that 30 days of noise exposure caused phosphorylation of the tau protein in the hippocampus (Gai et al., 2017), which was accompanied by an increase in expression of corticotropin-releasing factor (CRF), indicating that tau phosphorylation could be the result of a stress response. Interestingly, the phosphorylated tau protein and CRF were colocalized in the hippocampus. The upregulation of the CRF receptor 1, together with the CRF, points to the proinflammatory state of the hippocampus. A similar increase in phosphorylation of the tau protein in the hippocampus was observed in another study where rats were exposed to impulse noise of high sound pressure (Cui et al., 2012). In both studies (Gai et al., 2017)

and (Cui et al., 2012), tau was hyperphosphorylated, which blocks the binding of microtubules, rather than facilitating this binding (Hashiguchi and Hashiguchi, 2013). A study in a mouse model of Alzheimer's disease demonstrated that exposure to gestational noise stress induces earlier and more severe symptoms in the offspring (Jafari et al., 2019). The study showed that the hypothalamic–pituitaryadrenal axis was more activated in the noise-exposed offspring group and that accumulation of the Aβ had an earlier onset with heightened progression. Other groups have also observed impact of the gestation period noise exposure on the development of Alzheimer's-like pathology and dementia (Jafari et al., 2018; Jafari et al., 2017; Jafari et al., 2019). In these studies, it was noticed that Aβ is deposited in the olfactory region of the brain, which was also supported by other animal studies where stress was responsible for a lack of smell memory (Belnoue et al., 2016). From the mechanistic point of view, there remain many unanswered questions pertaining to the connection between noise and neurodegenerative disease, but it is clear that the stress response, followed by neuroinflammation and oxidative stress, is playing a decisive role.

3. Recent epidemiological/observational evidence on the association of noise exposure with neuropsychiatric outcomes

3.1. Stroke

In a cohort of 20,012 subjects from Stockholm County in Sweden, Pyko et al. examined the influence of exposure to road traffic, railway, and aircraft noise on incident risk of ischemic heart disease and stroke (Pyko et al., 2019) (Fig. 3 and Table 3 summarize all recent epidemiological/observational evidence). A pronounced suggestive risk of stroke was observed in subjects exposed to all three traffic noise sources (≥45 dB L_{den}; hazard ratio (HR) 1.42, 95% confidence interval (CI) 0.87–2.32). In a large case-control study from Germany (N = 1,026,670), an increased risk of stroke was found in response to aircraft noise (odds ratio (OR) 1.07, 95% CI 1.02–1.13 for subjects exposed to < 40 dB of 24-hour continuous aircraft noise ($L_{pAeq,24h}$) and ≥ 6 events of maximum nightly sound pressure levels ≥ 50 dB) (Seidler et al., 2018). In addition, road traffic and railway noise exposure were found to be positively related with risk of stroke (OR 1.017, 95% CI 1.003–1.032 and OR 1.018, 95% CI 1.001–1.033, respectively). Herein, the authors discriminated between ischemic and hemorrhagic stroke demonstrating higher OR for the latter for aircraft and railway noise. The relationship between noise from wind turbines and risk of incident myocardial infarction and stroke was the subject of a nationwide Danish cohort study from Poulsen et al., which is of special importance, since wind turbine noise has been reported as more annoying than traffic noise at similar levels (Poulsen et al., 2019). The authors have revealed significant evidence for a relationship between mean 1- and 5-year nighttime outdoor wind turbine noise exposure groups and risk of stroke (e.g. incidence rate ratio (IRR) 1.10, 95% CI 1.03–1.17 for 30–36 vs. < 24 dB(A)). In 23,912 Danish nurses, weaker evidence for a relationship between wind turbine noise and stroke incidence was found (Brauner et al., 2019). In a further nationwide Danish study, a 4% (IRR 1.04, 95% CI 1.03–1.05 per 10 dB increase at the most exposed façade) higher risk of incident stroke was found in response to road traffic noise, while no association was found for railway noise, possibly due to the circumstance that railway noise is generally perceived as less annoying than road traffic noise (Sorensen et al., 2021). Interestingly, not only stroke risk but also severity has been associated with residential noise exposure as revealed in 2,761 patients hospitalized with acute ischemic stroke in Barcelona (Vivanco-Hidalgo et al., 2019). While higher residential surrounding greenspace was associated with decreased risk of severe stroke, increased residential noise exposure (L_{den}) was associated with a pronounced risk of severe stroke (OR 1.30, 95% CI 1.02–1.65). The influence of exposure to road traffic noise and stroke incidence was examined in 25,660 Danish nurses indicating no substantial effect after adjustment for $PM_{2.5}$ or NO_2 (Cole-Hunter et al., 2021). In contrast, stronger evidence was found for all-cause (HR 1.06, 95% CI 1.01–1.11 and HR 1.09, 95% CI 1.03–1.15 per 10 dB increase of 5-year and 23-year

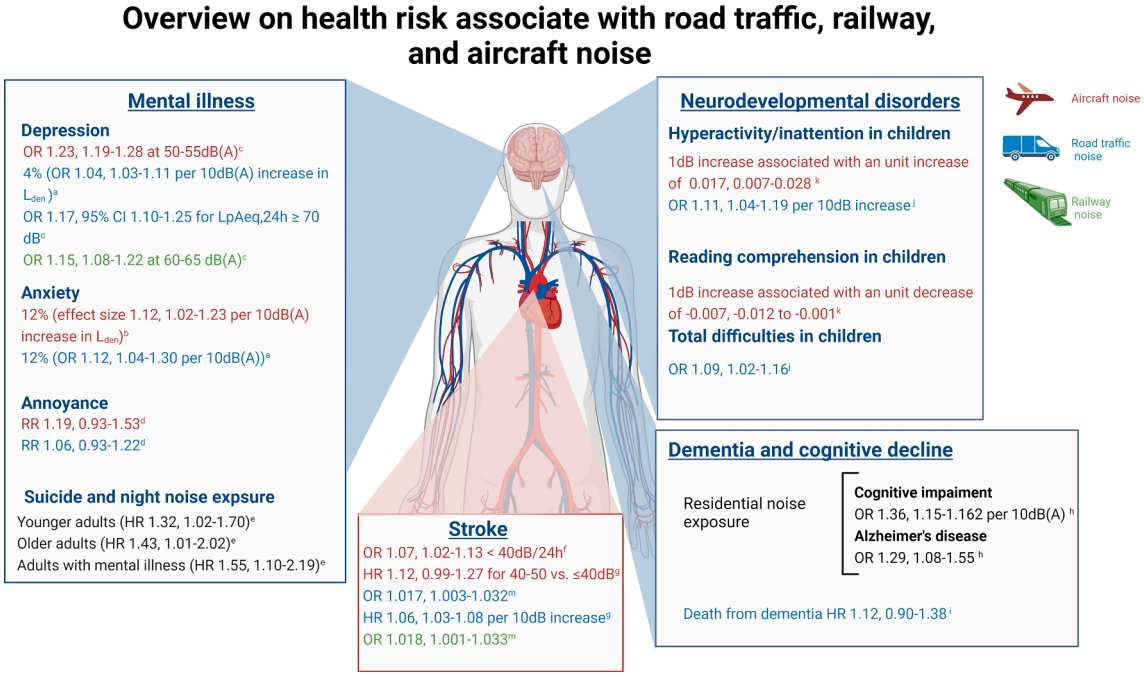

Fig. 3. Hazard ratio/odds ratio/ relative risk (HR/OR/RR) or adverse effects (percentages) for aircraft, road traffic, or railway noise associated health risks or complications based on selected representative studies. All alphabetical cross references in this figure ($^{a, b, c, \ldots}$) are linked to literature references as follows: Mental illness reports: a (Dzhambov and Lercher, 2019), b (Hegewald et al., 2020), c (Seidler et al., 2017), d (Eze et al., 2020), and e (Min and Min, 2018). Stroke source reports: f (Seidler et al., 2018), g (Roswall et al., 2021); and m (Poulsen et al., 2019). Neurodevelopmental disorders reports: j (Schubert et al., 2019), k (Clark et al., 2021). Dementia and cognitive decline reports: h (Weuve et al., 2021), i(Cole-Hunter et al., 2022). Note of caution: The presented values are based on selected representative studies with different quality levels of evidence highlighting the need for more research. Created with BioRender.com.

Table 3
Tabular overview of selected human studies on the association between aircraft, road traffic, or railway noise and neuropsychiatric outcomes.

Study	Population/cohort/design	Risk associated with	Major outcome	Ref.
Stroke				
(Seidler et al., 2018)	All people aged ≥ 40 years living around the Frankfurt airport (N = 1,026,670) between 2005 and 2010	All three traffic noise sources (road traffic, railway, and aircraft)	Stroke risk was statistically significantly increased by 7% (were exposed to < 40 dB of 24-h continuous aircraft noise). For road and railway traffic noise, there was a positive linear exposure-risk relation: Per 10 dB the stroke risk increased by 1.7%, and for road traffic noise by 1.8%	(Seidler et al., 2018)
(Roswall et al., 2021)	Scandinavian cohorts (seven Swedish, two Danish), totaling 135,951 participants	All three traffic noise sources	Road traffic noise (L_{den}) was associated with risk of stroke, with a HR of 1.06 per 10 dB higher 5-y mean time-weighted exposure. Stroke was associated with moderate levels of 5-y aircraft noise exposure (40–50 vs. ≤ 40 dB) with a HR of 1.12. Railway noise was not associated with stroke.	(Roswall et al., 2021)
Mental illness				
Dzhambov and Lercher, 2019	For depression (N = 1,201,168) and for anxiety (N = 372,079)	Road traffic	4% higher odds of depression and 12% of anxiety associated with a 10 dB(A) increase in L_{den}.	(Dzhambov and Lercher, 2019)
(Hegewald et al., 2020)	31 studies (26 on depression and/or anxiety disorders, 5 on dementia)	All three traffic noise sources	Depression risk increased significantly by 12% per 10 dB L_{den} by aircraft noise. The *meta*-analyses of road and railway traffic noise indicated 2–3% (not statistically significant) increases.	(Hegewald et al., 2020)
(Seidler et al., 2017)	Individuals aged ≥ 40 years that were living in the region of Frankfurt international airport between 2006 and 2010	All three traffic noise sources	For aircraft noise, the risk estimates reached a maximum OR of 1.23 at 50–55 dB. For road traffic noise, a linear exposure-risk relationship was found with an OR of 1.17. For railway noise, risk estimates peaked at 60–65 dB with a OR of 1.15.	(Seidler et al., 2017)
Eze et al., 2020	4,581 SAPALDIA participants without depression in the year 2001/2002	All three traffic noise sources	A linear exposure-risk relationship was observed for road traffic noise OR 1.17 for $L_{pAeq,24h}$ ≥ 70 dB. For aircraft noise, the highest risk estimate was observed for exposures at 50–55 dB with a OR of 1.23 and for railway noise at 60–65 dB with a OR 1.15. The combination of all three exposures (above 50 dB) yielded the highest risk estimate with an OR of 1.42.	(Eze et al., 2020)
Min and Min, 2018	A total of 155,492 adults constituted the study sample: younger adults (20–54 years, N = 124,994), or older adults (≥55 years, N = 30,498), and adults with mood and anxiety disorders (N = 34,615)	Nighttime noise	315 (0.2%) died of suicide. With interquartile range increases in nighttime noise, the HR for suicide death was significantly increased: 1.32 for younger adults, 1.43 for older adults, and 1.55 for adults with mental illness.	(Min and Min, 2018)
Dementia and cognitive decline				
(Weuve et al., 2021)	Participants of the Chicago Health and Aging Project (≥65 years) underwent triennial cognitive assessments (N = 5,227 participants)	Residential noise exposure	An increment of 10 dB in noise corresponded to 36% and 29% higher odds of prevalent mild cognitive impairment (OR 1.36) and Alzheimer's disease (OR 1.29).	(Weuve et al., 2021)
(Cole-Hunter et al., 2022)	22,858 females from the Danish Nurse Cohort	Road traffic	Increased risk of death from dementia in response to road traffic noise (HR 1.12).	(Cole-Hunter et al., 2022)
Neurodevelopmental disorders				
(Schubert et al., 2019)	14 articles from 10 studies examining the effect of transportation noise exposure on the mental health of children	Road traffic	Hyperactivity/inattention and total difficulties was significantly increased by 11% (OR 1.11).	(Schubert et al., 2019)
(Clark et al., 2021)	Data from three methodologically similar studies carried out in 106 schools near London Heathrow, Amsterdam Schiphol, and Madrid Barajas airports	Aircraft	1 dB increase in aircraft noise exposure at school was associated with a − 0.007 decreased reading score. Also, there was an association with a 0.017 increase in hyperactivity score.	(Clark et al., 2021)

dB: Decibel, h: hours, L_{den}: day-evening-night noise levels, y: year, HR: hazard ratio, OR: odds ratio, $L_{pAeq:}$ equivalent continuous sound level.

mean L_{den}, respectively) and stroke mortality (HR 1.10, 95% CI 0.91–1.31 for 5-year mean L_{den}) within the same cohort (Cole-Hunter et al., 2022). The substantial role of traffic noise exposure in the risk of increased stroke mortality was also confirmed in two nationwide studies from Switzerland (Heritier et al., 2017; Vienneau et al., 2022), whereas a study from Brazil found no substantial association between aircraft noise exposure and stroke mortality (Roca-Barcelo et al., 2021). The effect of occupational noise exposure on stroke risk was examined in a systematic review and *meta*-analysis from Teixeira et al. (Teixeira et al., 2021). The body of evidence for acquiring stroke (relative risk (RR) 1.11, 95% CI 0.82–1.65, two studies, 170,000 participants) and dying from stroke (RR 1.02, 95% CI 0.93–1.12, three studies, 195,539 participants) was judged as "inadequate evidence of harmfulness". Likewise, in 5,753 Swedish men, occupational noise exposure was not accompanied by an increased risk of stroke (Eriksson et al., 2018). Conversely, in 194,501 Swedish workers, moderate and high occupational noise exposure was associated with increased stroke mortality (RR 1.15 and 1.19, respectively) with no evidence for an interaction effect associated with living and working in cold conditions (Pettersson et al., 2020). Further *meta*-analytic evidence comes from a study from Weihofen et al. evaluating the relationship between aircraft noise exposure and the incidence of stroke (Weihofen et al., 2019). The *meta*-analysis of seven studies revealed a RR of 1.013 (95% CI 0.998–1.028 per 10 dB increase in L_{den}). Analyzing data from nine Scandinavian cohorts (seven Swedish, two Danish resulting in N = 135,951 participants) revealed road traffic (HR 1.06, 95% CI 1.03–1.08 per 10 dB increase) and aircraft noise exposure (HR 1.12, 95% CI 0.99–1.27 for 40–50 vs. ≤ 40 dB) to be associated with incident stroke risk, whereas no association was found for railway noise (Roswall et al., 2021). In the Northern Manhattan Study, subjects living < 100 m from a roadway, as a surrogate for higher noise exposure, had a 42% (HR 1.42, 95% CI 1.01–2.02) higher rate of ischemic stroke versus those

living > 400 m away (Kulick et al., 2018). Interestingly, the findings of Osborne et al. indicate that traffic noise exposure associates with cardiometabolic diseases via a neurobiological mechanism that is centered on stress-associated limbic (amygdalar) activity, which is also highly suggested in the development of noise-induced neuropsychiatric outcomes (Osborne et al., 2020; Osborne et al., 2021; Munzel et al., 2020; Hahad et al., 2021).

3.2. Mental illness

A *meta*-analysis from Dzhambov and Lercher found road traffic noise exposure to be associated with 4% (OR 1.04, 95% CI 1.03–1.11 per 10 dB(A) increase in L_{den}) higher odds of depression and 12% (OR 1.12, 95% CI 1.04–1.30) of anxiety. However, it is important to note that most of the included studies were of cross-sectional nature and overall lower quality (Dzhambov and Lercher, 2019). Accordingly, Hegewald et al. revealed substantial *meta*-analytic evidence on the association between traffic noise exposure and depression and anxiety including 26 studies (Hegewald et al., 2020). Herein, aircraft noise exposure was found to increase depression risk by 12% (effect size 1.12, 95% CI 1.02–1.23 per 10 dB increase in L_{den}), whereas the effect sizes obtained from road traffic and railway noise studies were of smaller magnitude (2–3% not statistically significant increases in depression risk). A *meta*-analysis of nine studies reported 9% higher odds of anxiety in response to traffic noise exposure (Lan et al., 2020). In the Netherlands Study of Depression and Anxiety (N = 2,980), high levels of traffic noise levels were associated with the presence of depressive and anxiety disorders (Generaal et al., 2019). A large case-control study from Germany examined the risk of depression in response to aircraft, road traffic, and railway noise exposure (Seidler et al., 2017). A linear exposure-risk relationship was observed for road traffic noise (OR 1.17, 95% CI 1.10–1.25 for $L_{pAeq,24h} \geq 70$ dB). For aircraft noise, the highest risk estimate was observed for exposures at 50–55 dB (OR of 1.23, 95% CI 1.19–1.28) and for railway noise at 60–65 dB (OR 1.15, 95% CI 1.08–1.22). The combination of all three exposures (above 50 dB) yielded the highest risk estimate (OR 1.42, 95% CI 1.33–1.52). Baseline data from the UK Biobank study suggests symptoms of anxiety, tension, or depression and bipolar disorder to be positively associated with road traffic noise exposure, whereas a negative relationship was found in case of major depression (Hao et al., 2021). In the Swiss cohort study on air pollution and lung and heart diseases in adults (SAPALDIA), risk of incident depression in response to road traffic, railway, and aircraft noise exposure (L_{den}) as well as noise annoyance was investigated (Eze et al., 2020). Suggestive evidence was found for road traffic (RR 1.06, 95% CI 0.93–1.22) and aircraft noise exposure (RR 1.19, 95% CI 0.93–1.53) as well as a robust effect of noise annoyance (RR 1.05, 95% CI 1.02–1.08). In a cohort of 2,398 men from the UK, road traffic noise exposure (OR 1.82, 95% CI 1.07–3.07 for 56–60 dB(A)), noise annoyance (OR 2.47, 95% CI 1.00–6.13), and noise sensitivity (OR 1.65, 95% CI 1.09–2.50) were associated with incident psychological ill-health (Stansfeld et al., 2021). In a cohort of 140,456 women from Canada, the relationship between residential noise exposure during pregnancy and later depression hospitalization was evaluated (He et al., 2019). The results revealed strongest association for increased nighttime noise exposure (HR 1.68, 95% CI 1.05–2.67 for 70 vs. 50 dB(A) L_{night}). Importantly, short-term exposure to traffic noise has also been demonstrated to influence emergency hospital admissions due to anxiety, dementia, and suicides in the city of Madrid (Diaz et al., 2020). Risk of death by suicide in dependence of noise exposure was also subject of a Korean study (N = 155,492) indicating that higher nighttime noise exposure was associated with elevated risks of suicide death in younger adults (HR 1.32, 95% CI 1.02–1.70), older adults (HR 1.43, 95% CI 1.01–2.02), and adults with mental illness (HR 1.55, 95% CI 1.10–2.19) (Min and Min, 2018). In a further Korean study (N = 45,241), exposure to occupational noise and vibration increased the odds of anxiety in both males (OR 2.25, 95% CI 1.77–2.87) and females (OR 2.17, 95% CI 1.79–2.61) (Park et al., 2022). Interestingly, the adverse consequences of noise exposure may differ between subjects with mental illnesses as data from 2,745 subjects from the German Heinz Nixdorf recall study suggest a pronounced decrease in cognitive function in response to traffic noise when comparing depressed vs. non-depressed subjects (Tzivian et al., 2020). A Finnish study (N = 7,321) also demonstrated traffic noise exposure, noise annoyance, and sensitivity to correlate with the use of psychotropic medication including sleep medication, anxiolytic, and antidepressant medications (Okokon et al., 2018). In the Gutenberg Health Study from Germany (N = 11,905), Beutel et al. showed that noise annoyance due to different sources is a substantial predictor of incident depressive, anxiety, and sleep disturbance (Beutel et al., 2020). In a US sample of urban adolescents (N = 4,508), evidence for a relationship between living in a high-noise area and later bedtimes was found, whereas this relationship was weaker for mental health disorders (Rudolph et al., 2019). Data from the Danish Nurse Cohort study also suggested an association between road traffic noise exposure and mortality from psychiatric disorders (HR 1.11, 0.78–1.59) (Cole-Hunter et al., 2022).

3.3. Dementia and cognitive decline

In 5,227 participants from the Chicago Health and Aging Project (≥65 years), residential noise exposure resulted in 36% and 29% higher odds of prevalent mild cognitive impairment (OR 1.36, 95% CI 1.15–1.62 per 10 dB(A) increase) and Alzheimer's disease (OR 1.29, 95% CI 1.08–1.55) (Weuve et al., 2021). Additionally, lower global cognitive performance (perceptual speed), but not consistent cognitive decline, was related to noise exposure. Likewise, data from the German Heinz Nixdorf Recall study indicates that traffic-related noise exposure is associated with a lower global cognitive score and a mild cognitive impairment (Tzivian et al., 2016). Interestingly, stronger associations were observed in former and current smokers as indicated by a significant interaction, suggesting that lifestyle risk factors may potentiate the negative cognitive effects of noise exposure (Tzivian et al., 2016). Importantly, the authors also demonstrated that air pollution and road traffic noise exposure may act synergistically to negatively influence cognitive function (Tzivian et al., 2017). In 288 elderly women from the German longitudinal study on the influence of air pollution on lung function, inflammation and aging (SALIA), road traffic noise exposure was shown to be associated with impaired total cognition and the constructional praxis domain (neuropsychological assessment battery), which remained stable after further adjustment for air pollution exposure (Fuks et al., 2019). In the Irish Longitudinal Study on Ageing, road traffic noise exposure was found to negatively impact executive function (Mac Domhnaill et al., 2021). Also, in study of 1,612 elderly Mexican-American participants from Sacramento, the authors found suggestive evidence of traffic noise exposure to increase the risk of dementia and cognitive impairment (Yu et al., 2020). Interestingly, a subsequent study demonstrated metabolic dysfunction (hyperglycemia or low HDL-cholesterol) to negatively modify the influence of traffic-related air pollution and noise exposure on these outcomes (Yu et al., 2020). Linares et al. revealed the short-term association of traffic noise and risk of dementia-related emergency hospital admissions in Spain (Linares et al., 2017). In contrast, Andersson et al. found no effect of road traffic noise exposure, either independently or in combination with traffic-related air pollution, on dementia risk in 1,721 subjects (Andersson et al., 2018). In a larger study of 130,978 subjects from London, the relationship between night-time traffic noise exposure and the incidence of dementia became statistically insignificant in multipollutant models including various air pollutants (Carey et al., 2018). Likewise, while road proximity and air pollution were positively associated with risk of dementia and Parkinson's disease in a large Canadian study (N ~ 678,000), noise exposure displayed no relationship with these outcomes (Yuchi et al., 2020). Most recently, a nationwide study from Denmark including almost 2 million adults aged ≥ 60 years examined

the influence of road traffic and railway noise exposure and incident risk of dementia (Cantuaria et al., 2021). The results indicated that both road traffic noise and railway noise exposure were associated with increased risk of Alzheimer's disease, while road traffic, but not railway, noise exposure was also associated with an increased risk of vascular dementia. Data from the Danish Nurse Cohort study may also indicate an increased risk of death from dementia in response to road traffic noise (HR 1.12, 0.90–1.38) (Cole-Hunter et al., 2022).

3.4. Neurodevelopmental disorders

The *meta*-analysis of three studies revealed increased odds of hyperactivity/inattention (OR 1.11, 95% CI 1.04–1.19 per 10 dB increase) and total difficulties (OR 1.09, 95% CI 1.02–1.16) in response to road traffic noise exposure in children (Schubert et al., 2019). In contrast, prenatal and childhood road traffic noise exposure were not associated with emotional, aggressive, or attention-deficit/hyperactivity disorder-related symptoms in children obtained from two European birth cohorts (Essers et al., 2022). In agreement, in 1,710 children from the TRAILS study in The Netherlands, road traffic noise exposure was not associated with symptoms of attention-deficit/hyperactivity disorder (Zijlema et al., 2021). However, the *meta*-analysis of studies investigating the influence of aircraft noise at school on children's reading comprehension and psychological demonstrated that a 1 dB increase in aircraft noise exposure at school led to a − 0.007 (95% CI − 0.012 to − 0.001) decreased reading score and 4% higher odds of scoring well below or below average on the reading test (Clark et al., 2021). Furthermore, a 1 dB increase in aircraft noise exposure at school was associated with a 0.017 (95% CI 0.007–0.028) increase in hyperactivity score. Lastly, in a cohort of 886 adolescents in Switzerland, problem behavior in response to road traffic noise exposure was investigated indicating a positive relationship in cross-sectional analysis, whereas no association was found in prospective analysis (Tangermann et al., 2022).

4. Conclusions and future considerations

Recently the hypothesis was put forward that genetic (familial) predisposition for non-communicable diseases may be outcompeted by environmental risk factors and leading environmental health experts are calling for an environment-wide association study (EWAS) (Sainani, 2016). This change of dogma is also reflected by statements such as "Genetics loads the gun but the environment pulls the trigger" (Bray et al., 2004; Olden and Wilson, 2000), also put forward by F. Collins, the director of the NIH. This shift was triggered by the exposome concept based on the study of life-long environmental exposure and its association with biochemical changes in the organism and adverse health effects (Wild, 2005; Vrijheid, 2014). Whereas it is well accepted that environmental chemical pollution contributes dramatically to the global burden of disease and mortality (up to 9 to 12.6 million annual deaths, reflecting 16–20% of total mortality worldwide), as reported by the Lancet Commission on Pollution and Health (Landrigan et al., 2018), the (WHO, 2016), and the Global Burden of Disease Study (Cohen et al., 2017; Collaborators GBDRF, 2017), the impact of mental stress and physical environmental factors causing mental stress, especially traffic noise, are far less well studied. Most societal prevention action plans and global estimations of environmental adverse health effects neglect the non-chemical environmental health risk factors mental stress, noise, nocturnal artificial light exposure, and climate changes (Daiber and Munzel, 2020). In order to address this research gap and to respond to the associated research need, we have summarized the current knowledge on the adverse effects of noise on the brain and the relation to neuropsychiatric outcomes. The cardiovascular health impact by noise was summarized in full detail by a systematic review of the WHO Environmental Noise Guidelines for the European Region (Kempen et al., 2018). Also the impact of noise on mental health was summarized by a systematic review of the WHO Environmental Noise Guidelines for the European Region (Clark and Paunovic, 2018), supported by specific assessment of adverse effects of noise on annoyance (Guski et al., 2017), cognition (Clark and Paunovic, 2018), and sleep (Basner and McGuire, 2018). With our present review we aimed to provide a mechanistic link for the observed clinical outcomes.

In order to further increase the quality of existing clinical/epidemiological data, future large-scale exposome studies addressing the health side effects of noise exposure on the brain and mental health are urgently warranted. Considering the accumulation of environmental risk factors in urbanized areas (e.g. noise, light pollution, air pollution, and psychosocial stress), the health problems, disease burden, and number of deaths associated with the totality of these environmental stressors may even be higher than all estimations in the past (Daiber and Munzel, 2020; Munzel and Daiber, 2018). Mitigation strategies and preventive measures at this level may result in substantial lowering of societal consequences by unhealthy environments, e.g. lowering of the global burden of disease and public health costs. Future animal and human studies on adverse health effects of noise should focus on markers of oxidative stress (e.g. 3-nitrotyrosine and markers of lipid peroxidation) and inflammation (e.g. IL-6, sVCAM-1) in order to obtain a quantitative image of the inflicted damage (Munzel et al., 2021; Bagheri Hosseinabadi et al., 2019). Also, mechanistic studies would be helpful addressing changes of circadian rhythm (e.g. Per1, Cry1, BMAL1 and CLOCK) as well as regulators of circadian rhythm (e.g. FOXO-3, NRF2) (Kroller-Schon et al., 2018; Bayo Jimenez et al., 2021). In addition, measurement of stress hormones such as catecholamines, cortisol, or down-stream activated endocrinal systems such as the renin-angiotensin-aldosterone axis could provide important insights into the degree of noise-mediated stress responses and activation of detrimental hormonal pathways (Munzel et al., 2021; Daiber et al., 2020). Human studies associated noise annoyance, anxiety disorders, and depression with the clinical manifestation of atrial fibrillation (Beutel et al., 2016; Hahad et al., 2018; Hahad et al., 2021), underlining the strong stress-dependent component in the adverse health effects of noise. Animal research should clearly define the applied noise on a qualitative and quantitative basis, which includes besides the duration of exposure also mean sound pressure levels, frequencies, pattern (continuous versus interrupted) as we have reported previously that continuous white noise at similar exposure duration and mean sound pressure levels was not harmful in contrast to aircraft noise with irregular breaks (Munzel et al., 2017). Human studies should clearly state the mean sound pressure level (e.g. L_{eq} or L_{den}) and at least try to report separate health effects by noise at day versus at night as nighttime noise is more detrimental for cardiovascular health and probably also other systems' dysregulation (Munzel et al., 2020). Preferably, human studies should measure the real noise exposure in the sleeping room during night and not the mean sound pressure values at the address level as many factors may influence the indoor noise exposure such as the presence of sound insulation windows or sleeping with open windows. This research complications may also require to conduct more mechanistic field studies with clearly defined nocturnal noise exposures and assessment of an advanced set of functional as well as biochemical parameters as done by us in the past (Schmidt et al., 2013; Herzog et al., 2019; Schmidt et al., 2021). Human studies should not only concentrate on noise exposure-clinical outcome associations (e.g. calculate the increased risk of ischemic heart disease, hypertension, or diabetes with increasing mean sound pressure levels) - whereas these association studies are highly important, e.g. for defining safe legal limits for noise exposure, mechanistic insights from large population studies with clearly defined sophisticated endpoints such as changes in epigenetic markers or arterial stiffness are also highly warranted (Foraster et al., 2017; Eze et al., 2020). As we also know that environmental noise co-localizes with other environmental risk factors such as air pollution, light pollution or heat islands in highly urbanized areas, especially big cities (Munzel et al., 2021; Munzel et al., 2021), future human studies should carefully adjust for these other environmental risk factors besides the common confounders such as sex, age,

social status, work strain, and others. Research gaps may comprise the knowledge on the reversibility of noise-induced damage as not much is known on the persistence of the adverse health effects of noise. Also, resilience should be addressed in more detail to understand why some individuals are more resistant to noise-mediated stress responses. This could also help to identify new targets for pharmacological or life style interventions against the adverse health effects of noise.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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