



The Future of Neurotoxicology: A Neuroelectrophysiological Viewpoint

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Neuroelectrophysiology is an old science, dating to the 18th century when electrical activity in nerves was discovered. Such discoveries have led to a variety of neurophysiological techniques, ranging from basic neuroscience to clinical applications. These clinical applications allow assessment of complex neurological functions such as (but not limited to) sensory perception (vision, hearing, somatosensory function), and muscle function. The ability to use similar techniques in both humans and animal models increases the ability to perform mechanistic research to investigate neurological problems. Good animal to human homology of many neurophysiological systems facilitates interpretation of data to provide cause-effect linkages to epidemiological findings. Mechanistic cellular research to screen for toxicity often includes gaps between cellular and whole animal/person neurophysiological changes, preventing understanding of the complete function of the nervous system. Building Adverse Outcome Pathways (AOPs) will allow us to begin to identify brain regions, timelines, neurotransmitters, etc. that may be Key Events (KE) in the Adverse Outcomes (AO). This requires an integrated strategy, from *in vitro* to *in vivo* (and hypothesis generation, testing, revision). Scientists need to determine intermediate levels of nervous system organization that are related to an AO and work both upstream and downstream using mechanistic approaches. Possibly more than any other organ, the brain will require networks of pathways/AOPs to allow sufficient predictive accuracy. Advancements in neurobiological techniques should be incorporated into these AOP-base neurotoxicological assessments, including interactions between many regions of the brain simultaneously. Coupled with advancements in optogenetic manipulation, complex functions of the nervous system (such as acquisition, attention, sensory perception, etc.) can be examined in real time. The integration of neurophysiological changes with changes in gene/protein expression can begin to provide the mechanistic underpinnings for biological changes. Establishment of linkages between changes in cellular physiology and those at the level of the AO will allow construction of biological pathways (AOPs) and allow development of higher throughput assays to test for changes to critical physiological circuits. To allow mechanistic/predictive toxicology of the nervous system to be protective of human populations, neuroelectrophysiology has a critical role in our future.

Keywords: neurotoxicology, neurophysiology, adverse outcome pathway, neural networks, mechanistic

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INTRODUCTION

A proposal of future directions for application of neuroelectrophysiological techniques in toxicology must define some of the current and future problems facing the science of neurotoxicology. Currently (and in the foreseeable future), two major emphases in the field of neurotoxicology are: 1) mechanistic information and 2) human cognitive alterations (including diseases such as attention deficit hyperactivity disorder (ADHD), autism, learning disabilities, motor and sensory deficits, etc.). Both areas can be advanced through the systematic collection of targeted functional mechanistic data based on known or presumed biological pathways (Adverse Outcome Pathways (AOPs) in the field of neurotoxicology). Neurophysiology has the ability to bridge mechanistic data and behavioral changes—a critical linkage. As indicated below, the collection of mechanistic data to understand the function of the nervous system has been occurring for a long time.

PAST

When considering future directions for neuroelectrophysiology as applied to neurotoxicology, it is beneficial to consider the historical progression of advancements and how the area of neurophysiology has contributed to the fields of neuroscience. Electrophysiology has provided a valuable basic understanding of nervous system function in neurobiology and neurotoxicology for centuries. The history of neurophysiology has been detailed in more exhaustive reviews and is only summarized here (Collura, 1993; Muley et al., 2009; Piccolino, 1998; Verkhratsky and Parpura, 2014). In the 1660's, Dr. Jan Swammerdam dissected a frog leg and discovered that muscle fiber contraction could be induced by stimulation of nerve fibers (Muley et al., 2009; Verkhratsky et al., 2006). In 1791, Luigi Galvani published seminal work regarding nerve-muscle preparations in a frog, leading to the understanding of stimulus-response and muscle contractions (Galvani, 1791; Muley et al., 2009; Piccolino, 1998; Verkhratsky et al., 2006), and proposed that accumulation of positive and negative charges along the surface of muscles and nerve fibers resulted in “animal electricity”. Also using a nerve-muscle preparation, Leopoldo Nobili recorded the first evidence of the involvement of electrical activity (Nobili, 1828), although he apparently failed to appreciate the intrinsic biological origin. In about 1848, a crude recording of an action potential was made by Emile du Bois-Reymond (du Bois-Reymond, 1848). A few years later, a measure of nerve conduction involved in producing muscular contraction was made by Hermann Ludwig Ferdinand von Helmholtz in 1850 (Helmholtz, 1850a; Helmholtz, 1850b), and published with graphics in 1852 (Helmholtz, 1852). The first “true” measure of nerve conduction velocity (NCV) was published in 1868 by Julius Bernstein (Bernstein, 1868; Bernstein, 1871), who also verified that an action potential involved a charge movement which exceeded the resting membrane potential. Continuing the

evolution of knowledge relating to nerve electrical activity, the involvement of ions (potassium) in nerve currents was proposed in 1912 (Bernstein, 1912). The theory of local circuits was proposed by Ludimar Hermann (Hermann, 1872; Hermann, 1873) postulating that a nerve contained a conductive “core”, an insulating sheath, and an external fluid medium, and that an electrical disturbance would result in nearby portions of the nerve completing current loops. However, it was Charles Overton who demonstrated that sodium ions were involved in the action potential overshoot (Overton, 1902). The electrical activity in single sensory fibers, and the encoding of stimulation intensity in muscles as the firing rate of the sensory fibers was reported in 1926 (Adrian, 1926; Adrian and Zotterman, 1926). This finding formed the basis for explaining how intensity could be encoded in the “all-or-none” triggering of what are today known as action potentials. The development of the voltage clamp technique allowed researchers to accurately monitor current flow across neuronal membranes (Cole, 1949; Marmont, 1949). The involvement of ionic sodium in action potentials was finally described by Hodgkin and Katz in 1949 using giant squid axons (Hodgkin and Katz, 1949), leading to the development of the Hodgkin-Huxley model for the ionic generation of action potentials (Hodgkin et al., 1952; Hodgkin and Huxley, 1952). The Hodgkin-Huxley model, coupled with the invention of the patch clamp technique in 1976 (Neher and Sakmann, 1976), allowed ionic flux thorough single channels to be studied. After approximately 185 years, the biophysical basis for the “animal electricity” proposed by Galvani was defined in detail.

While the above discoveries were obtained in peripheral nerve/muscle preparations, electrical activity in the brain was also being investigated. Early investigations involved brain stimulation and observing motor responses, which initiated the science of mapping the regions of differing brain function (Hitzig and Fritsch, 1870). In 1875 and 1877, Richard Canton recorded electrical activity from the brains of animals (Caton, 1875; Caton, 1877). These recordings involved Electroencephalogram (EEG) changes in sleep and awake states, as well as responses to auditory and somatosensory stimulation. These latter experiments may represent the first recordings of sensory evoked responses. The impact of peripheral stimulation on cortical desynchronization and recording responses localized on the cortex surface of animals was reported by Adolf Beck in 1890 (Beck, 1890; Coenen and Zayachkivska, 2013). Spontaneous human EEG recordings were first published by Hans Berger in 1929, documenting the importance of electrical activity in the human brain (Berger, 1929). In 1932, Dietsch introduced Fourier analysis of the EEG signal, a process that is still in use today to describe different EEG waveform bandwidths (Dietsch, 1932). The use of multichannel EEG recordings allowed description of spatial and temporal variations (Adrian and Matthews, 1934). As the techniques evolved, applications of EEG monitoring to localization of various brain waves was developed. An early medical application of human EEG involved localization of epileptic seizures, for

subsequent surgical treatment (Jasper et al., 1940). These examples briefly show the valuable historical contribution of *in vivo* neurophysiology to the world of biology and medicine.

PRESENT

Mechanistic Neuroelectrophysiology

Simultaneously with the advancement of knowledge of basic biological physiology, integration with pharmacology and toxicology was occurring. This, in turn, led to investigations into the mechanism of action of various chemicals using neurophysiological techniques. In general, recordings can be made from single cells (allowing examination of cell action potentials, ion flux through channels) or field potentials from the extracellular space (that may represent activity from multiple neurons). Some basic descriptions of methods mentioned below and considerations in their application are summarized in **Table 1**.

Again, while the scope of this manuscript prevents exhaustive methodological and toxicological details, it is hoped the reader can use the examples provided as a basis for additional research. One of the first toxicological mechanistic studies was in 1857, when Claude Bernard used a neuromuscular preparation to show that curare interfered with neurotransmission at the level of the neuromuscular junction (Bernard, 1857; Gray, 1947). Mechanistic investigations can also be exemplified by proof of dichlorodiphenyltrichloroethane's (DDT) effects on action potentials, which involved alterations at the level of sodium and potassium channels (Shanes, 1949; Narahashi and Yamasaki, 1960; Narahashi and Haas, 1967; Narahashi and Haas, 1968). Other investigators used *in vitro* preparations to demonstrate that mercury or lead altered presynaptic neurotransmitter release, presumably by interfering with calcium function (Manalis and Cooper, 1973; Manalis and Cooper, 1975; Kober and Cooper, 1976). *In vivo* neurophysiological measures of excitability and plasticity (indicated by population spikes, short- and long-term potentiation, kindling, etc . . .) (Goddard et al., 1969; Lomo, 1971; Racine et al., 1972; Bliss and Lomo, 1973; Douglas and Goddard, 1975; Racine et al., 1983) opened the door for investigations related to network function and plasticity. Studies using these techniques illustrated the effect of lindane on GABA-mediated inhibition in the hippocampus (Joy and Albertson, 1985; Joy and Albertson, 1987; Joy et al., 1995). The effects of lindane, dieldrin, and endosulfan on increasing neuronal network excitability were also investigated using seizure models such as kindling (Joy et al., 1980; Joy et al., 1982; Gilbert, 1992, Gilbert, 1995; Gilbert and Mack, 1995). An increased decay of long-term potentiation was shown following long-term exposure to lead in drinking water (Gilbert and Mack, 1998). A paradigm known as paired-pulse inhibition was used to following treatment with cismethrin (Type I) or fenvalerate or deltamethrin (Type II) pyrethroids, and indicated changes in sodium channel kinetics supported the data better than changes in GABAergic function—providing a mechanistic basis for the

altered network physiology (Gilbert et al., 1989). Although some authors have expressed limitations with respect to extrapolations to behavioral changes (Hölscher, 1997), neurophysiological phenomena such as long-term potentiation/depression have been used as models to study the neural plasticity associated with biological constructs such as learning and memory (Lynch, 2004; Nicoll, 2017; Abraham et al., 2019). In conjunction with methods discussed later in this paper, these types of studies addressed issues such as *in vitro* to *in vivo* extrapolation and the need to examine higher cognitive function, which are still pressing issues of concern in toxicology.

Evoked Potentials With Clinical Applications

While less mechanistic in nature than the above examples, other neurophysiological procedures, such as evoked potentials (EPs) have contributed to both the fields of neurobiology and toxicology. To record this type of neurophysiological response, a stimulus is presented to the test subject, and the time-locked signal of the nervous system is recorded (often involving signal averaging). As mentioned previously, this type of procedure may have first been used by Canton (Brazier, 1984; Caton, 1875; Caton, 1877). Evoked potentials have served as a neurological technique to characterize and help localize the neuroanatomical basis of neurotoxicity.

Assessment of changes in the peripheral nervous and muscular system has served to characterize the neurotoxicity of numerous chemicals. Examination of the nerve-muscle physiology can involve electromyographic (EMG) examination. These tests have been shown to be sensitive to several types of environmental toxicants or experimental manipulations, and many of these procedures have been described by others (Arezzo et al., 2011; Howard, 2013; McNeil et al., 2013) and will only be briefly described here. Perhaps the simplest test is of spontaneous EMG activity, which often increases in the presence of neurotoxicity or disease (Hnik et al., 1982; Ross and Lawhorn, 1990; Daube and Rubin, 2009). Stimulation of motor nerves allows recording of muscle action potentials (M-wave), which can be altered in the presence of neurotoxicity (Ross and Lawhorn, 1990). The elapsed time from the stimulus to the recorded neurophysiological response is known as the distal latency, and reflects the conduction velocity of the motor fibers in the stimulated nerve when the M-wave is recorded (Mallik and Weir, 2005). This measure has been shown to be a sensitive measure for intoxication with 2,5-hexanedione (Nachtman and Couri, 1984). A method known as single fiber jitter testing (voluntary or stimulation methods), measures the variability in neuromuscular transmission time between successive muscle action potentials (Stålberg and Sanders, 1981; Stålberg and Sonoo, 1994). Changes in neuromuscular jitter have been reported in mice after treatment with the organophosphates (OPs) mipafox or ecothiopate (Kelly et al., 1994). Decrements in muscle action potential amplitude after repetitive nerve stimulation (RNS) have been shown after treatment with the OPs dimethoate (Dongren et al., 1999), fenvalerate, or phoxim (Yang et al., 2001) or the depolarizing

TABLE 1 | Example types of neuroelectrophysiological methods.

Peripheral/Central Nervous System	Advantages	Considerations
Single Electrode Electrode Array	Can use primary cell culture, immortalized cell lines, iPSC, neurospheres Mechanistic information can include single channel function Network level effects, higher throughput (48 and 96 well plates)	Single cell, typically low throughput Cell type/mechanism impacted can be unclear
Ex Vivo Methods		
Neuromuscular Junction	Mechanistic information from “more intact” preparation Isolate changes to pre- vs postsynaptic changes in neuromuscular transmission; Long history of use in multiple species	Isolated from influences of intact central nervous system; Specialized preparation; Human examples are rare
Excised Peripheral Nerve	Action potential conduction velocities; Influences of specific ions can be examined	Limited to single nerve measures; No information on interactions with other nerves
Brain Slice	Known circuitry. Change in long-term potentiation, paired pulse inhibition, kindling; May reflect neuroplasticity	Low throughput; Often more successful in early post-natal animals
In Vivo Methods		
Neuromuscular Recordings	Human clinical interpretation	Important to control temperature effects
M-Wave	Muscle response following stimulation of motor neurons; Can assess changes in large motor neurons/neuromuscular junction	No assessment of sensory neurons; Must determine nerve vs muscle effects
Distal Latency	Time from stimulation to M-Wave; Assess speed of conduction in motor neurons	No assessment of sensory neurons
F-Wave	Muscle response recorded after antidromic activation of motor neuron; Assess entire length of large motor neurons	Changes may reflect subtle alterations in nerve fiber composition; Difficult to assess changes in motor neuron excitability; Possibly altered by supraspinal/spinal interneuron influences
H-Wave	Muscle response after orthodromic activation of afferents in motor neuron; Includes sensory component; Correlations with sensory-motor neuropathy	Possibly altered by supraspinal/spinal interneuron influences; Not easily measured in all muscles
Repetitive Nerve Stimulation	M-waves recorded after repetitive stimulation of motor neuron; Can identify deficits in presynaptic vs postsynaptic neuromuscular changes	Need to assess neuromuscular units altered by disease/toxicants; Movement artifacts need to be controlled
Single Fiber Electromyography	Record extracellular action potentials from single muscle fibers with repetitive activation; Can detect changes in neuromuscular function (such as jitter) not detected by RNS; Assess safety factor for neuromuscular transmission; Can use stimulation or normal contraction techniques	Requires needle electrodes; Movement artifacts need to be controlled; Should assess multiple neuromuscular junctions
Electromyographic Activity	Can detect changes due to denervation/reinnervation, Active contraction or spontaneous	May require needle electrodes; Typically, only involves superficial muscles; Movement artifacts need to be controlled; Need to identify nerves/muscles affected by toxicity
Peripheral Nerve	Human clinical interpretations	Important to control temperature effects
Compound Nerve Action Potential	Ability to detect changes in larger axons, or distribution of axon sizes within a nerve	Difficult to assess small sized axons without specialized techniques
Nerve Conduction Velocity	Measured between two sites on the nerve. Interpretation of changes in myelin or axon size are accepted	Standard methods do not assess small fibers; Testing non-superficial nerves can be difficult; Determining exact distance along actual nerve may not be possible
Small Fiber	Can assess changes in small nerve fibers	Can be technically challenging; Not all types of small nerve fibers are assessed
Threshold Tracking	Can assess changes in various ion channel function	Requires specialized equipment/software; Not a large toxicological database
Peripheral/Central Nervous System	Human clinical interpretations	Important to control temperature effects
Electroretinogram	Waveforms reflect transmission through photoreceptors, bipolar cells, and ganglion cells for pattern stimulation; Can measure sensory thresholds which are analogous to psychophysical	Requires control of ambient light and light adaptation of subject; May require anesthesia
Somatosensory	Waveforms reflect neurotransmission through lateral or dorsal spinal columns, brainstem dorsal column nuclei (or cerebellum), thalamic nuclei, thalamocortical projections, and neurons in the somatosensory cortex; Can use electrical or “natural” stimuli; Can measure sensory thresholds which are analogous to psychophysical procedures	Primarily assesses large diameter neurons; Usually involves signal averaging
Auditory		

(Continued on following page)

TABLE 1 | (Continued) Example types of neuroelectrophysiological methods.

Peripheral/Central Nervous System	Advantages	Considerations
	Waveforms reflect neurotransmission through auditory nerve, cochlear nucleus, olivary nuclei, lateral lemniscus, inferior colliculus, medial geniculate nucleus, auditory radiation, auditory cortex; Can use pure tones to assess frequency-dependent changes; Can measure sensory thresholds which are analogous to psychophysical procedures	Requires control of auditory stimulus and testing room noise; Usually involves signal averaging
Visual	Waveforms reflect neurotransmission through retinal photoreceptors and ganglion cells, optic nerve and tract, lateral geniculate, thalamocortical projections, visual cortex; Pattern stimuli can allow selectivity for different cell populations; Can measure sensory thresholds which are analogous to psychophysical procedures	Pattern stimulation requires specialized equipment/software; Requires control of lighting conditions during testing; Usually involves signal averaging
Motor Threshold Tracking	Electrical or magnetic stimulation; Assess function of descending motor tracts and peripheral motor nerves	Specialized equipment
Hippocampus	Known circuitry. Change in long-term potentiation, paired pulse inhibition, kindling; Can have mechanistic interpretations. Some tests reflect neuroplasticity	Low throughput; Specialized equipment; Only select human test correlates; Usually animal models
Seizures	Clinical applications; Gold standard for seizurogenic chemicals; Can localize seizurogenic sites	Animal-human extrapolation
Electroencephalography	Clinical applications; Responses can reflect higher cortical processing	Extrapolation of cognitive potentials between animals-humans may be difficult
Single Units	Ability to study network connectivity; Examine specific cell populations; Long history of analyzing brain function; Application of optogenetics	Selectivity bias for larger cells; Must consider animal-human differences; Usually animal models

neuromuscular drug decamethonium (Finley et al., 2009). As reviewed by Le Quesne, changes in EMG responses have been shown following exposure to acrylamide, lead, organophosphates, or hexacarbons (Le Quesne, 1978; Hnik et al., 1982). Additional measures such as the F-wave (antidromic propagation along motor axons to the motor neuron cell, with subsequent firing and production of a small M-wave) (Panayiotopoulos and Chroni, 1996) and the H-reflex (stimulation of sensory fibers which then activate motor neurons at level of spinal cord, with subsequent firing of motor neurons and eliciting a M-Wave) (Cliffer et al., 1998b; Tucker et al., 2005) are also possible, although they may be technically challenging (Mattsson et al., 1984). The H-reflex may help disassociate sensory vs motor changes, due to the involvement of the sensory component, which should be absent/reduced in the M- or F-responses (Hamers et al., 1991; Cliffer et al., 1998a).

Often closely associated with electromyography is the assessment of peripheral nerve function (Arezzo et al., 2011). Nerve conduction velocity is the measure of the speed of action potential propagation along a nerve (stimulation and recording are along the nerve itself) and generally reflects the conduction speed of the largest diameter axons (Stålberg and Erdem, 2000). Changes in myelin will alter the normal saltatory conduction and change the NCV, whereas damage/death of the nerve will tend to alter the amplitude of the nerve action potential (Kimura, 1984; Hamers et al., 1991; Mattsson et al., 1992). Because the size and shape of a nerve action potential reflects the different constituent nerve fibers of the stimulated nerve (Gasser and Erlanger, 1927), changes in the distribution of conduction velocities may provide insight whether different types of nerve fibers are preferentially affected by a toxicant (Dorfman, 1984; Caccia et al., 1993; Ruijten

et al., 1993). Examples of compounds that have been shown to alter nerve conduction and/or nerve action potentials include hexane (Howd et al., 1983; Rebert and Sorenson, 1983; Nylén et al., 1994), taxol (Cavaletti et al., 1995; Leandri et al., 2012), carbon disulfide (Herr et al., 1998), nitrile chemicals (Gagnaire and Marignac, 1999), hexachlorophene (DeJesus et al., 1978), and cisplatin (Rebert et al., 1984; Thompson et al., 1984; De Koning et al., 1987).

Stimulation of different sensory systems can be used to assess changes in somatosensory, auditory, and visual function (Dyer, 1985). Because the parts of the nervous system that generate these sensory EPs are generally known (Rebert, 1983; Mattsson and Albee, 1988; Herr and Boyes, 1995), the changes in EPs can help with neuroanatomical localization of altered physiological response, and can be integrated into a toxicological profile that includes targeted histopathological investigations (Mattsson et al., 1989a; Ross, 1989; Mattsson et al., 1990; Mattsson et al., 1992; Morgan et al., 2004; Arezzo et al., 2011). An example for the visual system is the electroretinogram (ERG). This response includes components reflecting activity at the levels of the photoreceptors, the bipolar-Müller cells, and for pattern stimuli, may include ganglion cell components (Baker Jr et al., 1988; see; Herr and Boyes, 1995 for review; Heynen and Van Norren, 1985; Maffei and Fiorentini, 1986; Miura et al., 2009). As a second example, auditory stimulation allows recording of the brainstem auditory evoked response. The EP consists of a series of peaks that include physiological responses from the cochlear hair cells, the auditory nerve, cochlear nucleus, superior olivary complex lateral lemniscus, inferior colliculus, medial geniculate nucleus, and can include the auditory cortex (see Herr and Boyes, 1995; Mattsson et al., 1992 for reviews). The use of analogous

neurophysiological techniques between laboratory animals and humans can assist in extrapolating effects across species (Hudnell et al., 1990; Benignus et al., 1991; Boyes, 1994). Additionally, test guidelines have been developed for using these techniques in a neurotoxicological setting (United States Environmental Protection Agency, 1998a; United States Environmental Protection Agency, 1998b). These guidelines cover the evaluation of peripheral nerve function, NCV, and sensory evoked potentials in toxicological studies for submission to the U.S. E.P.A., and can be adapted for acute, chronic, or developmental studies. These types of EP tests have been used to assess somatosensory alterations produced by dichloroacetylene (Albee et al., 1997), carbonyl sulfide (Herr et al., 2007), toluene or *o*-cresyl (Mattsson et al., 1989b), or hexane (Rebert and Sorenson, 1983). Changes in the auditory system have been shown following treatment with jet fuel coupled with noise exposure (Fechter et al., 2007), carbonyl sulfide (Morgan et al., 2004; Sills et al., 2004; Herr et al., 2007), chlordimeform or developmental glutamate (Janssen et al., 1983; Janssen et al., 1991), or polychlorinated biphenyls (Lilienthal et al., 2011; Poon et al., 2011). Changes in the ERG have been reported after exposure to methanol (Eells et al., 1996; Eells et al., 2000), cholinesterase inhibition (Jones et al., 1995), or lead (Fox and Rubinstein, 1989). Additionally, changes in the central nervous system function of the visual system (Boyes, 1992) have been shown following treatment with trichloroethylene (Boyes et al., 2005), carbon disulfide (Herr et al., 1992), 3,3'-iminodipropionitrile (Herr et al., 1995), and carbaryl or propoxur (Mwanza et al., 2008). The utility of these EP methods to detect, help localize the site of neurological dysfunction, and applicability to human neurology assures that such methods will continue to be applied in the future.

Neuroelectrophysiology and Cognitive Measures

Although largely in neuroscience and clinical settings, neurophysiological methods have also been used to study neural generators involved in cognitive processing of external stimuli using both methods based on recording EEG and/or evoked responses. The amount of literature regarding source localization (Grech et al., 2008; Asadzadeh et al., 2020) involving methods such as dipole source modeling (Wood, 1982; Koles, 1998), coherence measures (Nunez, 1995; Hoechstetter et al., 2004), neural networks (Abeyratne et al., 1991; Cui et al., 2019) and many other methods, is beyond the scope of this paper. However, such techniques (along with signal averaging) have been used to study associations between cognitive processing and neurophysiological responses. A negative peak recorded over the fronto-central regions of the brain at about 100 ms after stimulus delivery (N100) is proposed to be related to attentional processing, with the amplitude related to the salience of the stimuli (Haider et al., 1964; Hansen and Hillyard, 1980; Vogel and Luck, 2000). A negative potential at around 150 ms can be recorded after an incorrect response during tasks where the subject is required to identify a correct stimulus. It is recorded over the cingulate cortex and is thought to be a

subconscious reflection of error monitoring (Falkenstein et al., 1991; Gehring et al., 1993; Carter et al., 1998). A negative potential recorded over the frontal cortex between 200–350 ms (N200) has been related to response inhibition, attention orientation, and error detection (Wijers et al., 1989; Jodo and Kayama, 1992). A well-studied positive potential occurring about 300 ms (P300) after a stimulus has been related to the “significance” of the stimulus, and has been related to constructs such as attention and working memory (Sutton et al., 1965; Verleger, 1988; Polich, 2007). These types of studies move the application of neurophysiology beyond neurotransmission and sensory perception, and into the realm of higher cognitive processing.

FUTURE

Future directions for neurophysiology will incorporate the generation of data for functional changes as integrated into presumed, or known, biological pathways. Advances in *in vitro* high-throughput screening coupled with the recommendation of the National Research Council (NRC) (NationalResearch.Council, 2007; Krewski et al., 2010) has led to a resurgence in screening chemicals to rank and prioritize them for further testing. Critical to the success of this approach is the ability to relate the *in vitro* changes to adverse outcomes that are used for regulatory standards settings. Included in the realm of adverse outcomes are altered neurophysiology and changes in integrative functions such as cognitive abilities. Such a linkage can be incorporated into an AOP framework (Figure 1). Within this framework, neurophysiology plays a critical role in defining *functional* changes that can be related to both molecular/biochemical alterations, as well as behavioral changes *in vivo*.

In Vitro Approaches

Several lines of research are already underway to use neurophysiological methods to screen for functional changes produced by toxicants. Examples include higher throughput patch clamp methods (Dunlop et al., 2008; Obergrussberger et al., 2016; Obergrussberger et al., 2018; Liu et al., 2019; Gao et al., 2020), *in vitro* cell culture multi-electrode arrays (MEA) (Mack et al., 2014; Zwartsen et al., 2018; Shafer, 2019), and use of alternative (non-mammalian) species such as zebrafish (Milan et al., 2006; Meyer et al., 2016), or *Caenorhabditis elegans* (*C. elegans*) (Richmond and Jorgensen, 1999; Goodman et al., 2012; Lockery et al., 2012). The use of MEAs has been proposed as a method to screen for seizurogenic potential of chemicals/drugs, and has been used in human tissue for epilepsy studies (Dossi et al., 2014; Meyer et al., 2016; Cho et al., 2017; Bradley and Strock, 2019; Fan et al., 2019). Additionally, MEAs have been proposed to have some utility in classifying possible mechanisms of actions of chemicals on the neuronal activity (Mack et al., 2014). Recently, MEA recordings have been used to provide *in vitro* evidence of altered neurophysiology in dorsal root ganglion cells (DRG) (Johnstone et al., 2020) based on *in silico* predictions (Melnikov et al., 2020). The continued development of the types of neurophysiological methods described above will

Hypothetical Adverse Outcome Pathway Relationship

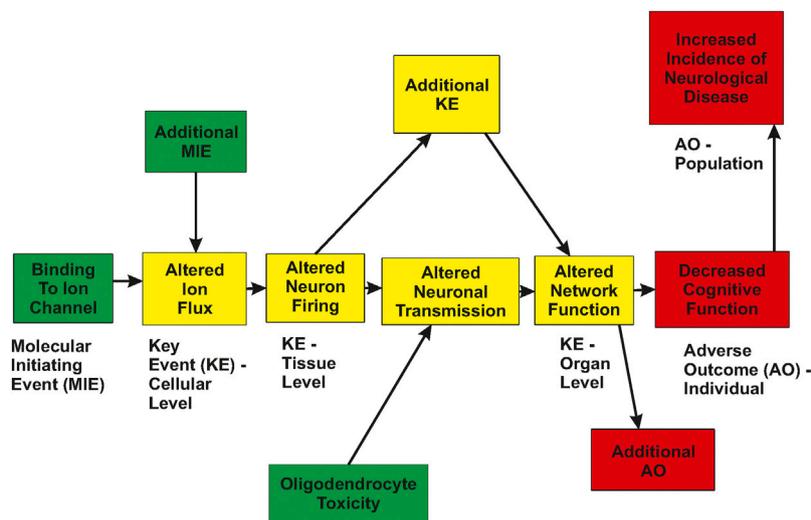


FIGURE 1 | Hypothetical Adverse Outcome Pathway relationship. A xenobiotic interacts with biological tissue and results in a Molecular Initiating Event (MIE). This change in biology produces an alteration in a measurable Key Event (KE), which in turn, results in the subsequent change in additional Key Events. This progression leads to measurable changes at the cellular, tissue, and organ levels of biology. Note that multiple MIEs can impinge on a single KE, and KEs can interact in a network manner. Eventually, the biology is altered sufficiently to result in an Adverse Outcome (AO) that is of concern to society. Altered ion flux could be measured using patch clamp techniques, altered neuronal firing could be measured using multi-electrode arrays, altered network function could be measured using evoked potentials or EEG measures.

allow scientists to detect and prioritize chemicals for further testing, based on changes in neuronal function, and to guide more targeted testing strategies with potential mechanistic information.

The future will require advancements using *in vitro* models to generate mechanistic data beyond screening applications. Applications using either human embryonic stem cells or induced pluripotent cells may allow better homology with human responses than rodent cells. Using cell culture conditions which allow development of electrically active three-dimensional (3D) cultures (Dingle et al., 2015; Sandström et al., 2017) may also help recapitulate the human nervous system, and such models have been proposed to study human neurodegenerative diseases (Jorfi et al., 2018; Faravelli et al., 2020). Such 3D models have been reported to have greater development of synaptic and ion transport mechanisms than two-dimensional cultures, suggesting that the neurons are in a higher state of maturation (Simão et al., 2018). In an example using electrical activity, the MEA activity of human neurospheres has been shown to be altered by methyl mercury, in the absence of changes in cell proliferation (Ylä-Outinen et al., 2010). Using a calcium flux measure, chemicals from multiple classes (drugs, flame retardants, industrial chemicals, poly-aromatic hydrocarbons, or pesticides) were tested in neurospheres and ranked for potency (Sirenko et al., 2019). Because this is a developing area of science, it is important to recognize the role and current limitations of electrophysiological measures in brain spheroids and brain-on-chip models (Forro et al., 2021). The technical issues such as planar vs. 3D electrodes, silicon electrodes, mesh electrodes, etc. . . . are largely due to the relative

recentness of this area of science. Many of these electrophysiological areas for advancement are similar as those for *in vivo* research (see below). All such *in vitro* models will require studies related to brain-related biology such as regional specific neural differences, hormonal influences on neuronal function, or gender-specific neuronal traits. Regional differences in neuronal composition may be assisted by bioprinting technologies using multiple cell types (see Zhuang et al., 2018 for review). However, the largest challenge will be inclusion of measures for cognitive function or emotion (Fritsche et al., 2018).

Although not restricted to electrophysiological preparations, methods will need to adequately not only model the diversity of neuronal cell types, but additional biological physiological functions will need to be included which can alter toxicokinetics for *in vitro* methods. While all areas of toxicology benefit from accurate modeling of chemical exposure, the blood-brain barrier (BBB) adds an additional level of complexity when considering the nervous system (Gumbleton and Audus, 2001; Bagchi et al., 2019). A developed BBB consists of endothelial cells connected by tight junctions, astrocytic projections, and the extracellular matrix, and can act as a barrier to passage of substances into the brain (Ward and Lamanna, 2004; van Der Helm et al., 2016). Additionally, transporter proteins such as a p-glycoprotein can move substances out (or into) the brain (Banks, 1999). Inclusion of these additional cell types and proteins to *in vitro* or *in silico* models (Shityakov and Förster, 2018) will be required to improve dosimetry estimates. Advances in this area have included transwell

systems (Stone et al., 2019) co-culture models, and microfluidic approaches using 3D cultures (Bagchi et al., 2019; Choi et al., 2020; Staicu et al., 2021). Such advances will need to be included in toxicity testing to closer reflect the biology of the *in vivo* situation.

In Vivo Neural Assessment

There have been some recent *in vivo* neurophysiological technique developments that allow assessment of both larger neurons and small sensory fibers and may provide some mechanistic insight into changes in peripheral motor or sensory nerve function. In contrast to traditional neurophysiological techniques, these methods use a series of nerve excitability tests that are translatable from humans to animal models. Several of the tests involve electrical conditioning pulses (some are 100 ms or longer) and track the stimulus intensity required to produce a criterion response in the nerve or muscle. The conditioning pulses activate or inactivate various ion channels, allowing some mechanistic interpretation of changes in neuronal responses (Bostock et al., 1998; Nodera and Kaji, 2006; Krishnan et al., 2008; Krishnan et al., 2009). These methods have been translated to both animal models and *in vitro* preparations (Maurer et al., 2007; Boërio et al., 2009; Mori et al., 2010; Nodera and Rutkove, 2012; Arnold et al., 2017), and have been begun to be used in a toxicological context. For example, the acute symptoms of treatment with oxaliplatin have been attributed to slowed inactivation of sodium channels (Heide et al., 2018), and changes in nerve excitability after Wallerian degeneration have been studied (Sawai et al., 2008). Importantly, these neurophysiological methods can be used repeatedly over time, allowing the onset and recovery of toxicological insult to be monitored (Nasu et al., 2014; Sung et al., 2014; Heide et al., 2018). Nerve excitability methods have also been used to assess small sensory fibers (Maurer et al., 2007; Howells et al., 2018), which are technically difficult to test (Bostock et al., 2003; George et al., 2007; Serra et al., 2010). Other investigators have used more traditional histopathological and neurophysiological techniques to assess small nerve fibers, using rectification of multiunit activity and binning the latencies into different ranges, to represent different conduction velocities (correlated with different sizes of nerves) (Zotova et al., 2008; Zotova and Arezzo, 2013). Recently, *in vitro* models for neurophysiological and histological assessment of rodent dorsal root ganglion or induced human motor nerve cells have been reported for assessment of chemotherapy-induced peripheral neuropathy with proposed expansion into environmental chemicals (Sharma et al., 2019; Anderson et al., 2021; Pollard et al., 2021). While these methods are not high throughput, continued development and application of such methods can start to bridge the mechanistic/functional gap in neurophysiological testing of sensory and motor fibers, which are known to be sensitive to toxicants (Le Quesne, 1978; London and Albers, 2007).

Network Connectivity

Another critical direction for neurophysiological investigations is the interrogation of network connectivity. Neurons, while

affected by toxicants individually, function as part of an integrated network. For years, investigators have used *in vitro* approaches such as brain slices as a reductionist approach to study neuronal networks (Dingledine et al., 1980; Joy and Albertson, 1985; Joy and Albertson, 1987; Joy et al., 1989; Gilbert, 2004). Recently, technological advances have allowed patch clamp investigations in brain slices (including human slices) to look at network connectivity (Radnikow et al., 2011; Peng et al., 2019). Other investigators have used cell culture-based *in vitro* MEA to begin to look at formation of synaptic connectivity and network interactions between cells (Jimbo et al., 2003; Berdondini et al., 2006; Müller et al., 2015). Formation of functional networks on MEAs has been described (Erickson et al., 2008; Robinette et al., 2011), and the influence of chemicals to alter network-related endpoints such as coordinated bursting or synchronous firing has been investigated (Brown et al., 2016; Frank et al., 2018). A mechanistic hypothesis for synaptic plasticity in hippocampal neurons cultured on MEAs has been proposed to involve NMDA receptors and ERK1/2 signaling, along with gene transcription and protein synthesis, for maintenance of synchronous bursting for days (Arnold et al., 2005). The need for assessments of neuronal connectivity is critical in a developmental context, and can also be assessed using alternative species such as zebrafish (Miller et al., 2018). To truly assess the impact of chemicals on *in vivo* integrated neuronal function, it is essential to include network interactions as a future direction for both *in vitro* and *in vivo* work.

Assessment of complex neuronal function (such as cognitive or sensory alterations) using neurophysiological techniques will require incorporation of methods developed in basic neuroscience research with continued use and development of methods applicable to humans. As described earlier in this manuscript, neurophysiological methods to assess changes in sensory or cognitive processing in humans have been described (Hansen and Hillyard, 1980; Verleger, 1988; Wijers et al., 1989; Jodo and Kayama, 1992; Vogel and Luck, 2000; Polich, 2007). Assessment of sensory perception is likely to continue to rely on evoked response methods (as described above), with the inclusion of larger arrays of electrodes to allow assessment of changes in the topography of neural responses (Junghöfer et al., 2000; Robinson et al., 2017). Interrogation of complex sensory or cognitive processing will require assessment of networks of neurons and/or brain regions (Buzsáki, 2004; Urai et al., 2021). Neurophysiology is uniquely suited for recording neuronal responses in virtually “real time”, in contrast to the longer time periods usually required for *in vivo* imaging methods (D’Esposito et al., 1999; Sack and Linden, 2003; Trachtenberg et al., 2002). To adequately map neuronal network responses, an array of electrodes is necessary. In humans, these are typically surface electrodes and may be coupled with performance of a behavioral task (Bekker et al., 2004; Sängler et al., 2014). However, mechanistic studies to provide the biological basis for these responses will require animal models and often involve implanted electrodes.

The recording and interpretation of neuronal network activity *in vivo* is an ongoing effort in neuroscience. Advancements in

electrode probe materials such as silicon (Senzai et al., 2019; Timme et al., 2021), carbon fiber (Kozai et al., 2012), or mesh probes that can be based on nanotechnology (Liu, 2015; Xie et al., 2015) have allowed long-term recordings of neuronal network responses. Multiple probes, each with multiple electrodes, allow sampling a three-dimensional array of neuronal activity. Multi-electrode methods allow assessment of the timing and correlation of firing between many neurons simultaneously in both anesthetized preparations and in alert and behaving animals. An eight probe array (with 64 recording sites) has been used to examine activity in the rat somatosensory and prefrontal cortex (Barthó et al., 2004). By examining the three-dimensional location of the neurons, the first movement of the autocorrelation, action potential waveform duration, and mean firing rates, the neurons were able to be classified as pyramidal cells or interneurons. A series of probes has been developed with over 5,000 recording sites, with 768 sites recorded simultaneously (Steinmetz et al., 2020) over an eight week period—allowing incorporation into future behavioral paradigms. Using a head-fixed preparation, about 30,000 neurons were recorded from 42 brain regions during multiple sessions of a visual discrimination task in mice. The regional brain responses to ipsilateral vs contralateral choices, and engagement timing were differentiated (Steinmetz et al., 2019). These multi-electrode methods allow assessment of cell outputs (action potentials) with great fidelity. However, it is much more difficult to measure the multiple inputs to a neuron's dendrites and spines. One approach to looking for changes in cellular inputs can involve measuring the extracellular current flow using a technique known as current source density analysis (CSD) (Mitzdorf, 1985; Szymanski et al., 2009; Senzai et al., 2019). While CSD does not have widespread use in the neurotoxicology field, it has been used to show increased current flow into the supragranular layer of the auditory cortex in rats after an acute dose of salicylate (Stolzberg et al., 2012), indicating changes in intracortical microcircuits. Other investigators have used CSD analysis to show reduction in electrical sinks in the stratum moleculare and decreased distance from the peak inward current (sink) to the granule cell layer of the hippocampus, suggesting a loss of entorhinal afferents to the hippocampal outer molecular layer after 20 weeks of ethanol exposure (Abraham and Hunter, 1982). Therefore, application of multi-electrode analysis, coupled with CSD techniques can begin to assess both neuronal network circuitry and alterations in synaptic inputs (field potentials).

Cognitive Function

The assessment of changes in cognitive function produced by toxicants is an on-going challenge. Once again, principles and advances in neuroscience will have to be adapted to advance toxicological procedures. Knowing where and when to look for altered physiological responses will remain an important question. Combinations of technologies, such as EEG, magnetoencephalography, and fMRI, may be used to examine sources of cognitive responses (Min et al., 2020). The role of frequency-based assessment of EEG has been linked to communication between different brain regions, memory

formation, and other cognitive processes in both human and animal models (Lachaux et al., 2012). In humans, decreased power in alpha and beta EEG frequencies, and reductions in P300 power, were found in high load working memory tasks (Chuang et al., 2019). However, investigations may also continue to rely on evoked responses to interrogate complex brain functions. As some examples, the P3 potential resulting from olfactory stimulation in humans was shown to be modulated by attention in the inferior frontal cortex, insula, and inferior temporal gyrus (Singh et al., 2019). Increased reaction time variability and a reduced amplitude of the P3 potential has been associated with increased ADHD Problems Scale scores on the Child Behavior Checklist (Liu et al., 2020). In rats, peak P2 was found to be related to target detection in an auditory go/no go task, but P3 was not altered (as frequently seen in humans). Increased low frequency power (1–7 Hz) was observed in the frontal cortex on hit trials, but 8–14 Hz power (alpha frequency range) was suppressed, compared to correct rejections (Nanda et al., 2020). These studies illustrate the power of neurophysiological techniques to study cognitive processing in real time, albeit with some differences between rodent models and humans, with an extensive range of cognitive processing remaining to be investigated.

Perturbation Methodology: Optogenetics

Using methods to perturb normal brain function in animal models will remain an important approach to uncover toxicological mechanisms. Traditional methods such as electrical stimulation, lesions, and pharmacological manipulations can still provide important mechanistic information (Nadler and Cuthbertson, 1980). A well-known caveat to lesion and electrical stimulation methods, is the non-specific nature of the technique. Not only are neuronal cell bodies affected, but so are axons of passage. Pharmacological manipulations can target specific types of neurons/receptors, etc . . . but may involve a relatively longer time scale of effects and may involve multiple brain regions (Cassaday et al., 1991; Singh et al., 1998; Berman et al., 2002).

Many of these limitations can be overcome with application of the relatively new technique of optogenetics, coupled with neurophysiology. Optogenetic tools allow targeting specific types of neurons with excitatory or inhibitory opsins, allowing neuron function to be controlled with light pulses in real time, and can be integrated with electrophysiology and neuroanatomical methods (Kim et al., 2017; Kuleshova, 2019). Optogenetic inhibition has been used to study the flow of neural network information from sensory to motor areas of the cortex in mice (Guo et al., 2014). Changes in EEG activity have also been examined using optogenetic techniques. For example, modulation of hippocampal theta activity by somatostatin positive, but not parvalbumin positive, GABAergic neurons in a mouse model of Alzheimer's disease has been demonstrated (Chung et al., 2018). Optogenetic re-activation of dentate gyrus neurons that were first activated during fear conditioning, induced freezing behavior in a different environmental context—indicating that these specific neurons were contributing to the memory engram (Liu et al., 2012).

Optogenetic stimulation of auditory presynaptic inputs to the lateral amygdala has been shown to serve as a conditioned stimulus (CS) during fear conditioning, substituting for an auditory stimulus. This study showed the importance of auditory inputs (traditional CS for fear training) to the lateral amygdala in fear memory formation (Kwon et al., 2014). The role of dopaminergic and GABAergic neurons in emotional reward (salience) during motivational behaviors has been dissected using optogenetic methods (Nieh et al., 2013). Closed-loop optogenetic techniques are under development that allow the brain's neuronal activity to control the optogenetic stimulation of neurons, resulting in extremely naturalistic stimulation paradigms (Grosenick et al., 2015; Bolus et al., 2018). Additionally, optogenetic and neurophysiological techniques can be used in conjunction with other methods such as fMRI, voltage imaging, calcium imaging, and neurotransmitter release (Liang et al., 2015; Renault et al., 2015; Burmeister et al., 2018; Adam et al., 2019) to examine the mechanistic basis of changes produced by xenobiotics on complex brain network functions, such as learning and memory, in nearly real time. Application of these sorts of tools in a toxicological setting can provide valuable mechanistic information that is related to changes in behavior.

CONCLUSIONS

To adequately solve the problems facing neurotoxicology, the generation of mechanistic data to fill data gaps and allow the construction of AOP networks is needed. Understanding the biological pathways involved in toxicological alterations will enable the predictive validity of *in vitro* screens and the physiological relevance of omic-based changes produced by toxicants to be verified. This type of validity is essential for regulatory purposes and will increase the translational relevance to humans. Given the impetus to use *in vitro* methods as the basis for future risk assessments (National

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Research Council, 2007; Krewski et al., 2010), the benefit/cost of animal research needs to be considered. At the current time, there is insufficient scientific knowledge to adequately develop *in vitro* tests to adequately assess and protect higher cognitive functions. Thus, judicious and hypothesis-driven *in vivo* research to determine mechanistic key events in AOPs and Integrated Approaches to Testing and Assessments (Organisation for Economic Co-Operation and Development, 2016) will provide toxicological linkages for regulatory purposes and allow the development of batteries of *in vitro* assays to eventually replace the majority of animal testing. It is the change in brain *function* that is of concern to the public. Since the 1700's, neurophysiology has been uniquely positioned to bridge the gap between mechanistic studies and *in vivo* alterations of the brain's neuronal networks, helping to fulfill the promise of systems biology to protect human and ecological health.

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