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Editorial

Bringing nerve excitability out of the research laboratory into the clinic

The study of nerve axonal excitability is not particularly new. In the last century, it was surpassed by techniques that gave rise to present standard nerve conduction techniques which yielded better information into number of conducting axons (amplitude) and the speed of the fastest conducting axons (conduction velocity). In some respects, these two broad categories of study are somewhat complementary. However, for more than 25 years, the study of nerve excitability has had a resurgence, not least because of the ability to conduct such experiments rapidly with the QTracs automated software protocol (Digitimer Ltd.®) developed by Hugh Bostock of University College London. The technique is often referred to as threshold tracking nerve (conduction) studies.

Very simplistically for readers who may not have had much exposure to the method, various developed protocols derived from previous observations of nerve behaviour in experiments on human and animal axons, are employed to study the properties of excitability in a short run of testing. Some 10–15 min are needed for motor and 20 min for sensory experiments in an intact human subject in typically the median nerve at the wrist. The process is widely accepted to involve minimal discomfort for the experimental subject, and has also been adapted for use in animal experiments. From this one site on the nerve under the stimulus where all measurements are collected and properties derived (hence its limitation with non-uniform nerve pathology), several perturbations that alter nerve threshold are made, and the required currents to return the excitability to status quo are measured. These include the length and strength of current and their relationship to each other (charge-duration relationship and the strength-duration time constant), the changes brought by subthreshold depolarizing and hyperpolarizing conditioning currents (current–voltage relationship and threshold electrotonus), and changes brought by preceding supramaximal conditioning currents of varying latency (recovery cycle). The advantage of the Qtracs technique is the ability to set a target response and quickly estimate the test current required to reproduce the target response after these perturbations.

The derived parameters and their properties give insight into axonal membrane potential, and properties of gated axolemmal ionic channels and pumps both at the node and internode. The interpretation of the measured data is beyond the scope of this editorial and readers are referred to introductions to the technique (Ng and Burke, 2007; Burke et al., 2001). Since the first seminal publication of this method (Bostock et al., 1998), there has been an explosion of such studies in peripheral nerve pathological states, and consensus guidelines exist (Kiernan et al., 2020). Following these, the method of threshold tracking was adapted to study cortical excitability (Vucic et al., 2006). The study of muscle excitability is somewhat different and via velocity recovery cycles (Z'Graggen and Bostock, 2009). This is designed to look at the property of muscle fibre conduction velocity and the effect of several conditioning stimuli and repetitive stimulation protocols on this parameter, and the list of articles published in this area is growing.

Most of the learnings from work in this area has forwarded our understanding of pathophysiology in various peripheral nerve disorders, although *trans*-synaptic and peripheral changes derived from central nervous system pathology such as multiple sclerosis have also been seen (Ng et al., 2008). From these early experiments, the logical follow up question was whether this technique could be used for diagnosis where other techniques like standard nerve conduction studies had not given the answer. It is evident from the plethora of publications that this is only sometimes the case, because unless the disorder was a pure channelopathy, it was unlikely that a single patient's recording was sufficiently outside normal confidence intervals. More has been learned from group-to-group comparisons.

Occasionally, this work has led to the rational selection of medication to trial in a disorder. For example, such as using a sodium channel blocker in Machado-Joseph disease (Kanai et al., 2003) where increased strength-duration time constant, and by inference, persistent Na^+ conductance, was found. Another notable area has been studies in chemotherapy induced peripheral neuropathy (Park et al., 2009). Although I know of no such translational computations, imagine if we could provide the oncologist an estimate of the likelihood in percentage terms of a further dose of a chemotherapeutic agent like a taxane to cause a clinically meaningful neuropathy; this could be based on predictive algorithms derived from previous work applied to an individual's serial tests following each treatment cycle. It is but one compelling reason to bring the technique to the clinic to complement the diagnostic armamentarium. Another could be to monitor a treatment effect of experimental agents in neurological disease, an area of study engaged in by the authors of the article in this volume of *Clinical Neurophysiology Practice* by Rutkove and colleagues (McIlduff et al., 2022).

To date, only a few specialised laboratories engaged in nerve and muscle research around the world perform such studies. So what has hampered the widespread adoption of this technique? To some extent, it was the availability of bespoke equipment and software required to conduct the experiments. For example, the

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most expensive component of the apparatus is the linear constant current bipolar stimulator (DS5, Digitimer Ltd.®). These obstacles can and have been overcome with commercialisation of the hardware and software (see article for full inventory), but the authors postulate the belief that the technique requires extensive training and experience to perform competently is the main reason impeding more widespread uptake. These authors, having experience with this method, set out to see if five operators who have varying levels of experience in clinical neurophysiology and naïve to the technique, could operate the setup successfully to obtain adequate recordings. This was arguably using more difficult sensory rather than motor studies because of signal to noise ratio. Questionnaires were administered for operators and subjects of the experiments.

The conclusion of this study was that the protocol could be performed adequately, but not without difficulties that were primarily related to the complexity of the software program. This is not an infrequent experience of first-time users as I can attest. However, this program was originally designed by Professor Bostock for research scientists and intended for operators cognisant of the principles of excitability testing, who had been coached and well versed in the methodology. To some extent, any attempt to bring into the mainstream for clinical neurophysiologists and technologists an understanding of how to conduct the test, was going to reflect the depth with which a locally written simplified manual was comprehensive enough a coverage of the methodology.

There are several points in that study to recapitulate. The actual preparation and placement of electrodes is rather standardised and unlike nerve conduction, there is less variance here. However, not unlike standard nerve conduction studies, there are many pitfalls to the technique, and one requires sufficient experience inside a laboratory experienced with it, to be able to deal with these and apply the technique correctly. Nevertheless, with a very well written and simplified manual (there are very many different recordings on the one screen during testing which can be appear overwhelming at times), an argument could be made for naïve users to complete a recording satisfactorily of not so diseased nerves; small potentials pose challenges just like in standard nerve conduction. However, diligent oversight by trained operators is required during testing in the initial training period. Even more care is required, this time by experienced personnel, in vetting the individual recordings for integrity and assembling the group data for interpretation, something that this paper did not aim to study. Mathematical models have been developed to better interpret the combinations of changes that may be seen in different portions of excitability testing. But we are still a long way from a recording that can be collected by a first-time user and plugged into a system that will output an unequivocal interpretation of a problem current or ionic channel. Before this can happen, as with all neurophysiological experiments, assiduous collection of technically sound recordings is the start and are key.

Conflict of interest

None.

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