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Editorial

The potential of visual physiology: An instrument with a place in MS translation

The contribution of Visual Evoked Potentials (VEP) to the diagnosis of Multiple Sclerosis has been superseded by magnetic resonance imaging and oligoclonal bands to collectively demonstrate the cardinal temporo-spatial dissemination of pathology (Modified MacDonald 2017 (Thompson et al. 2018)). The new criteria 'bring forward' diagnostic confidence providing an earlier opportunity to deploy licensed disease modifying therapies (DMTs). It is hoped earlier intervention with DMTs will reduce the initial inflammatory injury, which is both directly disabling and a probable precursor to the delayed axonal degeneration that underpins the progressive MS phenotype (Reich, Lucchinetti, and Calabresi 2018). However, 'No Evidence Of Disease Activity' data for even the most potent licensed therapies suggest that most patients will fail against this outcome within several years (Rotstein et al. 2015), and in response attention is now focusing on actively reparative strategies including putative remyelination therapies (RMTs).

A timely review by Barton and colleagues in this issue (Barton et al., 2019) focuses on the exquisite pathophysiological sensitivity of multifocal VEP (mfVEP) techniques, and thus suggests a potential new role for detecting RMT effects in MS. With the application of evoked potential techniques generally comes good construct validity in that latency parameters offer a causally-related index of demyelination and subsequent remyelination. The greatest challenge facing RMT translation is not a lack of putative agents worthy of evaluation, but rather the identification of a reliable biomarker against which they can be trialled (Ruggieri, Tortorella, and Gasperini 2017). That correction of conduction delays, due to demyelination, provides direct albeit partial symptomatic alleviation, is supported by the utility of the conduction-enhancing agent 4-Aminopyridine (Pavsic et al. 2015). Furthermore, the acute and longer term benefits of remyelination by oligodendrocyte precursors on axonal survival is suggested by empirical observations *in vitro* (Schultz et al. 2017) and from animal models (Gresle et al. 2016).

Whilst there may be a strong biological rationale for pursuing RMTs, several important considerations remain. Firstly, it is hoped that the more prolonged testing time for mfVEPs is not too hindered by the ubiquitous fatigue afflicting MS patients, which can limit even shorter standard VEP acquisition. Secondly, there remains concern surrounding the criterion validity of visual physiology to act as a surrogate of overall clinical disability in MS. Barton and colleagues recognise that the relationship between visual electrophysiology and clinical disability outcomes used in phase 3 trials is likely to be poor. Notably we are seeking RMTs that benefit overall disability, such that the resulting licensed indications are not restricted to *limiting* visual failure which affects a minority of patients (acknowledging that many may have milder or even subclinical deficits). It is questionable as to whether a provoked rectification of visual conduction would predict an improvement on overall ratings of disability. Unfortunately the therapeutically enhanced remyelination induced recovery of VEP conduction observed in phase 2 trials has not been consistently associated with a clinically meaningful improvement in visual function itself (Petrillo et al., 2018; Cadavid et al., 2017).

Utilising mfVEP as part of a multimodal Evoked Potential (mmEP) battery might strengthen the content validity by capturing more of the disseminated demyelination present. Indeed, multimodal approaches offer close association with the final phase 3 clinical disability measures (Canham et al., 2015). However, EDSS outcomes appear predominantly determined by myelopathic burden and long tract integrity (Daams et al., 2015). It may be erroneous to give equal weighting to visual and long tract EPs in the currently described mmEP rating systems, or to assume that their constituent fibres are all equally reparable. Whilst the human optic nerve and murine spinal cord currently used in RMT paradigms are not too dissimilar morphologically, there are orders of magnitude difference in scale and possible vulnerability between such pathways and the long tracts of the human spinal cord which determine disability. Nonetheless, the elegant visual electrophysiological techniques reviewed by Barton and colleagues suggest an approach that may allow investigators to favourably alter the difficult balance of candidate advancement and rejection in translational endeavours.

Conceivably, candidate RMTs could be tested in phase 2a paradigms utilising visual metrics. A standardised visual electrophysiological acquisition could be deployed alongside structural morphometrics, from both the eye itself by optical coherence tomography (OCT) and the retrobulbar pathways by diffusion tensor imaging. This would play to the mfVEP strengths of greater subclinical and subradiological sensitivity, enabling potential detection of RMT effect in the human setting, as envisaged by Barton and colleagues. There could be a smaller scale of study required from investigations using optic physiological and a morphometric OCT counterpart (a reliable equivalent of which is missing for the spinal cord), in comparison to the current mmEP batteries. One might start with this first step RMT 'screening' paradigm, rather than directly embarking on a larger and requisitely more resource intensive cord-based assay which could be undertaken subsequently, prior to a pivotal phase 3 trial. With this two-step phase 2 approach poorly remyelinating agents, without effect against a sensitive system, could be discarded on the basis of a small, practically achievable but nonetheless well powered study. Subsequent

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risk of failure at phase 3 could be minimized by testing against the higher-bar of long tract rescue beforehand in a hundred or so patients, which would causally-relate to the clinical outcome necessarily tested in nearly a thousand. The importance of possessing a reliable biomarker surrogate of the clinical outcomes accepted for use by regulatory authorities in pivotal phase 3 studies simply cannot be overstated. The phase 3 failure of fingolimod in primary progressive multiple sclerosis (INFORMS) (Lublin et al., 2016), an effort in part inspired by a positive response against brain volumetrics at phase 2 in earlier disease, was perhaps partly attributable to the lack of sufficiently meaningful relationship between the biomarker in question and the desired clinical disability outcome. The costs of such failures are not only the contemporaneous loss of fiscal resources and potentially unnecessary risk exposures to enrolled patients, but may provoke withdrawal of industrial efforts. Visual electrophysiology is evolving and may hold promise in accelerating translational endeavours in MS, aiming to achieve something previously considered impossible.

Declaration of Competing Interest

None.

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