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# Noise and Alzheimer's disease – the basic pathological concepts

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## ABSTRACT

Alzheimer's disease (AD) is the most common form of degenerative dementia and the seventh leading cause of death. Numerous influencing factors for AD have been investigated: aging, female gender, genetics, unhealthy diet, hearing loss, unhealthy lifestyle, physical inactivity, insufficient sleep, head injury, depression, hypertension, and environmental factors (air pollution, aluminum, silicon, selenium, pesticides, lack of sunbathing, electric and magnetic fields). Recent animal and human studies point to a possible relationship between noise exposure and AD. The aim of this narrative review is to present basic pathological concepts of this relationship. Possible mediating factors that explain the influence of noise on AD are sleep disturbance, excitotoxicity, oxidative stress injury in the auditory cortex and hippocampus, and systemic inflammation. Studies on animals point to cognitive dysfunctions related to noise exposure: anxiety-like behavior, impaired learning and memory, increased glutamate levels in the hippocampus and reduced expression of N-methyl-D-aspartic acid receptor 2B. Neuropathological changes in animals exposed to noise include necrosis and apoptosis of hippocampal cells, accumulation of amyloid β, tau hyperphosphorylation and peroxidative damage in the hypothalamus and the auditory cortex, and the elevated expression of proinflammatory cytokines and microglial activation in the auditory cortex and hippocampus. Human brain scan studies have pointed to the positive relationship between traffic noise exposure and white matter volume in the body of the corpus callosum at the level of the auditory cortex. In conclusion, there is a biological plausibility of noise-AD relationship, and noise countermeasures may be regarded as the prevention of AD.

Keywords: Noise, Alzheimer's disease, pathology

## INTRODUCTION

Alzheimer's disease (AD), named after the German psychiatrist and pathologist Alois Alzheimer[1], is the most common form of degenerative dementia, contributing to 60-80% of all cases of dementia[2]. Currently, about 50 million people in the world suffer from Alzheimer's disease, with nearly 10 million new cases every year. It is the seventh leading cause of death, and the major cause of disability and dependency among the elderly, with a financial burden of more than one trillion US dollars annually[3,4]. By the year 2050, the global prevalence of AD is expected to be around 115 million[5].

AD is pathologically characterized by shrinkage of the cerebral cortex and hippocampus, enlarged ventricles, neurofibrillary tangles (NFT) of the hyperphosphorylated tau protein[6], amyloid plaques due to the accumulation of beta-amyloid protein (Aβ)[7] and loss of neuronal synapses in the brain[8].

The characteristic symptoms of AD are loss of memory and concentration, mood swings and depression, disorientation of place and time, self-neglect, difficulties in speaking, reading, and writing, and in the late stage, disability to recognize the closest family and difficulties in swallowing and urination[9].

The cause of AD is still unknown. There are two major AD hypotheses: cholinergic hypothesis focuses on the reduction of acetyl-choline synthesis from choline and acetyl coenzyme A in the cholinergic neurons due to the decreased activity of enzyme choline acetyltransferase[10]; amyloid hypothesis explains neurodegeneration in AD with the neurotoxic effect of amyloid beta accumulation in the brain[11].

There are numerous risk factors for AD which can be classified into the following groups: genetic factors, age and gender, head injuries, infections, cardiovascular disease, lifestyle, obesity, diabetes mellitus, and environmental factors. About 70% of AD cases are related to mutations in the dominant genes[12]. Aging is the most potent risk factor for AD, especially 65 years and older[13]. AD affects women more often than men (65% vs. 35%, respectively)[14]. Head or brain injuries raise the chance for the onset of AD after 5 years by about 20%[15]. Chronic bacterial and viral infections of the central nervous system may lead to the accumulation of Aβ and NFT[16]. Cardiovascular diseases may cause the loss of brain tissue (stroke) or hypoxia due to reduced circulation in the brain (heart failure, atherosclerosis, hypertension)[17]. Concerning lifestyle, aerobic physical exercise[18], mental activity like playing chess or reading or crossword puzzles[19], leisure activities[20], continuing education[21], avoidance or cessation of smoking[21], adequate sleep[19], and techniques to decrease stress[22] may reduce the risk of AD. Obesity[23] and diabetes[24] are risk factors for AD due to neuroinflammation, oxidative stress, and amyloid-beta accumulation. Malnutrition[25] as well as saturated fatty acids and high calorie intake[26] increase the risk of AD, while fish and supplementation with polyphenols, antioxidants, and vitamins, may lower the risk of AD[26]. Concerning environmental factors exposure to air pollutants including low ozone, carbogen monoxide, particulate matter, nitrogen oxide, sulfur oxide and lead is related to oxidative stress, neuroinflammation, and neurodegeneration and tau phosphorylation, and Aβ accumulation in the brain cortex[27]. Finally, exposure to some metals is related to AD. Accumulation of aluminum in the brain may lead to phosphorylation of tau proteins[28], while exposure to lead and cadmium is related to aggregation of Aβ plaques in the brain[29].

According to the World Health Organization (WHO) burden of disease analysis it is estimated that around 1,6 million disability-adjusted life-years are lost each year due to environmental noise exposure in the European Union Member States and other Western European countries. Around 45.000 of lost DALYs are related to cognitive impairment of children[30]. Recent animal

and human studies point to a possible role of noise exposure as a new risk factor for AD, permanently testing the hypothesis on the noise-AD relationship[31,32,33,34]. The aim of this review is to present evidence for the noise-AD relationship and to discuss basic pathological concepts underlying this connection.

## MATERIALS AND METHODS

Full papers in the English language were searched in the PubMed database from inception to the 1st of April 2023, using keywords "noise" and "cognition" and "learning" and "memory" and "dementia" and "Alzheimer's disease". The inclusion factors were original studies or reviews about chronic noise exposure and cognitive functions in animals or humans. The results are classified into three sections: studies on animals, studies on humans, and pathological concepts.

## RESULTS

### *Studies on Animals*

**Cognitive effects of noise.** Exposure to noise during the gestational period led to a significant increase in corticosterone levels and stimulation of hypothalamic-pituitary- adrenal axis (HPA) in mice and post-partum detrimental effects on spatial learning and memory function[35]. Prenatal noise exposure also had a negative cognitive effect on the mice offspring in terms of affected spatial learning[36]. Beside offspring's cognitive impairment, a reduced expression of glucocorticoid and mineralocorticoid receptors in the hippocampus was found after exposure to noise during the last trimester of pregnancy in rats[37]. There was a difference in cognitive effects of short-term exposure (6 to 10 days) and long-term exposure (26-40 days) to combined traffic noise of 70 dB (A). The former had a stimulating effect on learning and memory of mice related to increased level of glutamate in hippocampus, while the latter showed a cognitive decline and lowered glutamate concentration[38]. Loud noise (95-97 dB, 2h/day,30 days) had detrimental effects on spatial memory and associative memory of rats. These behavioral changes were followed by the imbalance in the oxidative status in the cerrebelum and hippocampus. Reactive oxygen species were increased in the beginning of exposure and decreased after 30 days. On the other hand, antioxidant activity of hyppocampal catalase was increased throughout 30 days of noise exposure, while the activity of sodium dismutase decreased after the first exposure to noise, but it was raised after 30 days[39]. After the cessation of noise exposure (80 dB or 100 dB for 4 h per day, for 30 days) the impaired learning and memory functions as well as the decreased levels of hippocampal neurotransmitters dopamine, norepinephrine and 5-hydroxytryptamine in rats recover within 30-40 days[40].

**Neuropathological effects of noise**. Typical neuropathological changes in rodents exposed to chronic noise include persisting overproduction of Aβ and neuroinflammation related to elevated tumor necrosis factor-α[41], tau phosphorylation concomitant with the formation of NFT in the hippocampus and the prefrontal cortex, typical for AD brain[42], reduction of proliferating cells in the hippocampal formation related to elevated corticosterone serum levels[43], oxidative damage in the auditory cortex, and hippocampus[44], and the inferior colliculus - the principal midbrain nucleus of the auditory pathway. The hippocampus seems to be more vulnerable to chronic noise than auditory cortex, with more intensive peroxidation and tau phosphorylation[45]. Prenatal noise exposure leads to the development of amyloid beta (Aβ) plaques in offspring, particularly in females[46]. Exposure of adult rats to noise 100 dBA/4h per

day for 30 days caused a significant decrease of dendritic count in hippocampus and medial prefrontal cortex[47]. Another important biochemical effect of exposure of rats to chronic noise (100 dB, 4 h/d×30d) is the decrease of the expression of N-methyl-D-aspartic acid receptor 2B, resulting in tau hyperphosphorylation and neural apoptosis in hippocampus[48]. Hyperactivity of HPA in mice after exposure to noise for 30 days led to structural changes in brain in terms of reduction of brain volume, medial prefrontal cortex area, cortical thickness, hippocampal volume, and amygdala area[49]. Both acute noise exposure (one day) and subacute noise exposure (between postnatal days 15 and 30) of 95-97 dB SPL, 2h daily, caused histological changes in the hippocampal region CA3 of the rats in terms of the increased number of pyknotic cells and a total number of cells, indicating cell death due to necrosis and apoptosis[50].

### *Studies on Humans*

**Cognitive effects of noise.** Occupational noise of 68 dB had detrimental effects on participants' attention and short-term memory in terms of a higher number of errors and a longer reaction time compared to control acoustical conditions (45 dB). Participants also experienced higher levels of discomfort, stress, and annoyance[51]. The moderators of cognitive effects of experimental exposure to noise (slower psychomotor speed, reduced working memory and episodic memory, and more cautious decision-making) include subjective noise sensitivity, paranoia, sleep quality and cognitive disorganization[52]. After experimental nocturnal combined exposure to aircraft, rail, and road traffic noise pooled noise exposure data showed detrimental effects on performance in terms of prolonged reaction time compared to quiet conditions. There were no significant differences in the effects on performance regarding noise sources, but the level of noise annoyance was highest after exposure to aircraft noise[53]. When the performance effects of laboratory and field nocturnal aircraft noise were compared during 9 consecutive nights, a dose-response increased reaction time in the psychomotor vigilance task was found, and more pronounced in the field compared to laboratory noise exposure (0.3 ms/dB LAeq vs. 0.13 ms/ dB LAeq)[54]. Subjective noise sensitivity is an important moderator in the cognitive effects of noise. Persons with high noise sensitivity show worse mental performance results under noisy conditions and a higher noise annoyance level compared to subjects with low noise sensitivity[55,56]. Neurotic persons and introverts show enhanced arousal levels and worse results in cognitive tasks under noisy conditions compared to extroverts and more stable personalities[57,58] . Exposure of elderly women to residential road traffic noise ≥50 dB Lden had the effect of impaired total cognition and the constructional praxis domain measured by Consortium to Establish a Registry on Alzheimer's Disease (CERAD-Plus) Neuropsychological Assessment Battery, compared to <50 dB Lden conditions[59]. Concerning the effect of noise on children's cognition, aircraft noise seems to have some detrimental effect on reading comprehension and long-term and short-term memory, while having no substantial effect on attention and executive functioning[60]. Some occupations are under a relatively higher risk of noise induced cognitive effects. The fighter jet pilots show significantly lower accuracy in delayed verbal and visual memory tests in comparison to the controls. These cognitive deficits are followed by neuron dysfunction of the hippocampus, in terms of decreased gray matter volumes and regional homogeneity compared to controls[61]. However, there are also published results of the absence of significant relationship between environmental noise and the risk of dementia[62].

**Noise and degenerative dementia.** A recent meta-analysis based on 11 studies revealed the relative risk for AD of 1.18 (95% CI: 1.14–1.23) per 25 dB increase in noise exposure level [63]. In a 13-year cohort study in Denmark, both road traffic noise and railway noise were associated with a higher risk of Alzheimer's disease, with hazard ratios of 1.16 (95% confidence interval 1.11 to 1.22) for road $L_{den}$max ≥65 dB compared with <45 dB, 1.27 (1.22

to 1.34) for road $L_{den}$min ≥55 dB compared with <40 dB, 1.16 (1.10 to 1.23) for railway $L_{den}$max ≥60 dB compared with <40 dB, and 1.24 (1.17 to 1.30) for railway $L_{den}$min ≥50 dB compared with <40 dB[64] .The odds ratio (95%CI) for overall mild cognitive impairment and amnestic mild cognitive impairment was 1.40 (1.03, 1.91) and 1.53 (1.05, 2.24), respectively, with a 10 A-weighted decibel [dB(A)] increase in LDEN of traffic noise. The authors point to a possible synergistic effect of noise and air pollution with $PM_{2,5}$ on cognitive impairments[65]. In another population-based study the odds (95% CI) of prevalent mild cognitive impairment and Alzheimer's disease were 1.36 (1.15 - 1.62) and 1.29 (1.08 - 1.55), respectively with each increment of 10 A-weighted decibels (dBA)[66]. However, there are also published results of the absence of significant relationship between environmental noise exposure and cognition and cortical thickness in brain regions known to be affected by Alzheimer's disease[67]. In a 15-year cohort study in Sweden no significant association was found between exposure to residential noise levels (Leq. 24 h) > 55 dB and dementia risk (HR 0.95; CI: 0.57, 1.57)[68]. In a study performed in Madrid during a nine-year period there was no significant relationship between daily and night noise levels (dBA) and emergency Alzheimer's disease hospital admissions[69]. In a population-based cohort study on 2,2 million people aged 20-50 years in Canada the adjusted hazard ratio (HR) of incident dementia was 1·07 for people living less than 50 m from a major traffic road (95% CI 1·06-1·08), 1·04 (1·02-1·05) for 50-100 m, 1·02 (1·01-1·03) for 101-200 m, and 1·00 (0·99-1·01) for 201-300 m versus further than 300 m (p for trend=0·0349). The limitation of this study was that no distinction was made between degenerative and vascular dementias[70]. In another similar population-based study no significant relationship was found either between estimated noise level or proximity to major roads and the incidence of Alzheimer's disease[71]. The brain scans of cognitively unimpaired individuals aged 45 to 74 at increased risk of AD showed a positive correlation between traffic noise levels and white matter volume in the body of the corpus callosum at the level of the auditory cortex[72]. The limitations of the so far epidemiological studies on noise and dementia include the absence of distinction between degenerative and vascular dementia, uncontrolled hearing status, noise exposure bias (noise maps, proximity to busy roads, and traffic flow).

### *Pathological concepts of noise-AD relationship*

An interaction between noise exposure and gene mutations may lead to neuropathological changes characteristic of AD. When APP/PS1 mice were exposed to chronic noise significant increases in the hippocampal phosphorylated Tau and overproduction of Aβ were found, together with the activation of VDAC1 that is involved in the mitochondria-mediated apoptosis[73]. After senescence-accelerated mice prone 8 (SAMP8) were exposed to white noise of 98 dB SPL for 30 consecutive days a real-time PCR was used to determine the differential gene expression. Compared to controls, there were 21 protein-coding transcripts that were differentially expressed under chronic noise, of which 8 were related to AD. Noise significantly increased the expression of genes Arc, Egr1, Egr2, Fos, Nauk1, and Per2. and these genetic changes were followed by the hippocampal amyloid beta accumulation and increased hyperphosphorylation of Tau[74]. Neuropathological changes in the brain of SAMP8 after noise exposure were followed by the decrease of gut microbiome diversity, change in its composition, and detrimental effects on the microbiome-gut-brain axis in terms of, disrupted epithelial barrier function in the intestine and blood-brain-barrier[75].

Hearing loss has been related to cognitive impairments both in experimental and epidemiological studies. In animal models, hearing loss and Aβ administration to the rats' brain showed worse cognitive function and lower levels of synaptic proteins in the hippocampus compared to rats with only Aβ administration, only hearing loss, and without hearing loss or Aβ administration[76]. In a population based 3-year cohort study patients newly diagnosed with hearing loss were compared with a group with no hearing loss, matched by

sex, age, residence and SES. Patients with HL had a significant risk of dementia compared to the controls, and the highest risk was for the group aged 45-64 years (HR, 1.40; 95% CI, 1.12-1.75)[77]. Hearing loss has detrimental effects on the quality of life, contacts, and physical activity, and is related to depression and dementia[78]. A 4-year cohort study on older adults (mean age 65 years) showed that loneliness and social isolation are significantly and negatively related to cognition[79]. People with hearing loss use a much larger cognitive load while listening compared to people with normal hearing. The consequence is a reduction of available cognitive resources, and the acceleration of cognitive decline[80]. Noise exposure has toxic effects on the hippocampus consisting of oxidative stress and excitotoxicity, and consequently disruption of neurogenesis, synaptic loss, amyloid beta overproduction and tau hyperphosphorylation. Neuroinflammation that is often associated with NIHL[81] is also a contributing factor to the initiation and advancement of Alzheimer's disease[82]. After exposure of rats to noise levels of 100dB for two hours daily during 15- and 30-days cognitive impairments were associated with elevated levels of TNF-α, IL-6, IL-1α, and IFN-γ in both hippocampus and plasma. Pathologic cellular changes included an increase in the number of pyknotic and apoptotic neurons[83]. Experiments on rodents show that in addition to hearing loss other factors are needed to trigger the process of degenerative dementia, such as aging, APOE genotype, or microvascular disease[84].

Experiments with prenatal noise exposure of mice showed that anxiety-like behavior and reduced learning and memory performance were associated with the activation of the HPA axis in terms of elevated plasma cortisol levels[85]. The hippocampus and prefrontal cortex of the brain are particularly sensitive to the detrimental effect of the hyperactive HPA axis, showing reduced neurogenesis, dendritic atrophy, disordered synaptic plasticity, and functional impairment[86]. In the experiments on rats chronic noise caused the progressive overproduction of corticosterone and upregulated corticotropin-releasing factor (CRF) and CRFR1 mRNA and protein, followed by tau phosphorylation in the prefrontal cortex[87].

The pathway of the possible effect of chronic noise exposure on tau hyperphosphorylation may also be explained by the disorders in glutamate (Glu)-NMDAR signaling. Dizocilpine, also known as MK-801, which is a pore blocker of the N-Methyl-D-aspartate (NMDA) receptor, a glutamate receptor, decreased tau hyperphosphorylation in rats' hippocampus and PFC after noise exposure[88]. Chronic noise decreased the expression of B2 NMDA receptors, causing glutamate upregulation and tau hyperphosphorylation, and neural apoptosis in the hippocampus of rats[89]. Dendrites are particularly vulnerable to oxidative stress, energy deficits, and excitotoxic NMDA receptor activity[90].

Oxidative stress is another possible explanation for the noise-AD relationship. Tau protein may be hyperphosphorylated by protein kinases[91] that are activated with reactive oxygen species (ROS) formed during noise exposure[92]. ROS also may play a role in the disruption of lipid homeostasis and amyloid precursor protein formation[93].

Noise-induced psychological stress is characterized by the activation of the sympathetic adrenal medullary axis. Elevated levels of dopamine and norepinephrine in the rat's cerebellum and striatum have been found after exposure to noise of 100 dB for 4 h/day for 15 days. Monoamine oxidase metabolizes the excess amounts of dopamine to free radicals such as superoxide radical and hydrogen peroxide which mediate changes in the morphology of the cerebellar Purkinje cells[94]. The brain regions that are particularly sensitive to stress induced cellular changes like neuronal loss, dendritic retraction, or glial changes include the hypothalamus, hippocampus, amygdala, nucleus accumbens, prefrontal and orbitofrontal cortex[95].

These possible pathways of the effects of noise on cognition and dementia are shown in Figure 1.

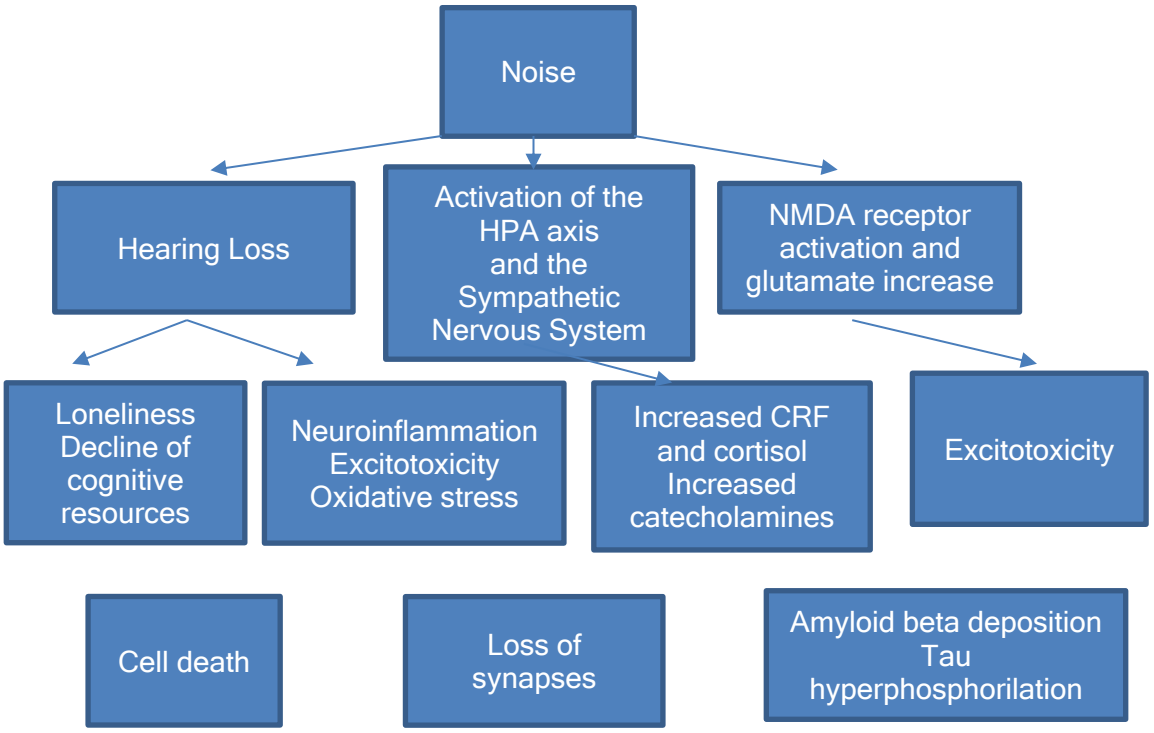


Figure 1. Noise and Alzheimer-s disease – possible pathophysiological mechanisms

## CONCLUSION

There is a biological plausibilty for the association between noise exposure and Alzheimer's disease. The pathways of this relationship include both hearing loss and no-hearing loss-related mechanisms like social isolation, a decline of cognitive resources, excitotoxicity, neuroinflammation, oxidative stress and psychological stress. Given the great public health importance of the mutual global growth of noise exposure and of the burden of Alzheimer's disease, continuing research of this relationship is justified. In further research, it would be interesting to investigate the effectiveness of hearing aids in reducing cognitive decline in the elderly. More studies on the noise-AD relationship are needed in industrial settings where much higher noise levels are recorded, intervention studies may be carried out and better control of confounding factors is possible compared to residential settings.

## Conflict of Interest

The author declares no conflict of interest.

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