Title:

Neurostimulation devices for children: lessons learned

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Keywords:

Neuromodulation, neurostimulation, deep brain stimulation, responsive neurostimulation, paediatric.

Commentary:

Intracranial neurostimulation therapies, namely deep brain stimulation (DBS) and responsive neurostimulation (RNS), are well-established in adult practice for the treatment of neurological disorders. There has recently, however, been an accelerated interest and use of these therapies to treat children with neurological diseases – in particular, epilepsy and dystonia. In paediatric medicine a well-respected doctrine is that *'children are not just small adults'* [1] and this sentiment should be followed when designing medical technologies for children. In current practice, however, most market available neurostimulation devices were designed for adults before later being repurposed for children. These devices are therefore sub-optimal for meeting the specific needs of children, who require additional design considerations to those of adult-centric technology.

In this commentary we define the child-specific requirements for the development of intracranial neurostimulation devices based on current evidence, experience, and patient/public involvement.

Although the literature for paediatric neurostimulation is relatively sparse, device design must learn from deficiencies and complications reported from clinical application. For example, Kaminska et al reported that frequent complications in 129 children (3-18 years) undergoing DBS for dystonia were electrode extension complications (18.4%)[2]. Standard subclavicular DBS technologies require a battery and pulse generator to be implanted in the chest wall which are subsequently connected by 'extensions' to the skull device. Devices with fixed-length extensions predictably cause extension complications (fracture, disconnection or tightening) in children. There is thus a need for devices that children cannot 'grow out of' – i.e. either unaffected or dynamic in response to child growth. It should be noted, however, that these complications reported in Kaminska's series are solely from children with dystonia. It is therefore difficult to discriminate between extension complications caused due to dystonic symptoms versus child growth. Hudson et al compared DBS devices to cochlear implants and remarked that the 'miniaturization' of DBS devices would mitigate extension complications[3]. The success of cranially-mounted implantable pulse generators (IPG) has been demonstrated by the RNS® system. Although not yet FDA licensed nor NICE approved, the RNS® system has an emerging evidence base for paediatric neurostimulation[4].

In addition, Kaminska's study quoted an infection incidence of approximately 10%[2] while data from cranially-mounted RNS were reported as 5.2%[5]. Thus, a further benefit of cranially-mounted systems for paediatric DBS is the probable minimisation of the risk of device infection. The potential disadvantages of cranial-mounting, however, is the challenge of pulse generator / battery replacement in the context of either device

infection and skull growth. There is no current evidence that convincingly gives guidance to the management of these factors.

The gold-standard device is one that does not require replacement – a difficult demand for neurostimulator and battery technologies asked to survive the lifetime of a child. Whilst, for example, first generation RNS devices are reported to have a median implant-to-replacement time of 3.5 years[6], we are now able to offer patients non-invasively rechargeable devices that do not require surgical replacement. That said, rechargeable batteries still have a limited lifetime and may 'stop working' due to issues such as battery fade (loss of capacity during repeated recharges). Additionally, there is evidence that battery lifespan is dependent on stimulation settings. Therefore, we have an ongoing challenge of developing advanced stimulation regimes to deliver more effective therapies without compromising the temporal resilience of the device.

Next generation technologies should allow not only stimulation, but also recording. The ability to record from the intracranial leads is an ability in RNS and some DBS devices designed for research, but is not possible in most market-available neurostimulators. The availability of a brain-machine interface in children with severe neurological disease should be regarded as an opportunity to derive the neuronal signatures of the disease and to develop more effective therapies. Additionally, real-time monitoring may better inform the delivery of adaptive and personalised neurostimulation regimes to maximize clinical benefit[7].

Frequent and in-person follow up may be intrusive to a child's lifestyle, education and overall quality of life. This is particularly relevant to children requiring frequent follow-up with quaternary and geographically distant clinical services. The COVID-19 pandemic has served as a catalyst towards the switch to remote/virtual consultations in clinical practice, and this has been shown to be safe and acceptable in adult DBS practice[8]. New generation neuromodulation devices that allow for remote programming and consultation will likely become essential feature of these technologies.

Device design must also learn directly from the perceptions of children and families. Our public and patient involvement exercises have detected themes of anxiety towards the technology, including device failure causing side effects; the idea that implantable brain devices could 'spy' on their thoughts, track their whereabouts or control their brain from afar without their consent. Another theme of concern from children regarding DBS therapy is that the primary goal is speculated as the ability to be or become a normal living child, like their peers, with the ability to be active in sports, play, swim, and education. Device design should consider these issues carefully – for example, the assurance of robust devices that deter the apprehension of impact risking injury to child or damage to the device.

The design of medical devices for children is an economical challenge. Device companies are unlikely to invest in child-specific technology and therefore we are reliant on "platform economics" where the development costs are transferable across multiple therapies[9]. We propose that an inversion of current technology design practice to instead prioritise the development of devices for children (for whom the technology demands are more challenging). This inversion could instead allow the repurposing paediatric developments to provide more robust devices for adults.

In summary, we have identified that intentional neurostimulation device development for children is essential. We identify the need for devices that are robust despite child growth, unfailing across a lifetime, infection avoidant, non-invasively rechargeable, provide adaptive/personalised therapy, remotely programmable, and trusted by children and parents. Lastly, robust clinical evidence is required to determine the real-world advantages of 'next generation' devices in paediatric neurostimulation. For this reason, we are setting up our own *Children's Adaptive Deep brain stimulation for Epilepsy Trial (CADET)* using a cranially-mounted neurostimulator aims to contribute such evidence.

Acknowledgements:

We are grateful to the Great Ormond Street Hospital Young Persons' Advisory Group for research and Professor Tim Denison for their time spent with us discussing neurostimulation devices for childhood epilepsy.

Declaration of interests:

The authors of this commentary are in the process of setting-up a clinical trial of deep brain stimulation for children with Lennox-Gastaut syndrome using the Picostim DyNeuMo device (Bioinduction Limited). None of the authors have a financial conflict of interest.

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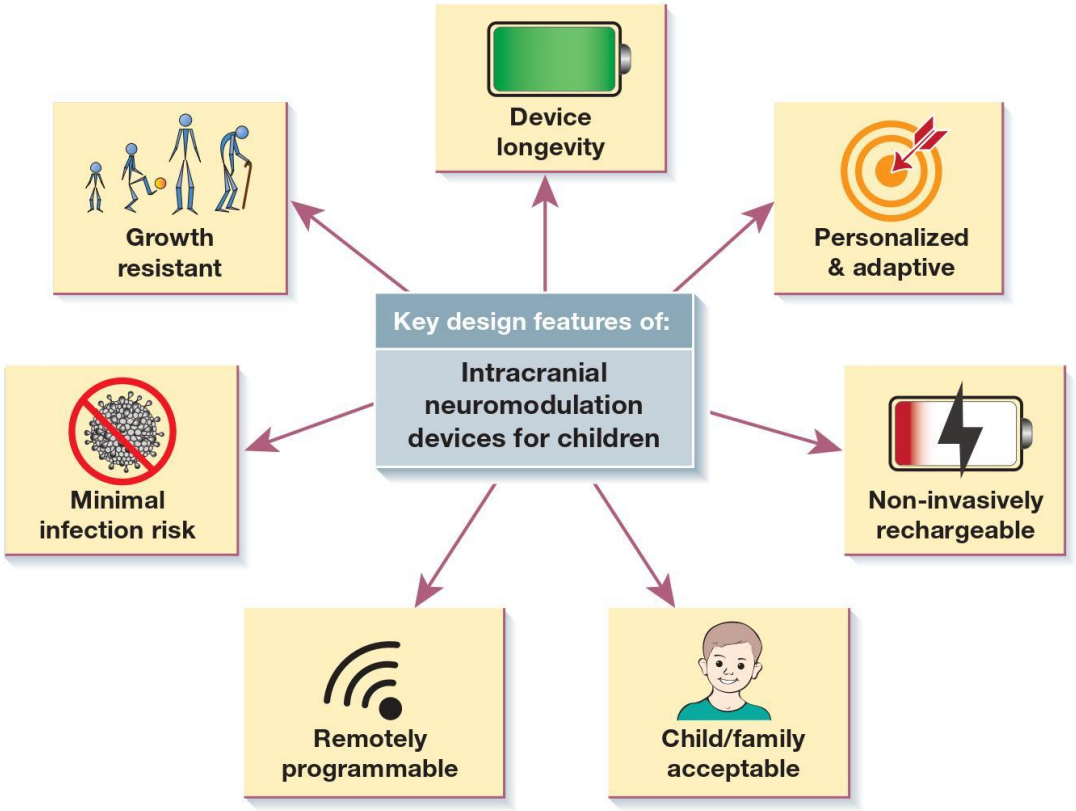

Figure 1: Pertinent design features of next-generation intracranial neuromodulation devices.

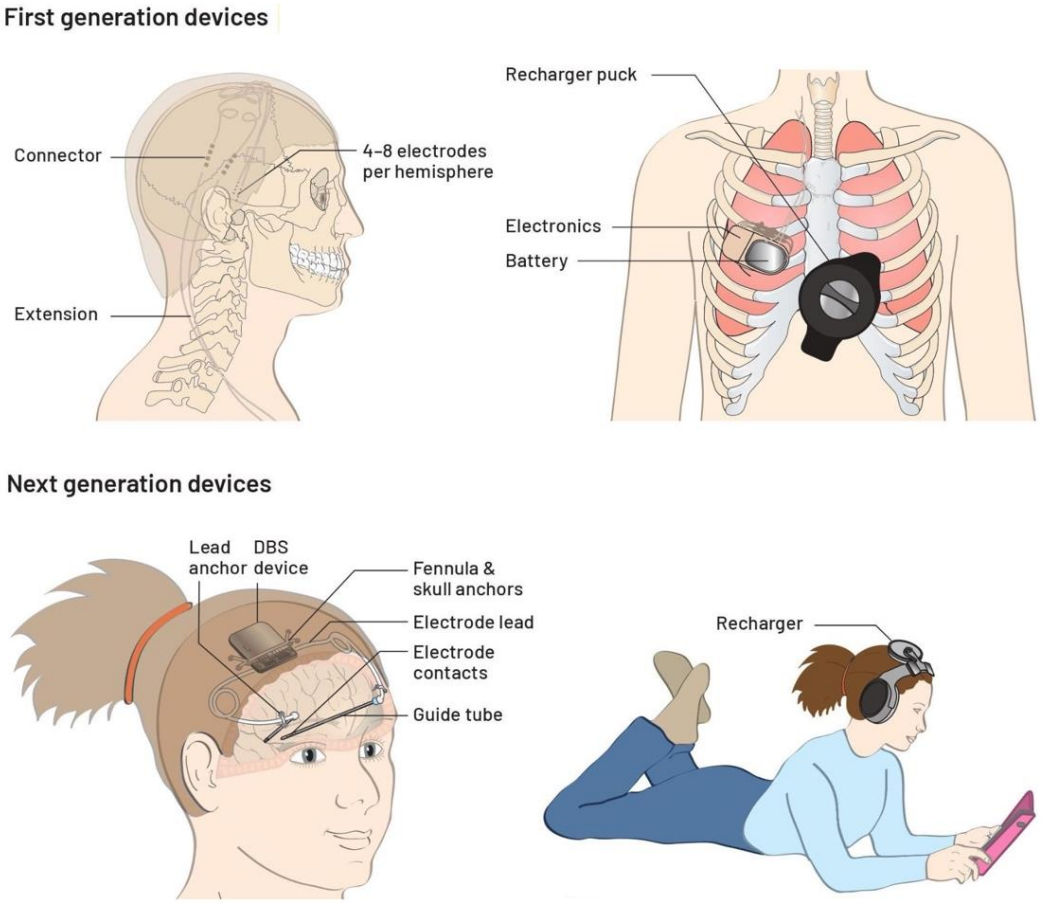

Figure 2. A visual comparison between 'first generation' (current) and the proposed 'next generation' (ideal) deep brain stimulation devices. Cranially-mounted devices remove the requirement for tunnelling extensions to a battery or pulse generator in the chest wall. As per some currently available neurostimulators, next generation devices should be non-invasively rechargeable by means that are convenient and acceptable to children.