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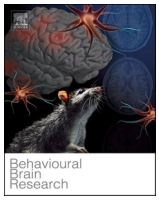

Review

An integrated approach to understanding the effects of exposome on neuroplasticity

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A B S T R A C T

Anthropogenic factors are those that occur due to human activities. The exposome is proposed to complement the genome, wherein an individual's exposure begins before birth. The range of exposures includes physical, chemical, dietary, lifestyle, biological, and occupational sources. Exposome has a positive or negative influence on neuroplasticity during different stages of life. A comprehensive study of the exposome is thus necessary to incorporate these factors and their influence on the individual, community, and the population as a whole. Exposomic research and global health present significant opportunities for interdisciplinary research. This review gives an overview of the exposome and its influence on neuroplasticity. It proposes methods to study the exposome on neuroplasticity across the lifespan of the individual. This is possible with the use of self-reported data, large-scale cohort formation, physiological sensors, neuroimaging, omics, molecular biology, and systems approaches. These approaches aim to provide a holistic understanding of an individual's neurological well-being and its implications for the population at large. This will also enable the designing of novel preventive and treatment strategies for managing neurological disorders.

1. Anthropocene and the exposome

The term "anthropogenic" refers to the environmental changes caused by human activities, either directly or indirectly. The term 'Anthropocene,' was introduced by Paul Crutzen and biologist Eugene Stoermer in the mid-1970s. It was initially used by Russian geologist Alexey Pavlov and British ecologist Arthur Tansley [1,2]. Anthropogenic factors are those that result from human actions and are often associated with chemical or biological waste released into the environment [3]. Rising industrial chemicals in soil, water, and air, along with mineral depletion, mining, deforestation, and waste from industries and medical facilities, pose major challenges to both human survival and environmental sustainability [4].

The term "exposome" refers to the total exposure of different types, a person experiences throughout their lifetime and its impact on health. Exposome concept was introduced by cancer epidemiologist Christopher Paul Wild in 2005 [5]. The exposome is intended to complement the genome, encompassing all exposures an individual encounters before birth. This includes chemical, physical, dietary, lifestyle, biological, social and occupational factors. These exposures interact with a person's unique genomic characteristics, influencing health in the short- and long-term (Figs. 1, 2, Table 1). Current epidemiological data indicate that only about 10 % of human diseases are linked to genetic anomalies, highlighting the significant role of the exposome or environmental factors in shaping health outcomes [6,7].

2. Neuroplasticity

Neuroplasticity, or brain plasticity, is the brain's ability to adapt structurally and functionally to internal or external stimuli by reorganizing its structure, functions, or connections at various levels. This process is evident in activity-dependent learning, where neuroplasticity is shaped by experience-based stimuli, both internal and environmental. There is a critical period during development when the brain is highly vulnerable, and the timing of exposure during this period is crucial (Fig. 1). Both genetic and epigenetic factors, encountered in utero and postnatally, influence this phase. In all species studied, including humans, these critical periods are key to proper development. If appropriate stimuli are missing or developmental pathways are disrupted during this time, neuroplasticity may be significantly diminished or constrained [9,10], due to the brain's heightened vulnerability.

Neuroplasticity involves diverse mechanisms, including neuronal sprouting, synaptogenesis (the formation of new inter-neuronal connections), and neurogenesis, which contribute to both developmental and adaptive plasticity in response to experience. Adult neurogenesis is unique and is extensively studied in the subventricular zone and subgranular zone of the dentate gyrus of the hippocampus. More recently, adult neurogenesis is shown to occur in other regions such as the arcuate nucleus, the median eminence, striatum, substantia nigra, habenula, cerebellum, cortex, and amygdala [11,12]. Molecular processes like angiogenesis (the formation of new blood vessels) and gliogenesis

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(generation of new glial cells) also contribute to neuroplasticity. Structural changes, such as dendritic plasticity, involve modifications in dendritic spines, particularly in the glutaminergic synapses and play a crucial role in synaptic plasticity. At a molecular level, neuroplasticity is regulated by gene transcription, protein synthesis, and intracellular signaling cascades. Calcium (Ca^{2+}) influx through N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) glutamate receptors activate pathways including Ca^{2+}/calmodulin-dependent protein kinase (CaMKII), extracellular regulated kinase 1/2 (ERK1/2), mitogen-activated protein kinase (MAPK), and brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB), which modulate synaptic plasticity. Cyclic AMP-response element-binding protein (CREB) and nuclear factor kappa B (NF-kB) regulate gene transcription, driving long-term plasticity. Functional plasticity includes synaptic strengthening (long-term potentiation, LTP) and weakening (long-term depression, LTD), essential for learning and memory. LTP involves increased intracellular Ca^{2+} and enhanced synaptic connections, while LTD is associated with reduced synaptic strength [13-16]. These neuroplastic changes can be understood by studying gene and protein expression, immunohistochemistry analysis of brain tissue samples, or through electrophysiological recordings from neurons.

2.1. *Importance of studying the exposome and neuroplasticity*

Brain plasticity offers both evolutionary (phylogenetic) and individual (ontogenetic). This adaptability enables organisms to better navigate their environments and enhance survival. However, the complexity and dynamics of the nervous system, especially related to learning, also make the brain vulnerable to various environmental insults. Environmental stressors refer to external factors, such as infections, drugs, pollutants, dietary additives, and lifestyle elements, that contribute cumulatively to cellular and systemic effects. Research shows that both genetic and lifestyle factors can impact brain plasticity in humans and animals [17]. Brain development is not solely determined by genetic inheritance but is shaped by numerous environmental, biochemical, and physical factors. Furthermore, the interaction between the genetic and epigenetic factors plays a role in the development of neuropsychiatric disorders (see [18,19]). In addition to genetics, factors such as diet, stress, drug exposure, and sensory and motor experiences can influence brain development in distinct ways. Even in adulthood, the brain retains plasticity, capable of being shaped by diet, exercise, stress, aging, and experiences such as sensory and motor stimulation, task learning, exposure to neurotrophic factors, and psychoactive drugs. Thus, almost every experience has the potential to induce changes in brain structure and behavior [20].

This review explores the various exposomic factors that affect neuroplasticity, beginning with an identification of these factors, their mechanisms of action (Fig. 3), followed by a discussion of recent approaches for studying the exposome's health impacts, particularly its effects on neuroplasticity. The review also suggests potential solutions for overcoming the challenges in researching the exposome's influence on health, including mental health. The information was gathered through independent searches of each exposomic factor, combined with the term "neuroplasticity," in PubMed and Google Scholar. While no specific time frame was applied to the search, it is notable that much of the exposomic research has been published post-2000. Given the rapid environmental changes and their increasing implications for mental health, studying the exposome's role in neuroplasticity has never been more essential to understanding how external factors shape brain function and resilience. Several exposomic factors can either enhance or hinder brain plasticity (Fig. 3) [21]. Many of these factors overlap with those that affect neuroplasticity. Below is an overview of these factors and their influence on neuroplasticity, with examples provided.

2.2. *Factors that hinder neuroplasticity*

Environmental factors significantly affect neuroplasticity and are

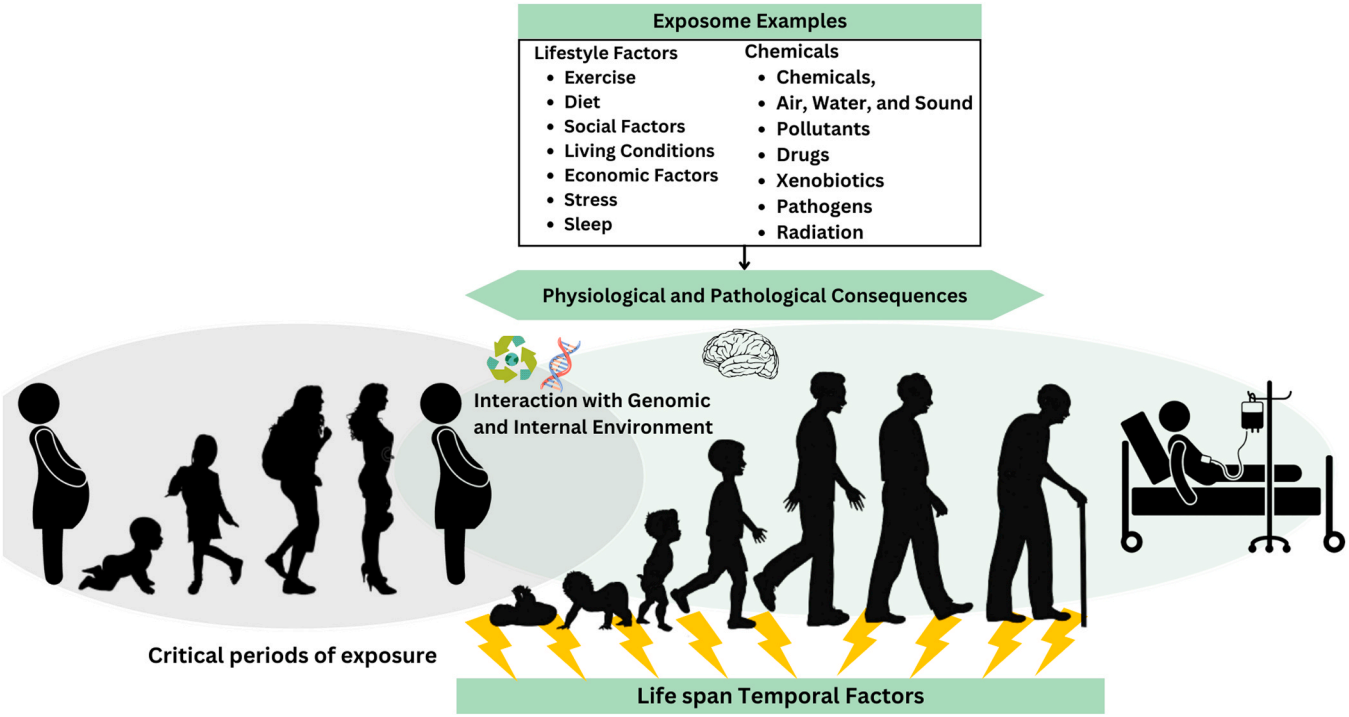

Fig. 1. The interaction of the exposome with unique genomic characteristics to affect health. Several lifestyle and environmental factors together act synergistically or counteract each other, producing physiological and pathological consequences through their interaction with one's genomic and internal environment. This figure shows how exposome interacts with the genomic environment of an individual and is often transmitted across generations. Pregnancy and early developmental periods are critical periods for determining the long-term effects of exposome factors on health and neuroplasticity.

often linked to the development of neurological diseases [22]. For instance, the incidence of multiple sclerosis, a demyelinating condition of the spinal cord, varies geographically, with higher rates occurring farther from the equator, although the reasons for this correlation are still unclear. Climate change can exacerbate brain disorders by increasing exposure to environmental neurotoxins, infectious diseases, and malnutrition-related conditions (see review [23]). Air pollution, elevated levels of particulate matter, nitrogen dioxide, ozone, and carbon monoxide, increases the incidence of migraines, Alzheimer's disease (AD), and Parkinson's disease (PD), with stronger effects noted on hotter days [24-27]. Fine particulate matter (PM2.5), has been demonstrated to cross the blood-brain barrier, hamper neurogenesis, and trigger oxidative stress and neuroinflammation, impairing neuroplasticity [28]. Temperature changes can impact gene expression [29], structural organization of the brain [30], and learning capabilities [31]. Hyperthermia can elevate the risk of epileptic seizures, damage neurons in the amygdala and hippocampus [32], and disrupt GABA receptor signaling [33]. Shifting climate conditions promote the growth of weeds and pests, which in turn increases plant diseases and necessitates greater use of herbicides, pesticides, insecticides, and other chemicals. These substances eventually enter the food chain, indirectly impacting molecular and functional neuroplasticity [34]. For instance, excessive use of insecticides like pyrethroids in malaria-prone areas has been associated with higher rates of developmental neurotoxicity [35].

Malnutrition during early development illustrates how environmental factors can influence mental health by affecting neurodevelopment [36]. Intake of lesser proteins, carbohydrates, iron, zinc, vitamins, or polyunsaturated fatty acids during early developmental periods affects brain regions such as the cortex, hippocampus, autonomic nervous system (ANS), striatum, cerebellum, and the eyes. The processes of synaptogenesis, neurogenesis, myelin deposition, gene

Table 1
Comprehensive list of the exposome factors impacting human health.

External		Factors
Biological		Virus, Bacteria, Fungi, Parasites
Physical	Home environment	Dust, household chemicals, mites, metals, plastics, pests, air pollutants, radiofrequency radiation
	Outside environment	Climate, temperature, humidity, wind, rainfall, atmospheric pressure, Air pollutants - Nitrogen dioxide (NO2), Sulphur dioxide (SO2), Carbon monoxide (CO), Ozone (O3), Particulate matter (PM), Ultraviolet radiation and other types of radiations, traffic, pollen, water pollutants, noise
	Socioeconomic environment	Population density, building density, economic stability, education, comfortable facilities, food supply, water supply, green space, walkability, neighborhood safety, accessibility to resources (e.g., hospitals, bus stations), noise, stress, social communication channels, cultural practices
	Occupational	Fertilizers, metals, pesticides, plasticizers, flame retardants, animal proteins, plants, heat/cold stress
Internal		
Lifestyle		Diets, physical activity, tobacco smoke, alcohol, drugs, sleep, stress, sexual behavior, artistic and cultural practices, cognitively enriching activities, routine use of chemicals eg: cosmetics
Health-related		Medicines, surgeries

Adapted from [8].

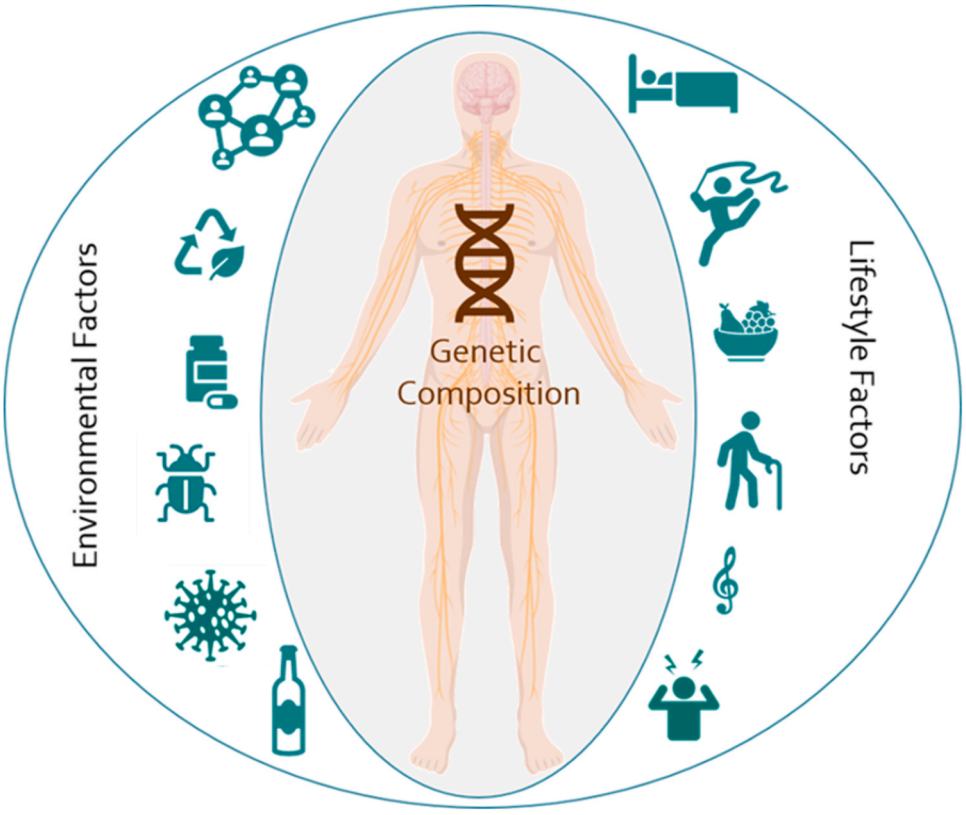

Fig. 2. The exposome interacts with the genome to impact the health of an individual. Environmental factors, such as socioeconomic factors, climate factors, living conditions, drugs including alcohol, chemical or toxicological exposures, biological factors such as bacterial or viral infections; Lifestyle factors such as diet, exercise, sleep, stress, health conditions or disease, cognitive enrichment factors – All exposures interact with the genomic composition of the individual, promote epigenetic changes, and impacts the overall health of the individual.

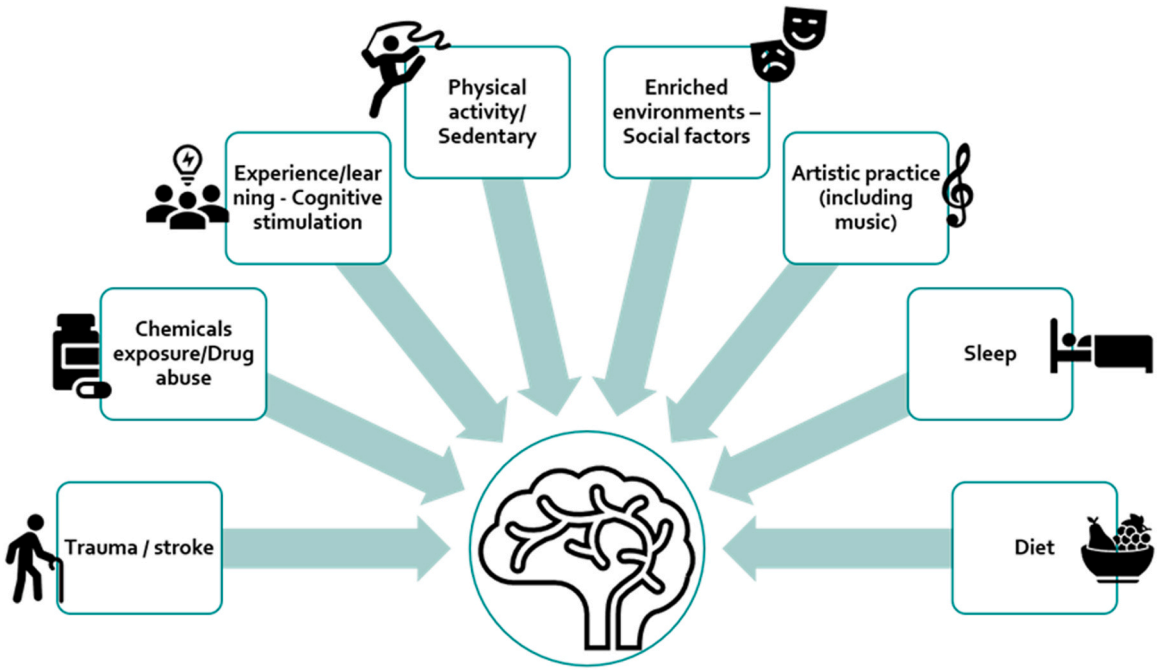

Fig. 3. Factors that affect Neuroplasticity. Brain injury or stroke, chemical exposures during the developmental period or adulthood, drug abuse, and sedentary lifestyle have negative effects on neuroplasticity; Environmental enrichment, regular exercise, healthy sleep practices, balanced diet, involvement in creative endeavors, cognitive stimulation promote positive neuroplastic changes in the brain.

expressions, neuronal differentiation, and neurotransmission are among the several neuroplastic processes that are affected [37]. Sedentary behavior negatively affects neuroplasticity. Magnetic resonance imaging (MRI) scans of sedentary middle-aged adults revealed reduced thickness in the medial temporal lobe [38], while overweight or obese children showed decreased gray matter volume in various brain regions [39]. A high-fat diet contributes to insulin resistance, oxidative stress, neuroinflammation, transcriptional dysregulation, impaired synaptic plasticity, compromised blood-brain barrier integrity, and reduced cerebral blood flow, collectively leading to cognitive deficits (reviewed in [40]). In obese children, a multidisciplinary treatment program involving dietary restriction, cognitive behavioral therapy, and physical activity improved neuroplasticity [41].

The term "stress" is widely used across different fields to describe the strain on a specific structure or entity. In life sciences, stress refers to any challenging life events or circumstances, including both physiological and perceived psychological stressors. Stress triggers adaptive bodily responses to maintain an organism's well-being or homeostasis [42]. It is a natural reaction to situations perceived as challenging, threatening, or demanding. Excessive or prolonged stress can lead to various physical health issues such as cardiovascular, digestive, and metabolic diseases, as well as mental health disorders like anxiety, depression, post-traumatic stress disorder (PTSD), schizophrenia, addiction, and relapse in humans. Notably, stress pathways link key areas of the limbic system, including the hippocampus, amygdala, hypothalamus, ANS, and the body's endocrine system, as explained further. McEwen and colleagues were the first to describe the stress-induced structural plasticity in the form of atrophy of hippocampal neurons [43,44]. The effects of stress on learning and memory depend on the type, duration, and intensity. Emotional arousal triggered by stress can enhance learning and memory through the synaptic plasticity of amygdala-dependent pathways, which may explain why traumatic events and PTSD often result in vivid, long-lasting memories [45].

Chronic stress is known to induce dendritic atrophy in the hippocampus, increase apoptosis, and inhibit neurogenesis. These changes result in reduced hippocampal volume, suppression of LTP, and impaired memory function. Moderate to severe stress impacts the amygdala in ways that contrast with its effects on the hippocampus and prefrontal cortex (PFC). Chronic stress can lead to hypertrophy of neurons in the amygdala, particularly in the basolateral amygdala (BLA) [46]. The amygdala is connected to almost all cortical areas, including the hippocampus [47]. The hypothalamic-pituitary-adrenal (HPA) axis plays a vital role in building resilience to stress. Stress triggers the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (cortisol in humans, corticosterone in rodents), which act on glucocorticoid receptors (GlucR) to form a closed-loop feedback system [48,49] (Fig. 4). The HPA axis plays a key role in regulating stress and hormone responses. Its main components are the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary, and the adrenal glands (Fig. 4). During stress, CRH prompts the release of ACTH into the bloodstream, which primarily targets the adrenal cortex to stimulate the secretion of glucocorticoids and mineralocorticoids. Glucocorticoids interact with GlucRs throughout the body, causing various physiological changes. The HPA axis is further regulated by glucocorticoids through GlucRs in the hypophysiotropic neurons of the PVN, the hippocampus, and the PFC via genomic, delayed feedback, and rapid nongenomic feedback systems. While the amygdala activates the HPA axis, promoting glucocorticoid production and stress responses, the hippocampus inhibits this activation [50]. Although glucocorticoids have adaptive functions, excessive activation of the HPA axis can lead to pathological conditions [51]. Stress-induced activation of GlucRs can result in long-lasting changes, affecting future stress responses through epigenetic mechanisms, and reduced dendritic complexity in the hippocampus [52].

Recent studies have demonstrated that, in addition to the cortisol response, acetylcholine (ACh) release increases in the hippocampus following acute stress [54,55]. Stress rapidly activates the septohippocampal cholinergic pathway, triggering changes in gene expression and leading to ACh-mediated neuroendocrine, emotional, and physiological responses by stimulating the HPA axis [56]. ACh functions as a neuromodulator, adjusting neuronal activity in response to environmental changes, much like glucocorticoids during stress (see review [57]). Furthermore, glucocorticoids and ACh interact in the brain [58]. Activation of α4/α6β4-containing nicotinic acetylcholine receptors

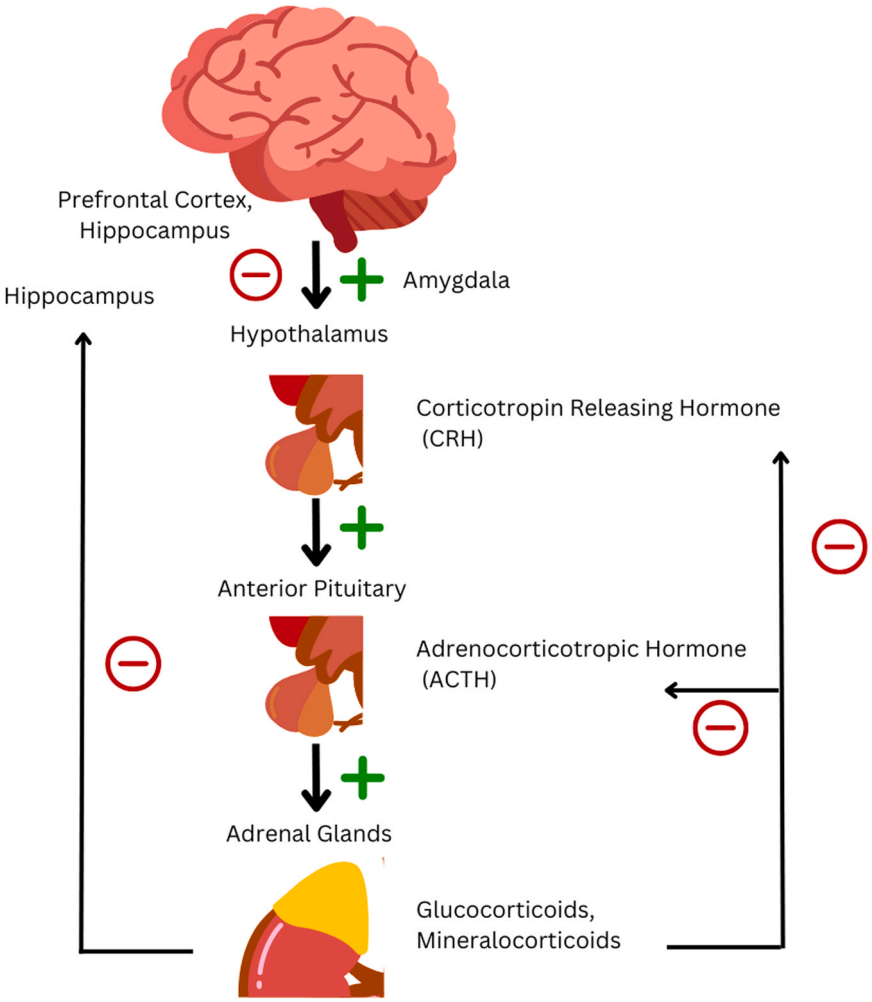

Fig. 4. The hippocampus, prefrontal cortex (PFC), and amygdala on the hypothalamic-pituitary-adrenal (HPA) axis [53].

(nAChRs) modulates dopaminergic transmission in the ventral tegmental area (VTA), α7 nAChRs influence glutamate release, and α4β2*nAChRs control GABA release [59]. The mesolimbic dopaminergic pathway involves extra-hypothalamic regions such as the PFC, hippocampus, amygdala, nucleus accumbens (NAc), and VTA, all of which influence the stress-HPA axis and receive input from cholinergic neurons in the basal forebrain [60]. Addictive substances like nicotine and ethanol affect both the central cholinergic and dopaminergic reward systems. Nicotine binds to nAChRs found on neurons in the mesolimbic dopaminergic pathway and plays a role in the rewarding and reinforcing effects of both nicotine and ethanol. Although ethanol does not directly interact with nAChRs, it enhances ACh release, which then modulates other neurotransmitters [61]. Optimal ACh levels enhance learning and memory through sustained attention. However, excessive ACh is linked to increased symptoms of anxiety, depression, and heightened stress reactivity (see reviews [62,63]). Studies have shown that during passive coping, ACh release is minimal, while moderate or brief stress triggers a transient release of ACh, which activates GABAergic interneurons and other neurons. In contrast, chronic stress leads to prolonged ACh release, disrupting the balance between excitatory and inhibitory networks, resulting in asynchrony and maladaptive behaviors [62].

Social factors such as early life stress (ELS), maternal care during the perinatal period, and environmental nurturing throughout life, significantly influence neuroplasticity, as outlined in a recent review [64]. Stress and early life adversity are particularly critical due to their profound effects on neuroplasticity. Early life adversity or stress (ELS) is a major contributor and a predictor to the development of mental illnesses such as depression and PTSD, accounting for 30 % of adult mental health conditions [65]. In both rodents and higher primates, ELS, perinatal maternal stress, maternal separation, variable foraging demands, or low maternal care - can lead to structural and functional changes in brain regions involved in neuroendocrine control, autonomic regulation, and vigilance [66,67]. ELS leads to lasting structural and regulatory changes in the neuroendocrine system, which can either predispose individuals to or protect them from stress-related diseases later in life [68-70]. A recent study on resilience showed that brief postnatal exposure to a low-resource environment, such as limited bedding and nesting, reduced addiction-related behaviors in male rats later in life [71]. Sensory experiences during the postnatal period regulate neuroplasticity for the entire lifetime. Mother-pup/ child interactions are crucial to modulating the neuroplasticity of the HPA axis, improving cognitive functions, and lowering stress responses (such as reduced CRH expression and increased hippocampal GlucR levels) [72-75]. During early brain development, several neuroplastic structures form multiple connections with the brainstem ANS centers to regulate its outflow and modulate visceral functions. These processes can be influenced by the 'intrauterine environment', including maternal preconception health and stress hormone levels during pregnancy [76], and can strengthen or weaken depending on environmental factors, stress, and other exposures [77].

While research has primarily focused on psychological stress, early exposure to neurotoxins (such as drugs, chemicals, or substance abuse) (Fig. 5) plays an equally significant role in the development of neurological disorders and can have a profound, lasting impact on brain architecture. Over 200 chemicals were identified as neurotoxic to adults,

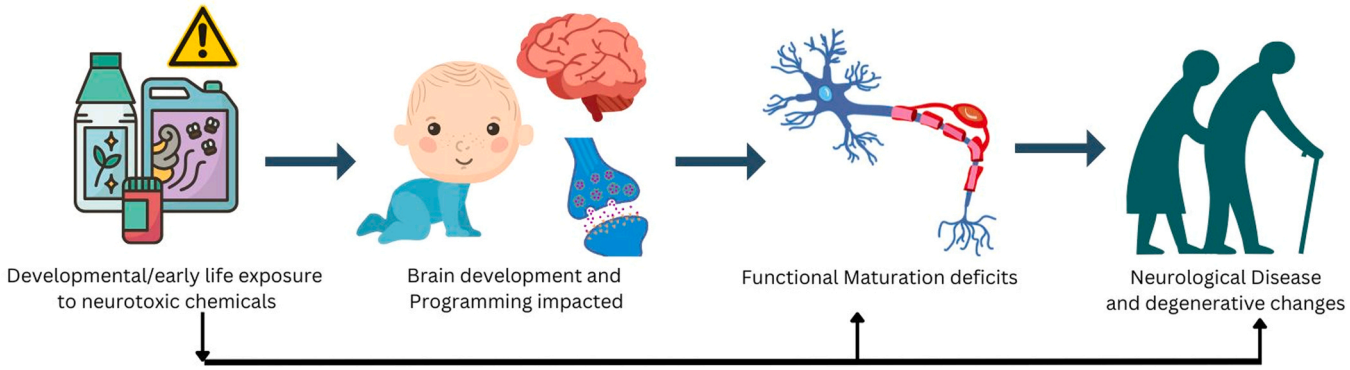

Fig. 5. Early exposure to neurotoxins and their consequences (reviewed in [78]).

with thousands of pesticides, solvents, and other industrial chemicals in widespread use that had never been tested for their neurodevelopmental effects [78]. Early-life chemical exposure is particularly harmful due to the brain's vulnerability during this critical stage. The placenta cannot block all environmental toxicants, the blood-brain barrier offers only partial protection, and postnatally, neurotoxins can be transferred through breast milk [79,80]. Chemicals such as Per and poly-fluoroalkyl substances (PFAS), Bisphenols (BPA, BPS), phthalates (N-butyl benzyl phthalate), and pesticides are found in human breast milk and also affect breast development and milk secretion. These chemicals act as endocrine disruptors, interfering with the HPA axis and influencing epigenetic mechanisms. This disruption contributes to precocious puberty, early-onset obesity, and associated metabolic syndromes [81-83]. Understanding the mechanisms behind developmental neurotoxicity is essential for effective preventive measures and creating targeted therapeutic interventions. Additionally, guidelines for testing developmental neurotoxicity may need to be re-evaluated. Policy makers need to push for the development and validation of innovative alternative models and tests for this purpose (see a recent review on risk assessment, alternative models, and recommendations [84]). Neurotoxicants can cause both acute and chronic effects. For instance, lead poisoning can result in psychosis, myelin loss, and axonal degeneration. Prolonged exposure to neurotoxicants is often linked to the onset of neurodegenerative diseases, such as AD and PD. Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been shown to induce behavioral symptoms resembling PD. While genetic factors are the primary contributors to AD, high levels of aluminum and zinc exposure have been proposed as potential risk factors. In addition to MPTP, various substances - such as industrial gases, organophosphate insecticides, certain pharmaceuticals, solvents like trichloroethylene, methanol, and ethanol, as well as household cleaners, metals, and pesticides (including paraquat and rotenone), and metals such as lead, iron, and manganese - have all been consistently implicated in the development of neurological diseases (see reviews [22,85]).

2.3. *Factors positively impacting neuroplasticity*

Exercise, diet, and sleep are key pillars of mental health due to their significant influence on brain structure and function. A healthy lifestyle depends on good nutrition, regular physical activity, and sufficient sleep [86]. A cross-sectional study found that quality sleep, adequate consumption of fruits and vegetables, and consistent exercise improve depressive symptoms and overall well-being in young adults [87]. Research in humans has demonstrated that exercise boosts levels of BDNF and other growth factors, promotes neurogenesis, enhances mental performance, and increases resilience to brain injury [88]. Epidemiological studies indicate that regular exercise lowers the risk of cognitive decline in older adults. Starting exercise even in mid-life reduces the risk of cognitive decline and dementia in later years [89]. Exercise helps mitigate neurodegenerative processes [90,91], improves mood in individuals with depression [92], and enhances cognition and sensory-motor attention in children with attention deficit hyperactivity disorder [93]. Animal studies have shown the beneficial effects of exercise on neuroplasticity. In AD mouse models, 12 weeks of treadmill exercise enhanced structural synaptic plasticity in the hippocampus and PFC [94]. Young male Wistar rats demonstrated improved motor performance and increased synaptic protein expression across limbic, striatal, and motor brain regions following acrobatic exercise, with or without an 8-week retention period, compared to sedentary rats [95]. Exercise intervention after brain injury improved the outcomes in patients and disease models. In a PD mouse model, intensive daily treadmill exercise improved motor function, enhanced dopamine release, and reduced dopamine clearance [96]. Physical exercise is a standard therapeutic component in stroke rehabilitation programs, where benefits including enhanced aphasia recovery, balance, and cognition are noted [97,98].

Many stimuli encountered by humans are beyond individual control, but nutrition is an exception. Certain diets positively influence neuroplasticity [100,101,99]. Randomized clinical trials show that vegetarian or plant-based foods - such as citrus fruits, grapes, berries, cocoa, nuts, green tea, and coffee - can improve specific cognitive functions, especially executive functions of the frontal cortex [102]. Intermittent fasting, exercise, and recovery cycles trigger repeated metabolic shifts, which have been shown to enhance neuroplasticity [103]. A recent meta-analysis highlighted the overall beneficial effects of whole-food diets on pain, emphasizing the need for further research in this area [104]. The influence of diet, such as the Western diet, ketogenic diet, caloric restriction, and interaction of diet with other exposomic factors on brain health was recently discussed in detail (see [105]). The study of nutrigenomics or nutrient-gene interaction was also reviewed to understand the basis of how micro and macronutrients in the diet influence mental health and cognition in conditions such as AD, dementia, and stroke [106]. ELS increases risky decision-making in adolescence. Nutritional supplements like saturated and polyunsaturated fatty acids during adolescence can mitigate this effect by restoring normal risk assessment and reducing anxiety-related risk-taking behavior [107]. This recent work highlights how interventions later in life can mitigate the effects of ELS or neuroplastic changes, promoting better brain health.

Sleep rejuvenates the brain, playing a crucial role in memory consolidation, learning, and neuroplastic mechanisms, and supporting recovery from clinical conditions like stroke, AD, and depression [108-110]. In rodent models, the sleep-wake cycle regulates gene transcription in the cortex and hippocampus, promoting synaptogenesis [111]. Thus, sleep enables homeostatic processes that optimize neural network function, essential for memory, cognition, behavior, and information processing [112]. In addition, several recent works on circadian influence on mental health have shown how the brain's clock

(suprachiasmatic nucleus in the hypothalamus) interacts with other peripheral local clocks (liver, muscle, adipose tissue) inducing genomic and epigenomic changes, to influence mental health, aging, and social behaviors [113-118].

Cognitive therapies and experience-driven activities, such as language learning, mindfulness meditation, and musical training, have demonstrated substantial positive effects on brain development and neuroplasticity in both humans and animals. A core principle of neuroplasticity is the "use it or lose it" concept. This highlights how learning, repetition, time spent in cognitively engaging activities, and the level of engagement can drive neurogenesis, synaptic plasticity, dendritic growth, and ultimately, neuroplasticity [119]. Sensory experiences, during critical developmental periods, rapidly organize the sensory-motor cortex. In adulthood, plasticity is more tightly regulated by complex cellular and molecular processes, yet remains susceptible to brain insults, resulting in neurological disorders like dementia, depression, and addiction [120]. A well-known example of learning-dependent neuroplasticity is the increased cortical representation of the fingers in violinists [121]. Learning highly rewarding musical stimuli can also drive neuroplasticity [122,123]. Studies have highlighted how music-induced plasticity can aid in preventing and treating neuro-psychiatric conditions, neurodevelopmental disorders, and acquired brain injuries (e.g., stroke), as well as support neurorehabilitation [124-128]. Similarly, participation in other cognitively stimulating artistic practices has been found to enhance neuroplasticity positively.

Environmental enrichment (EE) refers to a blend of complex inanimate and social stimuli [129]. In EE setups, lab animals are housed in spacious, stimulus-rich environments with a variety of objects that are frequently rotated and vary in shape. This setup aims to improve animal well-being by providing sensory and cognitive stimulation, increased physical activity, greater social interaction, and opportunities for exploration. EE significantly influences the central nervous system's function, structure, and gene expression both during critical periods and in adulthood. Animals in EE conditions show enhanced hippocampal LTP, linked to synaptic plasticity and memory [130]. Structural improvements include increased cortical thickness, enhanced dendritic branching, a higher density of dendritic spines, more synapses, and thickening of postsynaptic areas in regions like the hippocampus [131]. EE also boosts hippocampal neurogenesis, promoting the integration of new neurons into active circuits [130]. At the molecular level, EE alters the expression of genes related to neuronal structure, excitability, synaptic transmission, and plasticity [132]. It also modulates neurotrophic factors and neurotransmitter systems (cholinergic, serotonergic, and noradrenergic) systems across the brain [133,134]. Enrichment in humans involves social interactions, community activities, green spaces, culturally enriched environments, physical exercise, reading, meditation, and participation in artistic or creative pursuits [135,136]. Human-based EE research has shown that EE positively influences the brain's plasticity during early language or cognitive development [137] and among individuals with autism [138], traumatic brain injury [139], neurodegenerative diseases, and brain aging [140]. EE is now an integral part of management and rehabilitation programs for stroke patients (see reviews [141-143]). A summary of the mechanims through which the exposomic factors modulate neuroplasticity is given in Fig. 6.

3. Methodologies in exposomic research

The Exposome research can help identify specific environmental factors that contribute to neurological disorders. Currently, the effects of chemical or toxicological exposures are more extensively studied than biological exposures, as prior research largely focused on the acute impacts of biological factors. Furthermore, a key limitation in many exposome and health studies has been the narrow focus on individual elements of the environmental exposome and their connections to adverse health outcomes, including neurological ones. For example, multiple stressors such as psychosocial stress, socioeconomic status, and racial discrimination can collectively trigger chronic, stress-related noncommunicable diseases. Additionally, studies exploring the interaction between diet and chemical exposure have shown that dietary choices can influence how the chemicals affect the body [145,146]. Some of these factors may work synergistically to intensify the negative health outcomes. For example, a child exposed to ELS with a lower socioeconomic status in the family, adds up to induce higher neurological stress and adverse outcomes over the long-term. A few factors may nullify each other, such as ELS when combined with higher EE. Thus, exposomic

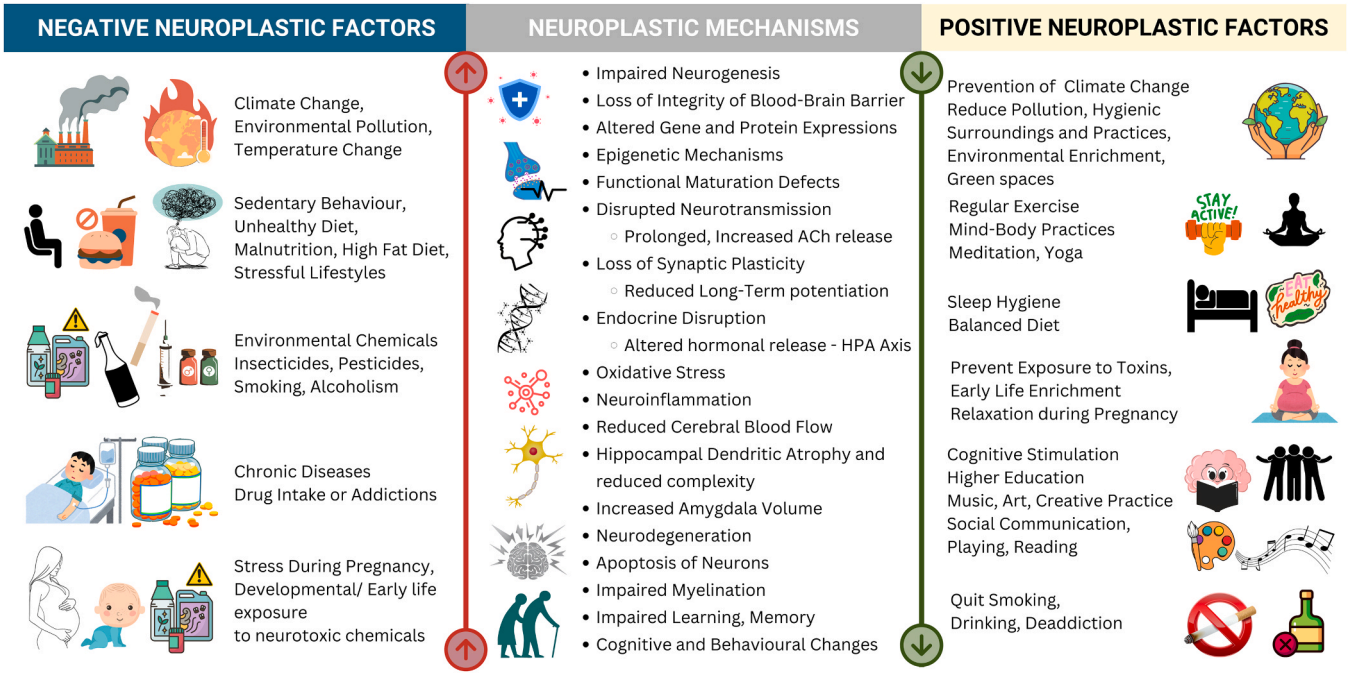

Fig. 6. Summary of the mechanisms through which exposome affects neuroplasticity. Multiple factors interact to either promote or suppress different domains of neuroplasticity and overall mental health [144].

research needs to integrate several exposomic factors to unravel the overall influence of these on an individual's health. The Genome-Environment-wide Interaction Studies (GEWAS) suggested analyzing only exposed subjects [147], which helps in improving efficiency, and reproducibility. There is still limited understanding of how combinations of various exposome factors impact health, and both epidemiological and toxicological studies often overlook the mechanistic links between exposure and disease. The recent exposome framework has advanced molecular toxicology by providing the tools for detailed mechanistic analysis of how the exposome affects health [148]. This framework emphasizes the need for multidisciplinary approaches to study the interactions. Some examples of such research initiatives include the European Human Exposome Network (EHEN) investigating environmental impacts on health [149]; the EU HEALS (Health and Environment-wide Associations based on Large Population Surveys) project [150]; the European Human Biomonitoring (HBM4EU) collaboration involving 30 European countries for hazardous chemical exposure assessment [151]; the Environmental Exposure Assessment Research Infrastructure (EIRENE) [152]; the France Exposome initiative [153]; the European Partnership for the Assessment of Risks from Chemicals (PARC) [154]; Human Early Life Exposome (HELIX) project [155], and the JHU Exposome Collaborative [156].

To highlight key methods and techniques used in large-scale exposome studies, the European Human Exposome Network (EHEN) serves as an example. The EHEN involves over 24 countries and 9 large-scale projects focused on understanding how environmental exposures throughout life impact human health. The project's primary goal is to ensure healthy living conditions by addressing environmental pollution, urbanization, air and water quality, hazardous chemicals, noise, industrial emissions, pesticides, and endocrine disruptors. One of its subprojects, Human Exposomic Determinants of Immune-Mediated Diseases (HEDIMED) [157], studies the effects of the exposome on diseases like type 1 diabetes, celiac disease, allergies, and asthma, tracking over 350,000 pregnant women, 30,000 children, clinical trial patients, and 7000 individuals through cross-sectional studies. The research emphasizes early life exposures and uses existing cohort data, health registries, clinical trial information, and environmental data, alongside new technologies like metatranscriptomics, sensors, and vigorous computational analysis. To assess a child's internal exposome, the project also explores cell cultures, gene expression, omics, epigenomics, non-coding RNA analysis, cytokine profiling, stool metabolomics, and circulating exosomes (see [158]). Similarly, LONGITOOLS (Dynamic Longitudinal Exposome Trajectories in Cardiovascular and Metabolic Non-Communicable Diseases), another project within EHEN, aims to study air quality, green space, noise levels, omics, and health trajectories, including anthropometry, glycemic index, cardiovascular, and lipid health from infancy to old age. The project plans to include over 11 million individuals across 25 projects in Europe, utilizing multiple cohorts, clinical trials, and databases [159]. These two examples demonstrate the feasibility of such approaches through multinational, interdisciplinary, multi-lab collaborations, highlighting how efficient health record systems and registries can support exposome research and long-term health follow-up. The other seven projects under EHEN include: REMEDIA, which examines the impact of exposome on lung disease [160]; Advancing tools for human early lifecourse exposome research and translation (ATHLETE), focusing on child health and brain development, following over 80,000 mother-infant pairs [161]; Exposome project for health and occupational research (EPHOR), which incorporates low-cost sensors for measuring occupational exposure to ultraviolet radiations, light, temperature, noise, and air pollutants, electrostatic stationary dust sampler at homes, along with small wearable samplers for untargeted substance detection [162]; EXIMIOUS, maps exposure-induced immune effects [163]; Early environmental quality and life-course mental health effects (EQUAL-LIFE), studying environmental pollutants, lifestyle, and socioeconomic background's impact on mental health in over 200,000 children from fetal life to 21 years [164]; EXPANSE, focuses on exposome-powered tools for promoting healthy living, in urban settings with focus on cardiometabolic-pulmonary health [165]; and HEAP, which aims to enhance bioinformatics tools for exposome data collection and analysis. The HEAP platform uses human cohorts screened for cervical cancer and pregnancy, combined with consumer purchase data (Purchased: Yes/No response) for over 10000 products from regional stores. HEAP tracks the exposure to exposome and their health effects over time using genomic, epigenomic, microbiome, metabolomic data, innovative wearable sensors, and advanced statistics [166]. Expanding such research to understand neuropsychiatric conditions and brain health is essential, as brain health, like overall health, results from a complex interaction of various factors.

Note that Multi-omics encompasses the comprehensive study of the genome, transcriptome, epigenome, proteome, and metabolome, each of which contributes to shaping an individual's phenotype. These molecular layers are constantly influenced by environmental factors, which interact with the genome to drive epigenetic modifications. Such changes regulate gene expression, impacting RNA transcription, protein synthesis, cellular functions, and metabolite production. In turn, these molecular processes create feedback loops that modulate cellular mechanisms, influencing physiological functions. The dynamic shifts in the biological systems across an individual's lifespan play a crucial role in health, adaptation, and disease susceptibility. By integrating multi-omics approaches, we can systematically measure these intricate molecular level interactions and their impact on the biological processes (Fig. 7). Genomics is the study of an organism's complete set of DNA, including genes and regulatory elements, to understand genetic variations, mutations, and structural changes that influence traits and diseases, measured using whole-genome sequencing, whole-exome sequencing, and genotyping arrays. Epigenomics investigates chemical modifications to DNA and histones that regulate gene expression without altering the genetic code, influencing cellular identity and response to environmental factors, measured using techniques like DNA methylation arrays, chromatin immunoprecipitation sequencing (ChIP-seq), and ATAC-seq. Transcriptomics examines RNA transcripts to assess gene expression patterns, alternative splicing, and regulatory networks that shape cellular functions, measured using RNA sequencing (RNA-seq) and microarrays. Proteomics analyzes the complete set of proteins expressed in a cell, tissue, or organism to understand protein interactions, modifications, and functional pathways, which is measured using mass spectrometry (MS)-based proteomics. Metabolomics focuses on small-molecule metabolites to reveal biochemical activities, metabolic pathway alterations, and disease biomarkers and is measured using nuclear magnetic resonance (NMR) spectroscopy and MS-based metabolomics (Fig. 7). Microbiomics has been also added to this list which involves studying all the microorganisms. Trans-omics refers to the integrated analysis of multi-omics data, to uncover the cross-links between these molecular layers and their functional interactions [167,168].

4. Neural exposome and recommendations for integrated research

Although the concept of exposome on neuroplasticity is new, the awareness of the inclusion of an overall integrated study of the exposome in understanding neuropathologies and the development of novel preventive and therapeutic strategies for the same is catching up. For example, a call for more work on the study of environmental factors in the pathophysiology of Amyotrophic lateral sclerosis was made [169]. To the best of current knowledge, only a few examples exist to date that address the neuroplasticity effects of individual exposomic factors. A recent study used metabolomic profiling of mothers' milk, along with machine learning (ML), to predict neurodevelopmental delays in infants [170]. Ethnicity-related differences in metabolites among individuals at higher risk for stroke and AD were noted [171,172]. A metabolome-wide association study identified 191 plasma biomarkers associated with

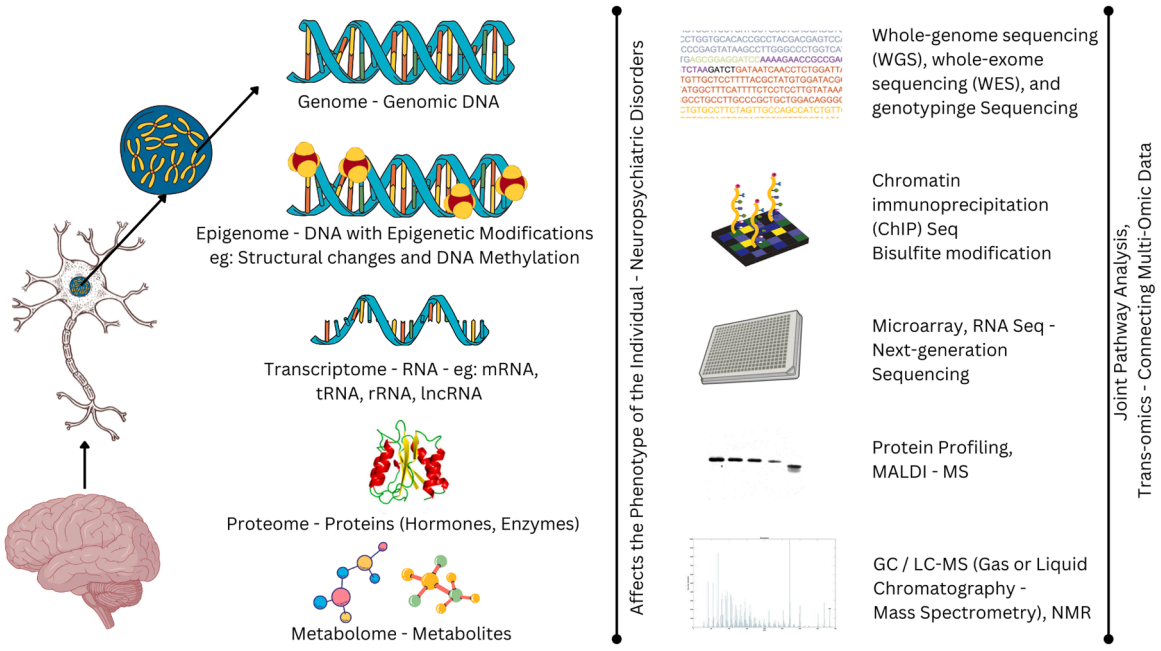

Fig. 7. Multi-Omics, Joint pathway analysis, and Trans-Omics are essential in Exposomic and Neuroplasticity Research. Genome, epigenome, transcriptome, proteome, and metabolome determine the overall phenotype of the individual and the occurrence of neuropsychiatric diseases. DNA – Deoxyribonucleic acid; RNA – Ribonucleic acid; mRNA (Messenger RNA); tRNA (Transfer RNA); rRNA (Ribosomal RNA); lncRNA (Long Non-Coding RNA); MALDI-MS (Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry); NMR (Nuclear Magnetic Resonance) Spectroscopy. Note: The brain contains both neurons and glial cells. The neuron is shown here only for representation purposes. Exposomic research requires to incorporate analysis of both to understand overall mechanisms and functional alterations in the brain.

Credits - Under Creative Commons Licences: Whole Genome Figure reproduced from Liu, D. et al. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-019-0501-5 (2020), Springer Nature Ltd; Chip Seq Figure from https://commons.wikimedia.org/wiki/File:Exome_Sequencing_workflow_1b-es.png; Mass Spectrometry graph from https://commons.wikimedia.org/wiki/File:Desmosterol_Mass_Spec_new.jpg.

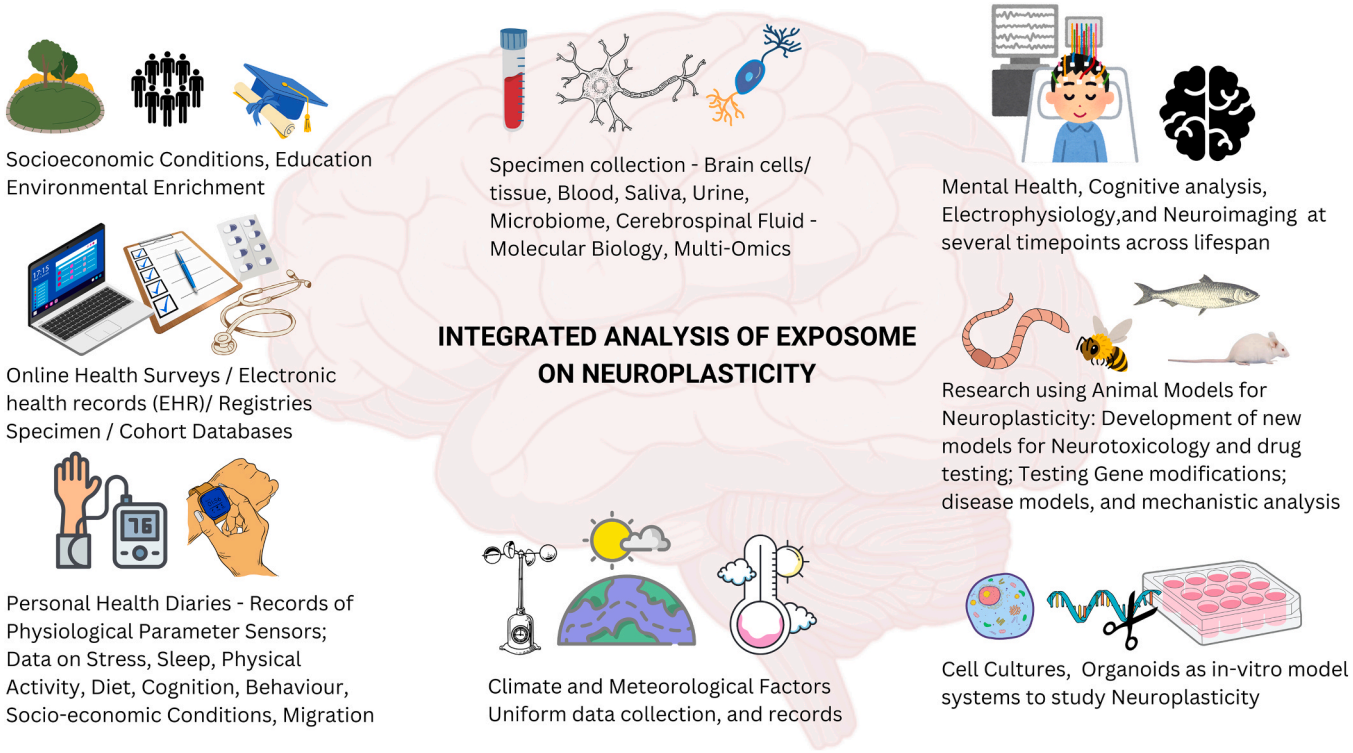

Fig. 8. Proposed integrated approach to study the neural exposome.

autism spectrum disorder (ASD), highlighting O-phosphotyrosine to have low odds for autism and glutathione to be associated with higher odds of ASD [173]. The NEUROSOME, a dedicated exposome-based project explored the causal links between genetic predispositions, cumulative environmental exposures, and neurodevelopmental disorders in children. By combining multiple mother-child cohorts, the project examined the impact of exposures - such as in-utero exposure to heavy metals and environmental toxins. The project also collected data on lifestyle, socio-demographic factors, and genetics, important in shaping neurodevelopmental conditions. In addition to human monitoring, the study incorporated experimental in-vivo and in-vitro analyses [174]. These studies have attempted to comprehensively examine the combined impact of exposomic factors on neuroplasticity and neurological outcomes, highlighting a critical gap in the field. The neural exposome (ONETOX), was initiated by the National Institute of Health (NIH) National Institute of Neurological Disorders and Stroke, to more actively involve the neuroscience community in exposomic research, with dedicated funding. The chief aim was to address non-genomic and environmental factors alongside genomic factors that contribute to neurological disorders with complex etiologies such as epilepsy, PD, AD, spinal cord injury, traumatic brain injury, and stroke [175,176]. While cohort studies demonstrate the environmental contributions to neurological disease onset and progression, the pace of mechanistic investigations has not kept up with the rapid emergence of cohort data. It has highlighted the challenges in translating findings from exposome research into targeted therapies [176].

An integrated approach to studying neuroplasticity following exposome exposure would incorporate a variety of methods, including socio-demographic data, lifestyle factors, dietary habits, and advanced omics techniques, alongside neuroimaging, electrophysiology, behavioral studies, and relevant technologies (Fig. 8). However, some elements of neural exposome research are integral to exposomics as a whole, as previously discussed. Additionally, factors such as education levels, and stress which specifically influence the brain, should be tracked and incorporated into exposomics data to better understand their impact on neuroplasticity, neurological outcomes, and predictive models.

4.1. *General components of exposomic research*

Exploring exposome-dependent neuroplasticity requires leveraging data from existing cohorts, clinical trials, pre-existing databases, and health registries. Similar to other exposome studies, it is crucial to track lifestyle factors, stress levels, socio-economic conditions, diet, and habits related to drugs, alcohol, and smoking to understand related neuroplastic changes. Additionally, family health history and pre-existing medical conditions should be monitored through health registries. Health-based questionnaires (covering all the aforementioned factors, socio-demographics, physical quality, well-being, and quality of life (QoL) [177]) administered by health professionals and online surveys would help in regularly updating individual-level data within a community or population. Questionnaires to record diet (Diet History Questionnaire III (DHQ III)) [178]; alcoholism - The Alcohol Use Disorders Identification Test (AUDIT) [179]; physical activity such as Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Global Physical Activity Questionnaire (GPAQ), and Six-Minute Walk Test (6MWT) [180,181] are the few examples of the exhaustive list of validated questionnaires that exist for collecting exposomic data. Continuous collection of pathophysiological data through wearable sensors is essential to capture time-based variations across individuals. Existing systems for tracking physiological parameters, such as smartwatches and actigraphy devices, should be complemented with the development of new technologies to monitor metrics like temperature, heart rate, blood pressure (via wearable electrocardiogram, ECG or photoplethysmogram, PPG sensors), blood oxygen levels (pulse oximeters), respiration (chest bands), and physical activity (accelerometers). Electronic health records (EHR) offer valuable longitudinal clinical data, lab results, and neuroimaging, which can complement multi-omics and wearable technologies [182]. Moreover, local and regional data on meteorological factors, pollution levels, and exposures to toxins such as insecticides, pesticides, heavy metals, and other drugs must be regularly recorded. By combining this information with biomonitoring data, computational and systems biology approaches can guide preventive and therapeutic measures at the individual, family, community, or population levels [148,183,184].

4.2. *Specific components of neural exposomic research*

Neural exposome research requires the collection of specific data related to mental health outcomes, including sleep patterns, stress, anxiety levels, depression indices, sensory issues (eg: loss of sensation, tingling), and motor behaviors (eg: gait, tremors, muscle tone). Cognitive and mental health assessments or questionnaire data need to be collected. Pre-existing validated questionnaires such as the Mini-Mental State Examination (MMSE) [185], Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI) [186]; Stress and Anxiety measuring questionnaires such as the State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety [187] need to be collected. Sleep monitoring using actigraphy devices or sleep-tracking rings, stress assessment via heart rate variability or galvanic skin response, and movement tracking through GPS-enabled devices are essential components. Serial measurements of motor, sensory, and behavioral assessments of learning, memory, and adaptation need to be made to track the changes over time, and correlated with exposomic exposure. ELS is a key factor influencing the onset of neuropsychiatric and neurological disorders, making it essential to track ELS data in neural exposome research [188,189]. Other factors, such as education level, play a significant role in cognitive function and neurocognition, with higher education correlating with better cognitive reserve as individuals age [190,191]. Tracking education levels and implementing policies to improve them can further support neuroplasticity research.

In parallel, an integrated molecular biological (gene or protein expression, immunoreactivity), and multi-omics approach (Fig. 6) that incorporates genomics, epigenomics, proteomics, and metabolomics is crucial. For instance, DNA methylation is a powerful tool for linking early-life exposures to long-term health effects, addressing challenges in exposome measurement [192]. Additionally, microbiome data, which is linked to conditions like AD, PD, and autism, should be integrated into exposome research [193]. Further advancements in understanding the exposome's impact on neurological conditions require innovative experimental models. Currently, limited data links specific environmental exposures to specific neuroplasticity markers, such as neurogenesis in the neurogenic zone, dendritic morphology, habituation, sensitization, synaptic density alterations, and synaptic plasticity as evidenced by electric potential variations (long-term potentiation/depression), neural connections, cell shape, size, and myelination, necessitating further in vitro and vivo studies. In-vitro cell or tissue cultures and brain organoids are powerful tools to delineate the mechanistic pathways and probable strategies to combat the negative effects of different exposome factors, including genetic modifications, and climate change put together in a dish [194,195] and are feasible within a short duration. Complying with the 3R principles for animal research (Replacement, Refinement and Reduction) , neuroplasticity analysis using embryo stages and larval forms of animals (*Caenorhabditis elegans*, drosophila, or zebrafish) facilitates research on various adverse outcome pathways (AOPs) for toxicological and chemical studies, and also the development of new reliable and sensitive models for exposome research [196-198]. A recent review proposed the development of novel mouse strains to understand the effect of the exposome on AD and also detailed several ML approaches that one could use to predict the occurrence and progression of AD [199]. Recent work suggests the use of

simple genetic models like Drosophila to study gene-environment interactions. These models can help analyze the effects of known single nucleotide polymorphisms associated with PD and expand our understanding of brain bioenergetics, behavior, and neurodegeneration. Additionally, in-vitro models like patient-derived induced pluripotent stem cells (iPSCs) and organoids were suggested to offer promising platforms for exploring the exposome's impact at the cellular level [200]. Databases such as the NIH Library of Integrated Network-based Cellular Signatures (LINCS) library provide valuable data on human inducible pluripotent stem cells (hiPSCs) and scientists can use this to understand how cells respond to various genetic and environmental stressors, supporting the development of targeted therapies for neurological disorders [201].

Incorporating advanced neuroimaging and electrophysiological techniques is also vital for understanding the neuroplastic effects of the exposome. To assess the broader effects of exposome factors on brain function, connectivity, and plasticity, neuroimaging and electrophysiological techniques are valuable. Functional MRI (fMRI) and positron emission tomography (PET) provide insights into brain activity and metabolic processes, while electroencephalography (EEG) and magnetoencephalography (MEG) offer high temporal resolution of neural dynamics. Diffusion tensor imaging (DTI) and digital tractography assess structural connectivity, and synaptic plasticity can be studied through electrophysiological methods like patch-clamp recordings. However, collecting comprehensive neuroimaging and electrophysiological data from every individual in a community is not feasible. Instead, such data can be retrieved from existing patient databases or collected during routine health check-ups. Additionally, portable two-channel EEG devices can serve as physiological sensors to monitor activity- and experience-dependent neural changes over time. Integrating these diverse data sources enables a comprehensive understanding of how environmental and internal factors, such as chronic stress and disease, influence brain function over time. This holistic approach is essential to uncovering the subtle, cumulative neurobiological effects of lifelong exposome exposures (Fig. 9).

5. Potential challenges in exposomic research and possible solutions

Exposomic research presents numerous challenges, yet through a unified approach and increased global awareness, many of these issues can be addressed effectively. The exposome is inherently interdisciplinary, requiring collaboration among medical professionals, epidemiologists, geneticists, molecular and systems biologists, bioinformaticians, climate and environmental scientists, corporate stakeholders, policymakers, and artificial intelligence (AI) and machine learning (ML) experts. Addressing these challenges necessitates changes in health data collection, technological policies, record-keeping, data sharing, and ethical and legal frameworks.

a) Standardization, Comparability of Data, and Predictive Modelling: A major issue in exposomic research is the lack of standardized methodologies and data across studies. Dependability on pre-existing cohort data or health registry data has several disadvantages. EHR data from individual clinical visits are often sparse, and it is not yet globally standardized. Variability exists in data collection techniques, terminologies, specimen collection, and technologies used in both environmental and internal exposome assessments. Sample size in each sub-groups across the studies remains currently unplanned, and non-uniform. For instance, large-scale projects like LONGITOOLS [159] have demonstrated inconsistencies in lifestyle, behavioral, and omics data availability across different age groups. Additionally, meteorological data collection and technological differences create regional variations that affect generalizability. Harnessing AI/ML for exposome research requires structured and high-quality data. However, inconsistencies and gaps in available datasets limit predictive modeling capabilities for disease risks, aging trajectories, and intervention responses.

Solution: Although seen as constraints in these initially planned big data exposomic projects that include pre-existing data, with increasing global awareness of the exposome, the lacunae can be reduced through the development of better health data collection systems, and infrastructure. Establishing standardized sociodemographic data, health data collection protocols, standard specimen collection protocols and databases, and reference datasets, similar to initiatives like the 1000 Genomes Project [202], would enhance data consistency. Centralized health databases and biobanks for storing biospecimens (blood, serum, urine, saliva, cerebrospinal fluid, and tissues) would serve as essential resources for exposomic research. AI/ML should be integrated with exposome data while adhering to standardized data collection and storage protocols. Global health authorities should collaborate to create unified health monitoring systems. A suggested possibility is to develop standardized scales (e.g., 1–10) to assess key health parameters such as diet, lifestyle, physical activity, and behavior. Combine genomic, epigenomic, transcriptomic, proteomic, and metabolomic data into a unified health index. For example, polygenic risk scores (PRS) are already used to assess genetic predispositions to diseases [203]. Using these scales and scores to generate a comprehensive health score index for

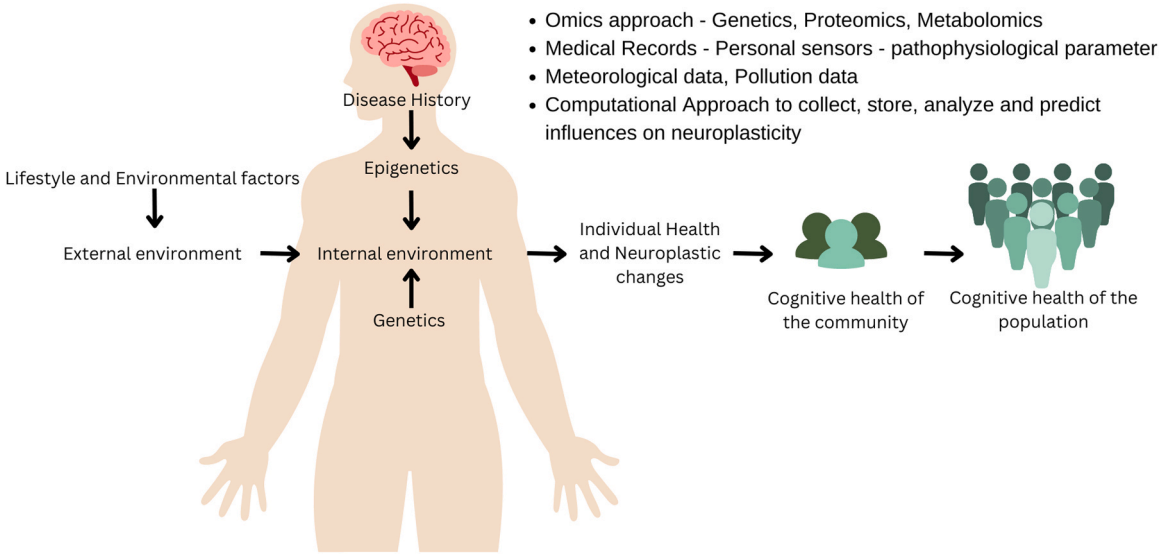

Fig. 9. Summary of exposome and its influence on brain plasticity and approaches to study the same.

each individual and tracking it over their lifespan, ensures uniform and measurable data collection worldwide, enabling consistent health monitoring at the individual, community, and global levels. Additionally, by analyzing trends over time, this system can help predict future health outcomes, allowing for proactive interventions and policy development. Ultimately, it facilitates the creation of a personalized health index for every individual. Using AI/ML to predict disease risks, aging trajectories, and responses to interventions, makes such a scoring system not just descriptive but also predictive. Predictive modeling allows individuals and communities to be informed about potential health consequences and take preventive actions to mitigate future risks and negative health outcomes. In the short term embracing data imperfections, as advocated by Gary W. Miller in 'Exposomics: Perfection Not Required' [204], will allow researchers to advance the field despite current limitations.

b) *Cost and Resource Constraints:* Advanced exposomic research, the sensors for physiological data collection, and multi-omics analyses (genomics, proteomics, metabolomics, epigenomics, and transcriptomics), are often expensive and resource-intensive. Furthermore, data storage of such big data at the population level is difficult to handle. This makes it inaccessible to many low- and middle-income countries, limiting global participation in exposomic research.

Solution: The development of cost-effective, scalable, and globally accessible technologies for data collection, processing, and storage is crucial. International funding agencies should support the expansion of exposomic research infrastructure in resource-limited settings, enabling broader participation. One example of making exposomic research cost-effective is treating every contact of an individual with the health care system as an integral time point to understand the effect of the exposome on the health of the individual at that point. To facilitate meaningful exposome research and proactive public health interventions, schools and workplaces may implement policies for routine health and exposure data collection and reporting. These data should be systematically recorded and made accessible to local healthcare professionals and assigned exposome researchers through a centralized system. This would not only advance exposome-related research but also enable cost-effectiveness.

c) Others: Several other challenges pertain to exposomic research such as data integration, accessibility, ethical, and legal issues, translatability, and policy implementation. Managing and integrating diverse exposome data remains a complex task. Large-scale exposome projects often rely on pre-existing data, which may not comprehensively cover all relevant environmental or biological factors. Furthermore, differences in data governance and privacy laws hinder data sharing and accessibility. Handling exposome data involves ethical concerns regarding privacy, data security, and informed consent. Legal frameworks for data sharing vary across regions, making international collaborations challenging. Despite advancements in exposomic research, the immediate translation of findings into health policies remains limited. Few countries have integrated exposomic data into public health strategies. Thus the immediate translatability of the conclusions drawn to make policies and changes to promote global health is still less understood; slowing the overall impact on global health improvements.

Solution: Implementing data federation techniques to connect scattered resources would facilitate AI-driven predictive analysis and data sharing while maintaining compliance with the FAIR principles (Findable, Accessible, Interoperable, and Reusable) [205,206]. Establishing internationally accepted ethical guidelines and legal frameworks for exposome data handling is essential. Policymakers should work alongside legal professionals to ensure compliance with global standards while protecting individual privacy. Policymakers, politicians, and global health authorities must collaborate with researchers to translate scientific findings into actionable health policies. This is possible through a global increase in awareness of the concept of the Exposome, radical change in health data collection, health, and technological policies, record keeping, sharing, and handling of ethical, and legal issues

Table 2
Strategies to overcome challenges in exposomic research and enhance integrated health analysis.

Category	Proposed Solutions and Recommendations
Awareness, Education, and Policy Development	Global awareness of the exposome concept through education, policy-making, public health initiatives, and dedicated funding.
Standardization and Uniform Data Collection	Implementation of standardized health assessments at defined time points across an individual's lifespan, recorded through a global uniform system. Development of global health record-keeping technologies to support cross-regional data integration. Establishment of uniform protocols for environmental and meteorological data collection worldwide.
Genomic and Epigenomic Research Integration	Creation of a genetic database for every individual. Systematic collection of multi-omics data (genomics, epigenomics, metabolomics, proteomics) at regular intervals to track molecular health trajectories. Analysis of omics after multi-exposure interactions and dose-dependent effects over time (using in vitro / in vivo methods). Research on potential reversal mechanisms for adverse genomic and epigenomic modifications.
Longitudinal and Personalized Health Monitoring	Establishment of large-scale, lifelong cohort studies to assess long-term exposomic effects on health. Encouragement of self-monitoring practices using lifestyle tracking tools, wearable sensors, and digital health assessment kits, with regular reporting (e.g., 2–3 times per year). Self-reporting of lifestyle, dietary habits, and mental health status through digital surveys and structured questionnaires. Maintenance of personal health records, including stress, sleep, and physical activity logs, accessible to local healthcare providers.
Predictive and Preventive Health Strategies	Integration of predictive health analytics to assess and communicate potential adverse health risks based on self-reported data, sensor readings, and environmental exposure levels. Fetal genome predictions based on parental genetic data. Development of genome-based prediction models for individual resilience or susceptibility to environmental stressors and diseases. Development of predictive models for epigenomic variations at individual and community levels, including cross-cultural and migration-related epigenetic changes. Repeated analysis of epigenomic changes following exposure to specific environmental factors will possibly enable predictive modeling of such changes based on an individual's genome, environmental history, and other exposomic data, along with forecasting their potential health consequences.
Infrastructure and Ethical Considerations	Establishment of biospecimen banks (e.g., stem cell repositories, postmortem tissue collections) for research into disease mechanisms. Development of a globally standardized digital health record system to facilitate secure data sharing and interoperability. Ensuring robust security, privacy, and ethical guidelines for exposomic data collection, storage, and accessibility. Establishment of regional and global organizations to address ethical and legal considerations in exposomic research. Development of Affordable Technologies for Data Collection and Storage - Innovations such as portable biosensors, AI-driven data compression, and cloud-based platforms with open-access

(*continued on next page*)

Table 2 (*continued*)

Category	Proposed Solutions and Recommendations
	frameworks can help democratize exposome research and ensure equitable participation worldwide.

(Table 2).

6. Conclusion

The genetic factors contributing to neurological disorders such as Parkinson's and Alzheimer's disease have been traced, but much of the data remains epidemiological, with only a few mechanistic links between environmental exposures and neuroplasticity identified. This review details the various non-genomic (environmental) and internal factors influencing neuroplasticity and the underlying mechanisms. Understanding the overall interaction of several such exposures with an individual's genetic makeup to impact the nervous system function throughout their lifespan, is essential, yet challenging to study. Future research should try to adopt an integrated approach to encompass several exposomic factors, tracking the sociodemographic, lifestyle factors, genomic, and epigenomics of individuals in combination with the environmental exposures and changes in neuroplasticity. One could draw several lessons from the currently ongoing or completed exposome research works studying other organ systems. Such an approach when applied to studying mental health, will provide a comprehensive understanding of the key drivers of neurological diseases, particularly the gene-environment interactions and the role of the exposome in neuroplasticity. Although exposomic research faces several challenges, standardized methodologies, improved data integration, cost-effective technologies, ethical frameworks, and predictive AI models can enhance its global applicability. Yet, due to the large-scale data that is required to be integrated into understanding the exposome effect on neuroplasticity, or health, one needs to embrace the inherent complexities and imperfections in exposomic data to advance the field effectively. By fostering international collaboration and policy development, exposomic research can contribute significantly to understanding and mitigating the overall, and specifically mental health impacts of environmental exposures, worldwide.

CRediT authorship contribution statement

Kirthana Kunikullaya U: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Visualization, Writing – review & editing.

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Data Availability

No data was used for the research described in the article.

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