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EC NEUROLOGY
Review Article

Artificial Intelligence in Predicting and Modeling Neurotoxic Outcomes

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Received: September 12, 2025; **Published:** October 07, 2025

Abstract

In toxicology, AI tools have been shown to be beneficial in predicting and modelling the neurotoxic outcome. Past neurotoxicity assessments were conducted through laboratory animals and cell cultures. These assessments took a lot of time and were also subject to debate. AI techniques, such as machine learning and deep learning algorithms, can be utilized for integrating high dimensional biological, chemical and omics data to identify predictive neurotoxicity biomarkers and mechanistic pathways. With these methods, predictive models can be built which can simulate the neuronal response to chemicals, evaluate the dose-response, and predict delayed neurotoxicity. AI further facilitates high-throughput screening by lightening experimental burdens while increasing accuracy and reproducibility. Despite having all these benefits, there are still some challenges that need to be faced like data heterogeneity. The future will see more AI used with systems biology, computational neuroscience, population based medicine, and personalized medicine, to assess risk and work on therapy. Artificial intelligence represents a powerful new paradigm in the prediction and modelling of neurotoxic outcomes and could increase the efficiency, efficacy ethical and predictive capabilities of toxicology.

Keywords: *Artificial Intelligence; Neurotoxicity; Predictive Modeling; Machine Learning; Risk Assessment*

Introduction

The human brain exhibits heightened sensitivity to injury, and its neurodevelopmental processes-neural progenitor cell proliferation, apoptosis, cell migration, neuronal differentiation, neurite outgrowth, myelination, synaptogenesis, and neurotransmitter development-are particularly vulnerable to external perturbations [1]. Disruption of these processes precipitates neuroanatomical, neurophysiological, and neurochemical anomalies [2]. Developmental neurotoxicity (DNT) disorders currently affect approximately 10 - 15% of births worldwide, with the incidence of autism and attention deficit hyperactivity disorder (ADHD) rising [3]. Evidence suggests that DNT disorders in childhood may predispose individuals to neurodegenerative diseases such as Alzheimer's and Parkinson's in later life [4].

Although genetic factors account for around 30 - 40% of DNT cases, environmental chemical exposure remains a principal determinant [5]. Thousands of substances have been implicated in acute or chronic neurodevelopmental damage, and the total number of neurotoxic chemicals is likely underestimated [6].

Background on neurotoxicity

Neurotoxicity refers to exposure to natural or synthetic substances that adversely affect the structure or function of the nervous system [1]. Neurotoxicants are distributed throughout the environment and human exposure is often an involuntary consequence of our everyday lives [7]. Because nervous system functions-including perception, memory, and motor control-are so critical to survival and quality of life, central nervous system (CNS) health and neurotoxic exposure are of serious concern [2]. The nervous system is vulnerable to chemical toxicants and is often targeted at low exposure levels [8]. Even small degrees of nerve damage can cause functional deficits that significantly decrease motivation, self-care, and productivity [9].

Several neurotoxicants impact CNS activity and structure, and potentially lead to chronic neurodegeneration. Neurotoxic mechanisms often trigger oxidative stress or disrupt neuronal function by modulating neurochemical signals, neurotransmitter production, or neurotransmitter metabolism through dopamine, serotonin, acetylcholine, or γ-aminobutyric acid (GABA) pathways [10]. Despite widespread concern, neurotoxicity screening remains largely anecdotal, and is predominantly limited to case reports and protocol-driven chemotherapeutic investigations [11]. Furthermore, experimental studies to determine neurotoxicity require specialized chemistries and labor-intensive techniques, making them costly even when analyzing one chemical at a time [12].

Definition and types of neurotoxins

Neurotoxins are substances that damage or destroy neurons, the fundamental components of the nervous system [13]. Neurotoxicity arises from various chemical, biological, or physical agents causing reversible or irreversible adverse effects on neuronal structures or functions [2]. Endogenous neurotoxins, such as neurotransmitters, free radicals, and cytokines, have biological functions at physiological concentrations but become harmful at elevated levels [14]. Exogenous neurotoxins include heavy metals, chemicals, environmental pollutants, and biological toxins [15]. These neurotoxins can enter the brain, disrupt its protective structures, and induce irreversible damage to nervous tissue through mechanisms like excitotoxicity, generation of reactive oxygen species, inflammation, and apoptosis [16]. Characteristic signs of neurotoxicity encompass neuronal injury, death, and altered activity in both the peripheral and central nervous systems, manifesting as symptoms that range from transient neuronal dysfunction to coma and death [17].

Mechanisms of neurotoxic damage

A comprehensive understanding of structure-activity relationships (SARs) and neurotoxic pathways is paramount in predicting and modelling neurotoxic outcomes [18]. The human brain is particularly susceptible to injury during neurodevelopmental processes such as neural progenitor proliferation, apoptosis, migration, differentiation, neurite outgrowth, myelination, synaptogenesis, and blood-brain barrier formation [19]. Disruption of these processes may lead to adverse neuroanatomical, neurophysiological, and neurochemical changes [1]. Developmental neurotoxicity (DNT) disorders currently affect approximately 10 - 15% of births, with an increasing prevalence of autism spectrum disorders and attention deficit hyperactivity disorders; early-life disorders may also confer susceptibility to neurodegeneration later in life [20]. While genetic factors account for roughly 30 - 40% of DNT cases, there is strong suspicion that environmental chemical exposure plays a substantial role [8]. Thousands of chemicals are recognized or suspected neurotoxins, and the actual number is likely underestimated [5].

Basic mechanisms of neurotoxicity include organelle dysfunction, oxidative stress, altered neurotransmitter levels, and neuroinflammation [21]. Consequently, chronic exposure to low doses of environmental chemicals can engender adverse outcomes leading to disorders such as Parkinson's, Alzheimer's, Parkinsonism, epilepsy, and memory deficits [2]. These effects may arise from a single mechanism that initiates various pathological events or from the combined influence of multiple initiating events acting individually or synergistically [22]. Throughout developmental and adult stages, a single adverse outcome may result from different molecular initiating events [23].

Hazard assessment requires detailed mechanistic information that maps molecular initiating events onto physiological and behavioural outcomes linked to DNT pathways [24]. This information supports the creation of computational models capable of predicting whether a chemical will induce specific neurotoxic events [25]. Kinetic models based on cellular compartments can simulate how a molecule reaches target tissue and predict its accumulation [26]. Toxicodynamics provide a general description of how a molecule perturbs cellular structures; dynamic-deterministic models allow for the prediction of multi-organ effects based on exposure parameters [27]. Artificial intelligence models are essential for simulating the effects of repeated low-level exposure to neurotoxic compounds [28].

Impact of neurotoxicity on human health

The impact of neurotoxicity on human health is broad, ranging from impaired motor skills to neurodegenerative diseases [29]. Neurotoxicity affects a significant portion of the population, as 10 - 15% of births experience lifelong neurological impairment, often resulting in conditions such as autism and ADHD; these disorders further increase susceptibility to age-associated neurodegeneration [30]. Genetic components account for roughly 30 - 40% of neurotoxin-related disorders, indicating that environmental chemical exposures substantially influence the prevalence of neurological conditions [1]. Although a small fraction, only 20 substances, of the several thousand chemicals known to affect neurodevelopment or nervous system function are tested for their neurotoxic potential, suggesting an underestimate of the true extent of the problem [25]. Traditional testing methods are resource- and time-intensive and thus unsuitable for large-scale screening [3]. Computational toxicology provides a promising alternative as it enables the prediction of chemical toxicity based on molecular structures; quantitative structure-activity relationship (QSAR) models quantify relationships between structural attributes of molecules and toxicological effects [31]. The adverse outcome pathway (AOP) framework supports systematic organization of mechanistic toxicity information by linking molecular initiating events (MIEs)-such as chemical binding to macromolecules-to sequences of key events that may culminate in adverse outcomes [32]. When a chemical activates an MIE pertinent to a neurotoxic AOP, it is considered potentially neurotoxic [33]. Hence, by combining QSAR models with AOPs, it becomes feasible to estimate a chemical's likelihood to modulate neurotoxic MIEs, enabling prioritization for follow-up studies [34]. An integrated computational system exemplifies this approach by predicting neurotoxic potential through the identification of activated MIEs from an AOP network and subsequent QSAR modeling, thereby facilitating early chemical screening and targeted testing [35].

Artificial intelligence overview

Artificial intelligence (AI) involves creating machines capable of performing tasks characteristic of human intelligence [36]. By examining the human brain, researchers aim to extract practical guidelines for developing such intelligent artifacts [37]. AI encompasses a wide range of research directions [38]. Traditional branches include systems that think like humans, systems that act like humans, systems that think rationally, and systems that act rationally [39]. Contemporary approaches focus on intelligent agents, defined as systems capable of autonomous perception of their environment through sensors, goal formulation, and execution of actions via actuators to achieve those goals [40].

Definition and types of AI

Artificial intelligence (AI) is defined as the simulation of human intelligence by machines. Three main types of AI-narrow, general, and super-that vary in scope and capability have been distinguished [41]. In narrow AI, the system is designed to perform one specific task [42]. General AI performs any intellectual task that a human is capable of doing, and super AI possesses capabilities that exceed the capacities of humans [42]. Significant advances in AI applications have been made in various medical fields, including drug discovery and diagnostics; imaging and healthcare management; and patient care and clinical support [1].

Several types of AI systems are broadly used. Machine learning (ML) provides algorithms and statistical models for vehicles to accomplish tasks with limited human intervention and training [43]. The scheme is widely used in tissue identification and tumour diagnosis; drug delivery and development; biomarker discovery and innovation; and patient stratification and personalized treatment [2]. Deep learning (DL) systems simulate the human brain and use neural networks with multiple layers to analyze data [44]. The approach has been used for an array of applications, including protein structure prediction; the design of drug candidates and peptides; genomic sequence analysis; and rapid food and drug safety analysis [45]. Natural language processing (NLP) permits computers to analyse and interpret human language; in hospitals, NLP automates medical coding and transcribes medical records [46]. The approach has also been used for drug development; pharmacovigilance; clinical decision support; and precision medicine [47].

Applications of AI in healthcare

Artificial intelligence (AI) encompasses technologies that enable computers to execute tasks previously thought to require human intelligence [48]. Machine learning is a subset of AI wherein algorithms discern generalizable patterns in data without explicit programming [49]. Ensemble learning extends this concept by combining multiple machine learning classifiers, which enhances predictive performance and robustness owing to a diversity of model structures [50]. These configurations facilitate the extraction of meaningful insights from voluminous datasets [1]. Medical professionals employ AI applications to support clinical decision making [51]. For example, machine-learning algorithms can efficiently explore extensive medical databases of millions of records to recognize acute neurological conditions such as strokes and seizures [2]. This capability enables the deployment of AI technologies in a clinical context, thereby contributing to more informed and timely healthcare interventions [52].

AI techniques in neurotoxicology

Applicable AI techniques include machine learning (ML), deep learning (DL), and natural language processing (NLP) [53]. ML automates the construction of predictive models from data [54]. DL exploits insights gained from the brain-inspired artificial neural network architecture; and NLP facilitates the interpretation of valuable knowledge from unstructured texts [53].

Machine learning approaches

Machine learning techniques enhance the computational prediction of neurotoxicity, a cytotoxic process that causes damage to the nervous system either selectively or as part of general cytotoxicity [3]. Various methods, including supervised and unsupervised learning, linear and nonlinear approaches, classification and regression, have been evaluated in computational toxicology [27]. Algorithms such as multiple linear regression, naïve Bayes classifier variants, k-nearest neighbors, support vector machines, decision trees, ensemble learning, random forests, neural networks, and deep learning play complementary roles [55]. Fragment descriptors, graph mining, and graph kernels contribute to the modelling toolbox [56]. Unsupervised techniques like Kohonen's self-organizing maps facilitate prediction combined with data analysis and visualization [57]. A broad application of machine learning methods is therefore critical in computational toxicology [2].

Deep learning models

Deep learning, a subfield of machine learning and artificial intelligence (AI) wherein computer algorithms learn and improve upon tasks without explicit human direction, has achieved dramatic success in many fields, including computer vision, natural language processing (NLP), and biomedicine [58]. Deep learning frameworks incorporate multi-level nonlinear operations to identify complex hidden structures within data [37]. For example, Convolutional Neural Networks (CNN) apply spatial filters to extract hierarchical features for image tasks [34]. Pre-established deep learning architectures such as Artificial Neural Networks (ANN), CNN, Recurrent Neural Networks (RNN), Long Short-Term Memory (LSTM), Graph Convolutional Networks (GCN), and Generative Adversarial Networks (GAN) have been employed to characterize molecular structure information relevant to analyzing environmental chemicals for toxicity prediction [60]. Graph-based neural networks facilitate both qualitative and quantitative chemical toxicity analysis [53]. In the quest for determining safe dosage concentrations of hazardous substances, a hybrid deep neural network (HNN-Tox) was developed to estimate dose range chemical toxicity from the extensive ChemIDplus database [61]. This model, trained on diverse chemical structures and toxicity information, outperformed similar machine learning techniques [33]. An architecture merging Convolutional Neural Networks (CNNs) with multilayer perceptrons (MLPs) processes varied data inputs to predict chemicals' lethal dose 50 (LD50) values [62]. Ensemble methods, combining HNN-Tox with Random Forests (RF), Bagging, or Adaptive Boosting (AdaBoost), further enhance predictive ability, with HNN-Tox paired to RF achieving the highest accuracy [63].

Natural language processing in toxicology

Natural language processing (NLP) represents a growing AI subcategory for toxicology-driven text mining [64]. NLP supports the construction of Adverse Outcome Pathways by extracting mechanistic details about adverse effects from scientific publications, enabling quantitative assessment of mechanistic support [65]. Semi-automated pipelines decrease literature-screening workloads and improve accuracy and reproducibility; the resulting Adverse Outcome Pathways enable researchers to concentrate more on weight-of-evidence evaluation [66].

Liver pathologies exemplify the benefits of automated mechanistic information extraction, with Adverse Outcome Pathways available for cholestasis, steatosis, and fibrosis [67]. Deep-learning language models and domain-specific tokenization facilitate recognition of pertinent entities and establishment of causal linkages, streamlining the identification of compounds associated with liver toxicity and the extraction of mechanistic details spanning molecular initiating events to adverse outcomes at the organism level [68]. Latest developments in Large Language Models present promising applications for future toxicology research [67].

Data sources for neurotoxic prediction

Predicting neurotoxic outcomes using artificial intelligence (AI) requires access to specialized data that captures chemical, biological, and clinical aspects of neurotoxicity [69]. Three key data types serve as inputs to AI models: toxicological databases, omics data, and clinical datasets [70].

Toxicological databases supply information on environmental and industrial chemicals implicated in neurotoxic effects [71]. The US Environmental Protection Agency's (EPA) ToxCast/Tox21 program, for example, has screened thousands of compounds using *in vitro* bioassays and toxicogenomics profiles [72]. Similarly, the Comparative Toxicogenomics Database curate relationships among chemicals, genes, phenotypes, and diseases [73]. Such resources provide chemical structures, exposures, biological effects, and dose-response measurements that enable multidisciplinary assessment [13]. The PubChem database further supports compilations of chemical structures and biological activities relevant to toxicity prediction [74]. Computational toxicology approaches use chemical structures-encoded as SMILES or molecular fingerprints-and coherence indices to construct predictive models based on molecular initiating events that precede adverse outcome pathways [75]. Given the impracticality of testing the vast chemical space experimentally, these resources facilitate screening and prioritization of compounds with unknown neurotoxic potential [76].

Omics data from proteomics, metabolomics, or transcriptomics yield another rich information source for neurotoxicity prediction [77]. By processing omics profiles measured on exposed cells, it is possible to identify analytes most strongly associated with neurotoxic drugs and leverage them to predict and quantify potential neurotoxicity with multi-label classifiers [78]. Unlike classical toxicogenomics frameworks that rely on supervised learning from discrete annotated labels, these machine learning (ML) methods accommodate multiple degrees of neurotoxicity from unsupervised phenotyping, thereby enabling toxicity ranking and signal prioritization [79].

Clinical data-including laboratory test results, genetic information, adverse event records, and diagnoses-constitute a third class of neurotoxicity data [8]. Collected in structured or semi-structured formats, such domain-specific data can be mined with specialized natural language processing (NLP) techniques to perform causality analysis and construct knowledge graphs characterizing relationships among medications, neurological conditions, and confounding factors [27]. By linking such information to prescribed drugs, patient cohorts can be identified for retrospective pharmacovigilance studies that analyze attribution patterns and assist in establishing drug-induced neurotoxicity [2].

Toxicological databases

Large amounts of toxicological data on specific neurotoxicants are available from repositories such as the Comparative Toxicogenomics Database (CTD) [1]. CTD provides information on chemical-gene/protein interactions, chemical-disease relationships and gene-disease relationships that helps understand the effects of environmental chemicals on human health [72]. For instance, all the chemicals in CTD associated with the MeSH "Neurotoxicity Syndromes" were retrieved for further processing and analysis [71].

Genomic and proteomic data

In the modern world, individuals are continually subjected to various chemical, physical, and biological agents that generate harmful effects, which can often be underestimated or remain largely unknown [80]. Investigating the impact of these agents on living organisms is thus of paramount importance [81]. This is especially relevant for neurotoxicity, a widespread feature that can be triggered by a wide range of exposures, such as drugs or substances of abuse, metals, pesticides, air pollutants, nanomaterials, and viruses, many of which cause severe damage to the nervous system [1].

Artificial Intelligence (AI) has become a fundamental tool in both academic and industrial settings, providing a wide range of algorithms that enable the derivation of solutions with very little prior knowledge [82]. These solutions can be applied to highly specialized domains, such as the analysis of omics data with the goal of identifying signatures associated with adverse conditions [83]. Several toxicological databases are available on the web, including specialized resources such as CTD and PubChem [84]. These databases contain critical information for the development of machine learning models that identify the inherent characteristics of agents capable of generating specific types of damage [85]. Clinical data, accessible through public resources comprising patient information, is also valuable for developing methodologies that monitor ongoing pathologies or predict susceptibility to specific damages [86].

Clinical data utilization

Clinical data comprise another key source of information that can be utilized as input for the prediction of neurotoxic outcomes [87]. Clinical data include electronic medical records (EMRs), which are regularly updated documents that serve to report patient information throughout their medical history, such as demographics, diagnosis codes, and laboratory orders [88]. Clinical data also includes clinical trials, which refer to medical experiments performed with real patients in order to test drugs or alternative therapies [89]. Toxicology articles and reports contain information about all the adverse events associated with toxic agents and can be considered another example of relevant clinical data [90].

Modeling neurotoxic outcomes

Models that link molecular initiating events (MIEs) with adverse outcome pathways (AOPs) leading to neurotoxicity provide a foundation for identifying neurotoxic compounds [1]. The AOP approach connects an initiating molecular-level perturbation through a chain of key events to an adverse health outcome, and chemicals that activate the same MIEs as established neurotoxic compounds are likely to exert similar effects [91]. These models are developed by applying molecular docking techniques to a curated set of molecular targets associated with MIEs linked to (developmental) neurotoxicity, thereby screening large chemical inventories for MIE-activating properties [92]. Quantitative Structure-Activity Relationship (QSAR) models constructed for each identified MIE enable the prediction of neurotoxic potential based on a compound's structural features [93].

Decision tree and Bayesian models have been employed to predict *in vitro* neurotoxicity of nanoparticles (NPs) by integrating NP characteristics, cell line attributes, and experimental conditions, with a focus on brain-relevant tissues [2]. For example, decision-tree frameworks calibrated on human epithelial and mouse neuronal cell lines facilitate the assessment of cytotoxicity for oxide NPs, incorporating chemical, toxicological, and quantum-mechanical data [94]. Similarly, tree- and Bayesian-based models have evaluated cellular toxicity of cadmium-containing quantum dots across diverse cell types and tissue contexts [95]. A Bayesian Network connects NP chemical properties, exposure parameters, and *in vitro* results to a spectrum of hazard outcomes including neurological, cardiovascular, immunological, inflammatory, genotoxic, and fibrotic effects [96]. The formulation of classifiers that deliver tissue-specific neurotoxicity predictions-validated on human neuroblastoma cell data-marks a progression beyond earlier approaches that inadequately dissect brain-related toxicological responses [97].

Conclusion

Advances in Artificial Intelligence (AI) have transformed neurotoxicology, enabling accurate prediction and detailed modelling of neurotoxic outcomes [32]. Employing a spectrum of AI tools-from machine learning and deep-learning to natural-language-processing methods-researchers now analyse diverse data sources to identify drivers of neurotoxicity and forecast specific adverse outcomes [1]. Continued progress is anticipated through enhanced AI techniques, multi-omic data integration and collaborative research efforts [24].

Human systems are particularly prone to neurotoxicity because of the brain's complex function, high oxygen consumption rate, high content of polyunsaturated fats and limited regenerative capacity [98]. Exposures can elicit diverse adverse effects, from developmental and learning disabilities, through motor and sensory impairment, to neurodegenerative disease [99].

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