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Commentary

Leveraging artificial intelligence to advance the understanding of chemical neurotoxicity

Michael Aschner [a,*], Robin Mesnage [b], Anca Oana Docea [c], Monica Maria Bastos Paoliello [a], Aristides Tsatsakis [d,e], Georgios Giannakakis [f], Georgios Z. Papadakis [f], Silvio Roberto Vinceti [g], Abel Santamaria [a,b,c,d,e,f,g,h,i,j,k], Anatoly V. Skalny [h,i], Alexey A. Tinkov [j,k]

[a] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, United States
[b] Gene Expression and Therapy Group, King's College London, Faculty of Life Sciences & Medicine, Department of Medical and Molecular Genetics, Guy's Hospital, London, SE1 9RT, UK
[c] Department of Toxicology, University of Medicine and Pharmacy of Craiova, 200349, Craiova, Romania
[d] Department of Forensic Sciences and Toxicology, Faculty of Medicine, University of Crete, 71003, Heraklion, Greece
[e] Department of Analytical and Forensic Medical Toxicology, Sechenov University, 119991, Moscow, Russia
[f] Hybrid Molecular Imaging Unit (HMIU), Foundation for Research and Technology Hellas (FORTH), Greece
[g] University of Modena and Reggio Emilia: Universita degli Studi di Modena e Reggio Emilia, Italy
[h] World-Class Research Center "Digital Biodesign and Personalized Healthcare", IM Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia
[i] K.G. Razumovsky Moscow State University of Technologies and Management, Moscow, Russia
[j] IM Sechenov First Moscow State Medical University (Sechenov University), Moscow, 119146, Russia
[k] Yaroslavl State University, Sovetskaya Str. 14, Yaroslavl, 150000, Russia

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ABSTRACT

Neurotoxicology is a specialty that aims to understand and explain the impact of chemicals, xenobiotics and physical conditions on nervous system function throughout the life span. Herein, we point to the need for integration of novel translational bioinformatics and chemo-informatics approaches, such as machine learning (ML) and artificial intelligence (AI) to the discipline. Specifically, we advance the notion that AI and ML will be helpful in identifying neurotoxic signatures, provide reliable data in predicting neurotoxicity in the context of genetic variability, and improve the understanding of neurotoxic outcomes associated with exposures to mixtures, to name a few.

1. Introduction

The environment is replete with neurotoxins, including metals, solvents and pesticides, to name a few (Vermeulen et al., 2020). Neurotoxicology is a specialty that aims to explain the impact of these compounds on the nervous system throughout the life span, whether during development, adulthood or senescence. While great strides have been made in describing the functional outcomes of these exposures and their underlying mechanisms of neurotoxicity, the discipline lags in predicting structure-based neurotoxicity, molecular modeling of neurotoxins, comparative neurotoxicity, and mixture-induced neurotoxicity. Hence, novel translational bioinformatics and chemo-informatics approaches, such as machine learning (ML) and artificial intelligence (AI), need to be integrated into neurotoxicology, as depicted in Fig. 1.

Artificial intelligence (AI) is based on the premise of genuine human-to-machine interaction, where a machine is coded to learn to perform a task using a set of algorithms (any form of automated instruction). Basically, an intelligent machine has the ability to comply with requests, connect small or large data points and ultimately provide conclusions. AI, in turn, is defined as the broad science of mimicking human abilities, while machine learning (ML) is defined as a set of algorithms that is fed with structured data in order to complete a task without being programmed how to do so (Haenlein and Kaplan, 2019).

We challenge the neurotoxicology family to address several specific questions, including: Can recent developments in AI and ML be applied in neurotoxicology as they are being applied in precision medicine and other fields? Are these applications sufficiently robust to identify neurotoxic "signatures"? Are they reliable in predicting neurotoxicity in

* Corresponding author.
E-mail address: michael.aschner@einsteinmed.org (M. Aschner).

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the context of genetic variability? Are they able to predict neurotoxicity associated with exposures to mixtures? Can they relate chemical structure or activity to neurotoxicity?

2. Artificial intelligence in neurotoxicology

We provide few examples on how these advanced tools can be utilized in future research. Acetylcholinesterase (AChE) functions to terminate neurotransmission by hydrolyzing acetylcholine. Accordingly, AChE inhibitors, such as organophosphates and carbamates, increase both the level and duration of the neurotransmitter action. A recent study by Pulikkal et al. (2017), taking advantage of novel chemoinformatics tools such as quantitative structure-activity relationship (QSAR) models, has identified physicochemical properties of AChE inhibitors (Pulikkal et al., 2017). Analogous QSAR models should improve the understanding on the biological activity of various organophosphates and carbamates in inhibiting AChE and their neurotoxic sequalae, and identify other agents which may target this enzyme.

In search of novel treatments for Schizophrenia, ML and computational chemistry have also been combined to determine the chemical properties of inhibitors of gamma-amino butyric acid (GABA), the primary inhibitory neurotransmitter in the adult central nervous system (Marunnan et al., 2017). While known to be affected by lead (Pb), polychlorocycloalkane and pyrethroid insecticides (Bloomquist et al., 1986), systematic studies predicting physicochemical properties of other neurotoxins have yet to take advantage of novel computational algorithms, such as AI and ML.

3. Advancing artificial intelligence (AI) techniques

Advanced AI techniques (such as feature selection, Machine Learning (ML) or/and Deep learning (DL)) have been recently employed for the prediction of neurotoxicity and the analysis of neurotoxicity-related mechanisms (Furxhi and Murphy, 2020; Jiang et al., 2020; Kuusisto et al., 2019; Monzel et al., 2020a), with AI and ML methods having been used for the analysis of *in vivo, in vitro* (Furxhi and Murphy, 2020; Monzel et al., 2020a) and *in silico* (Jiang et al., 2020) neurotoxicity.

Feature selection (FS) is an AI-based technique identifying the most significant and relevant features to the investigated problem. By removing redundant or unrelated information, FS increases discriminatory and predictive power, contributing significantly to the classification/prediction model (Chandrashekar and Sahin, 2014). FS is divided into filter, embedded selection and ranking methodologies (such as mRMR algorithm, Random Forest (RF), Recursive Feature Elimination (RFE) (Kuusisto et al., 2019), etc.) (Chandrashekar and Sahin, 2014). Machine Learning (ML) is an AI-based data analysis approach, capable of automatic identification of data patterns via establishment of computational models based on learning skills acquired from a training dataset. Several classification systems have been used in the literature (such as Naive Bayes (NVB), k-Nearest Neighbors (KNN), Support Vector Machines (SVM), artificial Neural networks (ANN), Random Forest (RF), etc.), with Random Forest being the most prominent and effective (Furxhi and Murphy, 2020; Monzel et al., 2020a) due to its increased discriminative power. Furthermore, Deep Learning (DL) is an AI-based methodology training neural network models with complex architectures and non-linear transformations. DL exhibits high performance with the limitations of the need for very large training datasets, and low generalizability power (Srivastava and Hanig, 2021). Imaging analysis tools provide highly valuable information for the automatic quantification of neurotoxic states and regions of interest (ROI) (Argyriou et al., 2019; Fitsanakis et al., 2006) which have been combined efficiently with the emerging DL and ML techniques (Falk et al., 2019; Kayasandik et al., 2020; Srivastava and Hanig, 2021), enabling the address of the automated identification of histopathological results identifying automatically neuronal damage or degenerated brain areas (Iqbal et al., 2019). The application of AI methods (such as Feature Selection, ML/DL) provide powerful and reliable tools for automating all the phases of neurotoxicity estimation procedure: artifacts removal, precise brain areas segmentation, detection of degenerated areas, extraction of their descriptive features and efficient model classification/prediction with increased accuracy [12].

4. Enabling the use of high-throughput “omics” technologies

Large and granular datasets are needed to develop ML models and get accurate predictions. Little data results in a poor approximation and may cause over-fitting. High-throughput “omics” technologies which are increasingly used to measure thousands of variables (e.g. metabolite levels, gene expression, or image acquisitions) are thus very suitable to develop ML algorithms. They can be used to identify harmful substances. Recent studies also include the construction of zebrafish developmental neurotoxicity networks by integration of transcriptomic datasets (Li et al., 2021), or toxicity predictions in brain organoids from image-based cell profiling (Monzel et al., 2020b). They also improve the predictability of current testing strategies. For instance, an in-depth molecular profiling in rats exposed to pesticides allowed the detection of perturbations that would remain undetected by standard regulatory measures (Mesnage et al., 2021b) or the effects of glyphosate on gut microbial communities (Mesnage et al., 2021a). Omics technologies also have applications for precision medicine. For instance, blood lipid profiles reflecting antecedent memory impairment can be used as diagnostic tools for early neurodegeneration of Alzheimer’s disease (Mapstone et al., 2014). Toxicogenomics strategies can even have regulatory application by facilitating the development of adverse outcome pathways and read-across strategies (Liu et al., 2019).

Altogether, we suggest that the use of omics technologies could facilitate the development of AI applications in neurotoxicology by providing datasets sufficiently large so that ML models can learn accurate prediction profiles.

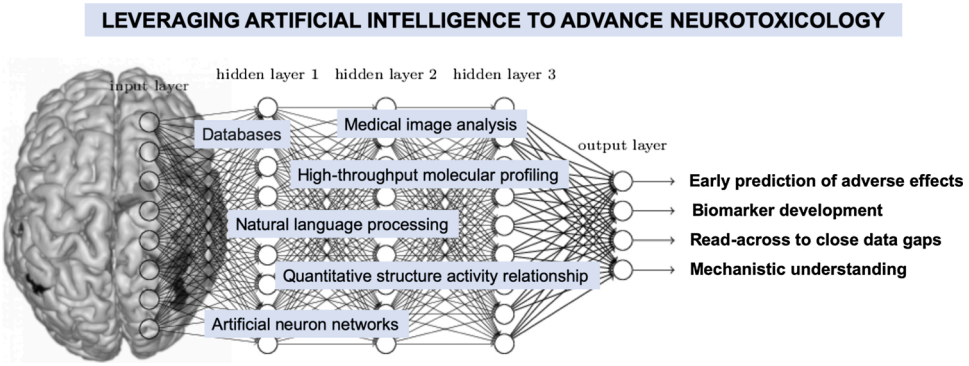

Fig. 1. A conceptual framework to leverage artificial intelligence and advance the understanding of chemical neurotoxicity.

5. Mixtures toxicity evaluation in the era of computational approaches

New evidence has shown that approaches based on single chemical toxicological evaluations for setting safe limits and reference doses are not sufficiently protective of human health. In real-life, subjects are not exposed to a single chemical, but a multitude of environmental chemicals through different pathways, making it exceedingly difficult for regulatory agencies to reliably determine safety limits to individual chemicals solely based on a single compound evaluation (Hernandez et al., 2020; Tsatsakis et al., 2017). Studies on non-commercial mixture toxicity have shown that exposures at low doses, below the safety reference dose for individual chemicals (in the mixture) induce neurobehavioral changes and/or neurotoxicity (Tsatsakis et al., 2019), emphasizing the need for integrated mixture toxicity analyses in the risk assessment process. Due to the complexity and multitude of chemical mixtures to which a subject might be exposed, classical toxicological testing cannot be performed for all the possible combinations, hence *in silico* tools and/or AI should be included in the chemical mixture toxicological evaluation to derive reference doses (RfD) and inform on combined possible toxic effects.

In conclusion, future validation of ML and AI outputs with existing experimental results, should overcome current limitations in neurotoxicology, allowing for better understanding at multiple levels, increasing predictability of neurotoxicity in the context of genetic variability, characterizing modes-of-action of neurotoxins, and providing class-specific neurotoxic signatures, to name a few.

Data availability

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

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