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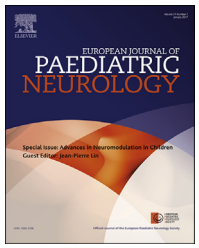

Original article

Advancing non-invasive neuromodulation clinical trials in children: Lessons from perinatal stroke

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ABSTRACT

Applications of non-invasive brain stimulation including therapeutic neuromodulation are expanding at an alarming rate. Increasingly established scientific principles, including directional modulation of well-informed cortical targets, are advancing clinical trial development. However, high levels of disease burden coupled with zealous enthusiasm may be getting ahead of rational research and evidence. Experience is limited in the developing brain where additional issues must be considered. Properly designed and meticulously executed clinical trials are essential and required to advance and optimize the potential of non-invasive neuromodulation without risking the well-being of children and families. Perinatal stroke causes most hemiplegic cerebral palsy and, as a focal injury of defined timing in an otherwise healthy brain, is an ideal human model of developmental plasticity. Advanced models of how the motor systems of young brains develop following early stroke are affording novel windows of opportunity for neuromodulation clinical trials, possibly directing neuroplasticity toward better outcomes. Reviewing the principles of clinical trial design relevant to neuromodulation and using perinatal stroke as a model, this article reviews the current and future issues of advancing such trials in children.

1. First principles of neuromodulation clinical trials

Non-invasive brain stimulation applications are exploding. There is great and justified concern that the rate of growth in the number of brains being stimulated is already far exceeding the level of science that supports the approach. There are major issues of unregulated use across broad and often vulnerable populations with immoral marketing of unproven, potentially dangerous devices. Examples range from shameless promotion of enhanced gaming performance to teenagers to do it yourself tDCS machines being made in people's basements. Ethical issues specific to the application of brain stimulation in children must also be considered. For these reasons, and in order to advance the responsible scientific study of neuromodulation in the developing brain, several principles merit discussion here.

It is highly unlikely that introducing a focal magnetic field or local current into a functional area of human cortex will

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magically create new, clinically relevant function. Instead, an endogenous substrate for neuroplasticity that might be altered by such neuromodulation seems a much more likely mechanism by which brain stimulation might produce lasting, therapeutic alterations in brain function. This fundamental tenet also helps correct for the known and large heterogeneity between subjects inevitably enrolled in such trials. That a TMS measurement as simple as the rest motor threshold can range from 20 to over 60% of maximum stimulator output across a sample of normal subjects of the same age and gender points to an even more enormous inter-subject variability in clinically diseased populations. However, if such subjects share fundamental neuroplasticity mechanisms within their cortex (e.g. long term potentiation) and are induced to activate them in the context of desired, functional activity, the potential for neuromodulation is likely greater.

In a similar context, an informed cortical target for modulation is also essential. Identification of such functionally relevant cortical regions is often difficult. As outlined below, studies of enhancement of motor learning with brain stimulation and have often logically targeted the primary motor cortex. This has logically extended to clinical populations with motor disability, targeting the motor cortex and related network components in common populations of motor disability such as adult stroke hemiparesis.[1] Importantly, this evolving process has not rested on such simplistic anatomical localization alone. Instead, neurophysiological models have been developed to first understand what happens to the system of interest in the disease state. These often include large bodies of evidence from preclinical animal models combined with human studies using advanced neuroimaging and other neurophysiology tools. Such an example for perinatal stroke will be presented below.

Such models not only identify potential targets but also a desired direction for change. For example, the lesioned motor cortex may be underactive while the homologous region of the contralateral, non-lesioned hemisphere may be relatively overactive. Such a model of "imbalanced interhemispheric motor inhibition" is probably over simplified but is well supported by large volumes of neurophysiological evidence and has driven the majority of non-invasive brain stimulation trials in adult stroke.[1,2] Recent summative evidence of rTMS therapeutic trials highlights this point by comparing modalities and targets across a wide range of such conditions.[3]

Importantly, each these three principles of *modulating an informed target in a specific direction during activation of endogenous plasticity* are arguably still not well defined in relatively concrete examples like adult stroke. In fact, such principles are often not entirely obvious (or even theoretically well defined) in many other stimulation clinical trials. While such failure should raise immediate concerns of validity, their presence is relatively sparse in the most defined therapeutic non-invasive brain stimulation population: adult major depression. High frequency rTMS of the dominant dorsolateral prefrontal cortex (DPFC) is FDA and Health Canada approved and rapidly expanding as an insured service. While based on some human evidence of regional dysfunction in this broad, highly connected area with functional implications for some symptomology, it could be argued that the ability of depression to satisfy the above criteria is modest at best.

This raises a final principle consideration of disease specificity. As a very common, disabling, and highly studied disease, major depression carries well-defined diagnostic and classification criteria. Despite this, there are innumerable factors, both measureable and unknown, that would likely influence response to neuromodulation. In contrast, autism is a heterogeneous disorder of social and communication development that is likely due to hundreds of different genetic disorders in addition to other etiologies. This does not mean that informed, symptom-specific targeting of cortical regions to enhance other therapies or learning is impossible. However, the breadth of heterogeneity must be acknowledged and adjusted for whenever possible if meaningful trials are to be designed. Trials of autism due to one specific mutation bring limitations of recruitment and sample size and are still not ideal; consider the phenotypic variability of tuberous sclerosis alone. However, striving for disease specificity whenever possible will likely advance progress in paediatric neuromodulation trials much faster. Extricating the very specific forms of perinatal stroke from the more complex world of cerebral palsy for motor learning neuromodulation trials provides a practical example.

2. Perinatal stroke

You will not likely incur a higher period of risk for ischaemic stroke than the week you are born.[4] A term newborn carries a risk >1:3500,[5] three-fold higher than a week in the life of a diabetic, hypertensive, smoking adult and eight-fold above all adults.[6] An additional 50% of perinatal stroke presents later in infancy.[7] Perinatal stroke is the leading cause of hemiplegic cerebral palsy (HCP) and most survivors suffer additional neurological sequelae including intellectual disabilities, language impairments, developmental and behavioural disorders, and epilepsy.[8–10] Frequent occurrence combined with lifelong morbidity generates large global burdens. Identification of a causative factor remains elusive in most cases[11] and with no means of prevention, perinatal stroke and HCP will burden thousands of children for decades to come.

An essential first step in improving outcomes from perinatal brain injury is to understand the underlying disease. We have defined distinct clinical-radiographic perinatal stroke syndromes,[11,12] refining perinatal stroke research toward specific disease states. Two main types predominate. These are summarized in Fig. 1. We have validated this imaging-based classification system and demonstrated it's research applications including the prediction of long-term neurological outcomes,[12,13] recognition of novel risk factors,[14–16] imaging markers of disease processes, and new targets for therapeutic interventions.[14,17] **Arterial ischaemic strokes (AIS)** are large brain injuries secondary to occlusion of major cerebral arteries. Some present at birth with acute seizures (called symptomatic neonatal AIS) while others are not recognized until infancy when hemiparesis becomes evident (called arterial presumed perinatal ischaemic stroke).[7,18–20] In contrast, **periventricular venous infarctions (PVI)** are subcortical white matter lesions acquired well before birth. Secondary to germinal matrix bleeds with subsequent medullary venous infarction, these lesions occur *in utero* before 34 weeks