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Translational considerations for the design of untethered nanomaterials in human neural stimulation

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ABSTRACT

Neural stimulation is a powerful tool to study brain physiology and an effective treatment for many neurological disorders. Conventional interfaces use electrodes implanted in the brain. As these are often invasive and have limited spatial targeting, they carry a potential risk of side-effects. Smaller neural devices may overcome these obstacles, and as such, the field of nanoscale and remotely powered neural stimulation devices is growing. This review will report on current untethered, injectable nanomaterial technologies intended for neural stimulation, with a focus on material-tissue interface engineering. We will review nanomaterials capable of wireless neural stimulation, and discuss their stimulation mechanisms. Taking cues from more established nanomaterial fields (e.g., cancer theranostics, drug delivery), we will then discuss methods to modify material interfaces with passive and bioactive coatings. We will discuss methods of delivery to a desired brain region, particularly in the context of how delivery and localization are affected by surface modification. We will also consider each of these aspects of nanoscale neurostimulators with a focus on their prospects for translation to clinical use.

1. Introduction

The field of neurostimulation has evolved significantly in the past decades with many alternatives to traditional clinical tools. For neurological disorders, the efficacy of preventive and drug-based treatments is limited, mainly due to blood-brain barrier permeability issues [1,2]. Instead, non-pharmacological approaches to modulate pathological neural activity have emerged, such as transcranial magnetic stimulation (TMS) [3], deep-brain stimulation (DBS) [4], or focused ultrasound (FUS) [5] as one of the newest strategies.

Among key considerations when selecting the best modulatory approach for a given application are the invasiveness of the technique, and the size and depth of the targeted area. As these variables are often conflicting, the most precise clinical treatments available, such as DBS, are often also the most invasive. Even with clinically-approved techniques like DBS and TMS, the exact mechanism and extent of the electrical stimulation delivered remains unclear (for review, see Refs. [6–8]). Additionally, the benefit from interventions such as DBS must be weighed against risks and side-effects common for all surgeries (e.g. infection, bleeding) and those specific to neuroprosthetics (e.g. implant rejection, electrode displacement, scarring) [9]. These risks limit their application to a smaller patient population, and only those with severe impairments [10]. To circumvent these risks, recent research into neural devices has focused on smaller and remotely powered devices. In particular, nanoscale, untethered, injectable materials are of particular interest, as they can be delivered via minimally invasive routes, and require no external wiring [11].

In pre-clinical research, several breakthroughs have been made in recent years in order to potentially resolve some of these issues. Minimally-invasive and cell-specific neurostimulation strategies have been made possible thanks to the advent of opto-, thermo- and chemogenetic tools [12–14]. Using ion channels responsive to light, heat, or a specific chemical, these approaches allow the user to selectively excite or inhibit neurons using the external stimulus. While many fundamental neuroscience discoveries have been made possible with these techniques in animal models, their translation to human neurostimulation is fundamentally

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challenged by their reliance on genetic engineering to deliver the responsive elements, such as ion channels. Other issues are also present, such as the temporal resolution of the techniques, which is particularly slow in chemo- and thermogenetics. While optogenetics does work with high temporal precision, it still requires an implanted device (e.g., fiber optic through a cranial window) or equivalent means to deliver light to the target site [15]. Moreover, these technologies carry the potential risk of altering the function of intrinsic cellular machinery as a result of the insertion of large numbers of foreign ion channels or pumps into the cellular membrane [16].

Considering these limitations, the use of targeted, field-transducing nanomaterials could complement the current clinical and pre-clinical options available for neurostimulation. Several key factors need to be addressed to realize them as neurostimulators: non-invasive delivery of the nanomaterials to a desired brain target, passive and active spatial selectivity of the nanomaterials' localization, and the use of endogenous neuronal responsive molecules (e.g., mechano- or voltage-sensitive ion channels) which interact with the nanomaterials transduced signal. In this review, we will explore properties of nanomaterials that can be used for neurostimulation, and how their material-to-tissue interfaces can be engineered to address these core issues.

While nanoscale neurostimulators have different requirements than other nanomedicines, the delivery and localization challenges that they face inside of the body are similar. As such, the design of nanoscale neurostimulators can take cues from nanomedicine as they move towards clinical use. In cancer theranostics, for example, nanomaterials are mainly used as environmentally-sensitive carriers of drugs or bioactive molecules, and can be actively or passively targeted to tumor cells, while ignoring healthy tissue. For neurostimulation, however, the nanomaterials themselves are typically the cargo, so that they may act as nanotransducers of external signals to modulate neuronal activity [17]. Similar properties have previously been exploited in clinically-approved thermal ablation procedures with magnetic iron oxide particles for some types of tumors [18]. Based on these transducing properties, and using less extreme energy fields, nanomaterials can be used in the brain to spatiotemporally stimulate or inhibit neuronal activity. Several comprehensive reviews of recent advancements in cancer applications of nanomaterials are already available, and can be used as guides for similar constructs [19,20]. This review will focus on exploring existing and potential combinations of surface coatings, avenues for systemic delivery, and tissue targeting strategies with untethered nanomaterials for applications in neural stimulation.

1.1. Conventional neurostimulation: strategies and limitations

Broadly, neuromodulation can be defined as the external manipulation of neuronal activity through either physical or chemical means, including electrode stimulation, as well as delivery of neuromodulatory drugs [21]. Within the broader scope of neuromodulation, neurostimulation typically involves only electrical alterations of neuronal activity in real time. While neurostimulatory patterns can cause longer term neuromodulatory effects, the signal transmission that neurostimulation requires present a unique set of challenges when devices are remotely powered.

In the clinic, electric and magnetic stimulation techniques can treat some neurological conditions. Generally, electric stimulation of neurons can be achieved either by direct contact between electrodes and brain tissue (e.g., DBS; subdural grids of cortical electrodes), or by an external electric field applied over the intact skin (e.g., transcranial direct (tDCS), or alternating current stimulation (tACS) [22]. Direct contact with electrodes normally requires minimally-invasive surgery involving a craniotomy and several long-term implants, with all the associated risks of bleeding, displacement, and infection [9]. Similar to tDCS and tACS, non-invasive stimulation of neurons can be achieved transcranially with a magnetic pulse (i.e. TMS) [3] or FUS [5]. While the non-invasive electromagnetic strategies are able to bypass some of the surgical issues, they are limited in terms of localizing the stimulatory output to a small brain region, reaching deeper areas, or increasing intensity without over-stimulating more superficial networks and tissues [23]. Additionally, the modulatory effects of repetitive transcranial stimulation, both electric and magnetic, are reported to be only transient for most patients and usually the effects wear off in less than a year [24,25].

While these modulatory options have been a significant improvement of clinical care for neurological diseases, their mechanisms of action are still poorly understood overall [7,22]. Gold-standard DBS treatments today still present considerable technical issues (e.g., there is often a suboptimal control of the overlap of the volume of tissue activation (VTA) with the desired neuronal target [26,27]) as well as limitations in their therapeutic effect (e.g., with current clinical approaches, it is hard to predict a patient's response to DBS treatment beforehand [28] or selecting the optimal brain region as a target [29]). Current non-invasive options are also unable to appropriately target most deep brain regions. The ability to manipulate specific neuronal networks has been partially enabled pre-clinically using opto-, thermo- and chemogenetic procedures, which have high spatial selectivity (for review, see Ref. [11]).

Optogenetics can be broadly defined as genetic engineering of neurons and other cells to enable photosensitivity via the expression of light-sensitive ion channels. Once stably expressed, a light source (e.g., a fiber optic implant) can be used to modulate the neuronal activity in the millisecond-scale [15,30]. Similar strategies use thermosensitive ion channels instead, which are activated by an increase in temperature after irradiation with light [12,31]. Chemogenetic strategies instead rely on the stable expression of a modified ion channel designed to interact with an exogenous molecule, which must be delivered to the modified neurons either directly (e.g., intracranial injection) or systemically. Consequently, the ability to observe neuronal modulation is constrained by the pharmacological profile of the stimulating drug, usually yielding relatively long response times (tens of seconds up to minutes) versus that of optogenetics [32], while also presenting limited spatial selectivity in the brain tissue when the drug is administered systemically. While the benefit of using these techniques in fundamental neuroscientific research is unquestionable, their translation to the clinic is currently limited by several technical challenges [33], including the frequent need for the targeted neurons to be genetically modified in order to achieve stimulation.

2. Nanomaterials for neural stimulation

Nanomaterials have several applications in the nervous system as drug delivery agents, immune modulators, and modulators of neurodegenerative pathways [34,35]. In such nanomedicines, the materials are often preprogrammed to carry out their role, and require no external input following implantation into the body. Conversely, nanomaterials for neurostimulation must act as transducers of an applied energetic field to achieve neural stimulation. As such, the materials suitable for neurostimulation carry different requirements and present different challenges than their neuromodulation counterparts.

The first step in the design of a neurostimulatory intervention entails the selection of the applied stimuli and an appropriate responsive nanomaterial. Organic and biological materials often do

not contain enough metallic elements and crystalline structures as to yield strong transducing effects. While they still may be used in the final nanostimulator design, the core transducing properties are normally provided by a metallic or inorganic compound [36]. Current wireless transduction methods include photothermal, photomechanical, photoelectric, photochemical, magnetothermal, magnetomechanical, magnetoelectric, or acoustoelectric interactions [37–40]. A further consideration for the input signal and transducing material is spatial selectivity. Depending on the transduction mechanism, and the ability of the input signal to penetrate tissue, spatial selectivity can be achieved either by localized signals, or localization of the nanomaterial, but with globally applied input stimulation. Fig. 1A shows a summary of these transducing mechanisms, and Table 1 lists all current nanomaterial designs used in neurostimulation. It should be noted that in some experimental settings, more than one of these transduction mechanisms may be present at once, as chemical, mechanical, thermal, and electrostatic energies all converge at the nanoscale [36]. The following section will therefore focus on the nanomaterials used for neurostimulation.

2.1. Gold nanoparticles

Gold nanoparticles (AuNPs), mainly gold nanorods (AuNRs) and nanospheres (AuNSs), have several applications in the biomedical field as a photothermal material which also provides chemical and physical stability, relatively low toxicity, and facile surface modification [41]. Common synthesis techniques for AuNPs include template-assisted gold deposition on a nanostructured surface, electrochemical reduction of gold clusters on an anode, and seed-growth mediated synthesis using nucleating and reducing agents. For further details, see Refs. [42,43]. AuNP photothermal properties are the result of the interaction of AuNPs with light in the visible or near-infrared range. This interaction, which is highly dependent on size and shape, produces a displacement of electrons in the material from their equilibrium position, and creates a resonant coherent oscillation known as the localized surface plasmon resonance (LSPR). In many optical biological applications, the LSPR peak is tuned in order to match the transparency range of biological tissues (600–1200 nm) and provide controllable heating in the immediate proximity of the AuNPs [41,44]. Since not all shapes allow for this tuning, morphologies apt for optical approaches are nanorods, nanoshells, nanostars and nanocages. Thus far, only nanorods and nanospheres have been employed in neurostimulation research (Fig. 1E) [38,45–49]. It should be noted that in the case of [48], the reported effect on neurons is stimulation of cell growth (e.g., neurite growth) and not the induction of action potentials, which would be considered actual neurostimulation. In addition to their photothermal capabilities, AuNPs can also exert photomechanical effects via the formation of small bubbles which open pores in the cell membrane, thanks to high energy output at the LSPR peak [44,50]. The AuNPs themselves can be used as free-standing devices [45,46,51] or be incorporated into nanostructured electrode arrays, such as nanoelectronic threads [52].

2.2. Carbon nanomaterials

Carbon nanomaterials present a wide diversity of structures, morphologies, physical properties, and chemical reactivity depending on the carbon allotrope used. While different synthesis protocols are possible, chemical vapor deposition using hydrocarbons as fuel and metallic nanoparticles as catalysts is the most common method [53,54]. Carbon nanomaterials can be nanotubes (CNTs) (single-walled (SWCNTs) or multi-walled (MWCNTs)), nanohorns, nanodiamonds, fullerenes, nano-onions, graphene dots and other variants. This class of nanomaterials is a promising tool for many biomedical applications in imaging, diagnostics, and therapeutics [55,56]. Since carbon nanomaterials show low toxicity with neurons *in vitro* [57–60] and remarkable physical and electrical properties, their main research applications have been directed towards neuroregeneration [55,61–63]. They have also been used as interface materials for recording and stimulation of neural tissue as components of a larger, tethered system [64,65]. However, most studies involving these nanomaterials are not focused on the central nervous system (CNS), and have rarely been tested *in vivo* [56]. Furthermore, novel carbon nanomaterials such

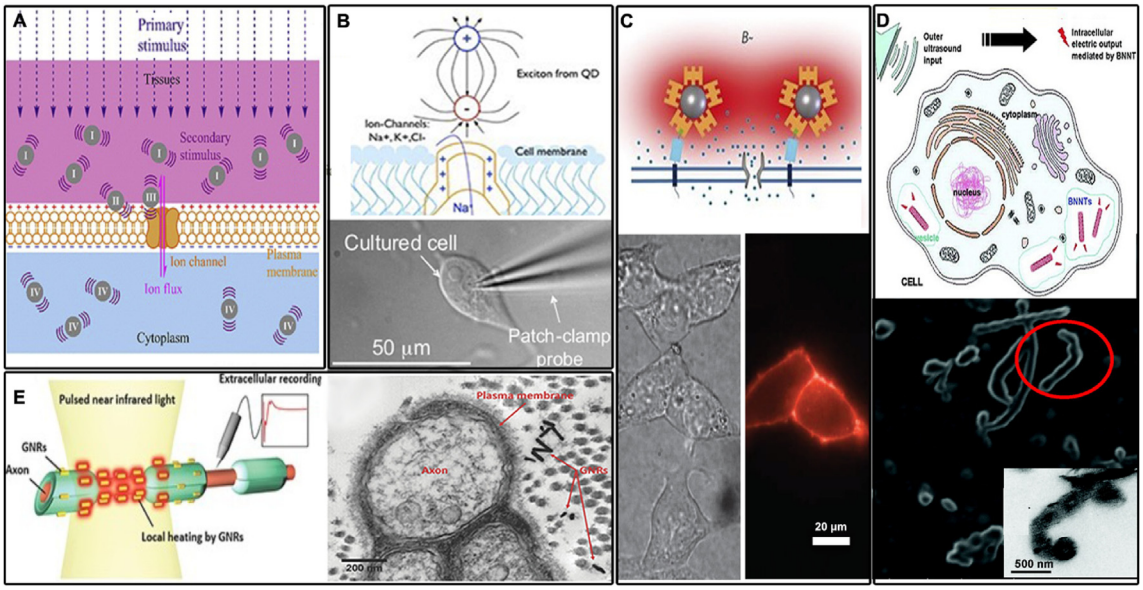

Fig. 1. Overview of transducing mechanisms and their respective nanomaterials. A: General transducing mechanism; B: Photoelectric stimulation with quantum dots; C: Magnetothermal stimulation with magnetic nanoparticles; D: Acoustoelectric stimulation with boron nitride nanotubes; E: Photothermal stimulation with gold nanorods. Reproduced with permission [14,39,45,77,89]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Current nanoparticle technologies for neural stimulation.

Nanomaterial	Type of nanoparticle	Publication	Input carrier signal	Output stimulation signal	Surface and ligands	Delivery method	Genetic modification	Dose	Stimulation read-out	In Vitro or *in vivo*	Experimental model
Gold	Nanorods	Yong et al., 2014 [46]	Optical	Thermal	PEG-thiol and silica coating	N/A	N/A	N/A (diluted until optical density absorption = 0.18)	Membrane clamp recording (mV)	In vitro	Rat primary auditory neurons
		Eom et al., 2014 [45]	Optical	Thermal	N/A (commercial)	*In situ* injection	N/A	3.4×10^{13} particles/ml	Compound nerve action potentials (mV)	In vivo	Rat peripheral nerve
		Nelidova et al., 2020 [49]	Optical	Thermal	Conjugated to antibodies	*In situ* injection	rTRPV1, sTRPA1, and GCaMP6s by viral transduction	Max. 2.5 μL at 10^{13} nanorods per ml per eye (mice)	Calcium imaging + Behavioral tests (mice)	In vivo and ex vivo	Live mice retina and ex vivo human retina
	Nanospheres	Carvalho-de-Souza et al., 2015 [51]	Optical	Thermal	Commercial streptavidin-conjugated NPs and biotinylated antibodies	N/A	N/A	50 nM to render 80 % cells sensitive	Membrane clamp recording (mV)	In vitro	Mice hippocampal slices
Carbon and structural derivates	Carbon nanotubes with Quantum dots	Bareket et al., 2014 [64]	Optical	Electrical	QD-glutathione embedded in acrylic acid-coated CNT film	N/A	N/A	N/A (film)	Membrane potential (mV)	In vitro	Embryonic chick retinal cells
	Carbon nanotubes	David-Pur et al., 2014 [65]	Optical	Electrical	Pure CNTs film in poly(dimethylsiloxane)	N/A	N/A	N/A (film)	Evoked activity + Firing rate	In vitro	Embryonic chick retinal cells
	Boron-nitride nanotubes	Ciofani et al., 2010 [77]	Acoustic	Electric	Glycol-chitosan dispersion	N/A	N/A	50 μg/mL	Neurite growth	In vitro	Differentiated PC12, and SH-SY5Y cells
Iron oxide and multiferroic ceramics	Fe_3O_4 (magnetite) spherical nanoparticles	Chen et al., 2015 [66]	Magnetic	Thermal	PAA and PEG coating	*In situ* injection	TRPV1 by viral transduction	2.5 μL solution (100 mg/mL) bilaterally	Fluorescence	In vivo	DBS of ventral tegmental area (VTA) in mice
	Ferritin-GFP construct	Stanley et al., 2016 [67] (disputed)	Magnetic	Thermal	N/A (GFP-tagged ferritin)	*In situ* injection	2 constructs (TRPV1-antibody and GFP-ferritin) by viral transduction	N/A (nanostimulators produced intracellularly by transfection)[a]	Membrane clamp recording + Calcium imaging + Chloride imaging	In vivo	Mice ventromedial hypothalamus (VMH) activation and inhibition
	Co−Mn-Ferrite core-shell nanoparticles	Munshi et al., 2017 [70]	Magnetic	Thermal	PMA dispersion with carboxyl activation via EDC	*In situ* injection	TRPV1 by viral transduction	Range (2−15 mg/ml)[a]	Calcium imaging + Behavioral tests	In vivo	DBS of striatum in mice
		Munshi et al., 2018 [69]	Magnetic	Thermal	PMA dispersion with carboxyl activation via EDC	N/A	TMEM16A by viral transduction	2 μg of MNPs (pre-wash out)	Calcium imaging	In vitro	Rat hippocampal neurons
	$CoFe_2O_4$−$BaTiO_3$ (tetragonal barium titanate) core-shell nanoparticles	Guduru et al., 2015 [121]	Magnetic	Electric	Glycerol-mono oleate dispersion	Systemic injection (tail vein) and magnetic gradient over brain	N/A	10 μg intravenously[a]	EEG recording	In vivo	Mice brain
		Kozielski et al., 2021 [17]	Magnetic	Electric	BaTiO3 surface, no ligands	*In situ* injection	N/A	1 μl at 100 mg/ml	Calcium imaging, c-Fos expression, and behavioral tests	*In vivo*	DBS of thalamus in mice
		Marino et al., 2015 [80]	Acoustic	Electric	Arabic gum dispersion	N/A	N/A	50 μg/ml	Calcium imaging	In vitro	SH-SY5Y cells
		Marino et al., 2019 [79]	Acoustic	Electric	DSPE-PEG-biotin dispersion + streptavidin-antibodies	N/A	N/A	Two doses (10 μg/ml and 100 μg/ml)	Calcium imaging	In vitro	Immortalized brain-derived endothelioma as a BBB model

	Hematite (α-Fe_2O_3) nanodiscs	Gregurec et al., 2020 [71]	Magnetic	Mechanical	Hematite reduced with oleic acid and functionalized with PMAO	N/A	TRPV4 by non-viral transfection (only HEK-293 cells)	60 μg/ml	Calcium imaging	In vitro	DRG, hippocampal and HEK-293 cells
Composite nanocrystals	CdS quantum dots	Winter et al., 2001 [88]	Optical	Electrical	MAA coat + peptides or antibodies	N/A	N/A	3×10^{-11} M, 1.5×10^{-11} M and 0.75×10^{-11} M	N/A	In vitro	SK-N-SH human neurons
	CdS and CdTe quantum dots	Gomez et al., 2005 [85]	Optical	Electrical	MAA coat + peptides	N/A	N/A	2 ml at 4 mM	N/A	In vitro	SK-N-SH human neurons
	HgTe quantum dots	Pappas et al., 2007 [86]	Optical	Electrical	Thioglycerol + poly(dimethyldialylammonium chloride)	N/A	N/A	N/A (film)	Photocurrent measurement	In vitro	NG108 rat neuroblastoma cells
	CdSe and CdTe quantum dots	Lugo et al., 2012 [89]	Optical	Electrical	Thioglycerol + mercaptoethylamine	N/A	N/A	N/A (film)	Membrane clamp recording	In vitro	Human LnCap cells and neonatal mice cortical neurons
	Lanthanide doped upconversion nanoparticles	Yadav et al., 2017 [30]	Optical (near infrared)	Optical (visible)	-Silica, $-NH_2$, -biotinylated PEG and −Nav coatings	N/A	V5-ChR2m construct by non-viral transfection	50 μg/ml	Membrane clamp recording + Calcium imaging	In vitro	HEK293T human cells

[a] = final dose/concentration in brain tissue unknown.

as nitrogen-doped ultrananocristalline diamonds have been recently developed and suggested for *in vivo* use, as they have shown promising preliminary results *in vitro* for optical neurostimulation [60].

2.3. Iron oxide nanoparticles

While magnetic fields are able to penetrate deeply into the skull and soft tissue, conventional transcranial approaches such as TMS lack proper spatial resolution, and the power densities required can yield significant off-target effects [23]. Paramagnetic and superparamagnetic nanoparticles such as iron-oxide nanoparticles (IONPs) or ferritin-based constructs can transduce magnetic energy into both mechanical and/or thermal energy, enabling neurostimulation. Unlike TMS, this enables a local stimulation effect, but in response to a global magnetic input signal (Fig. 1C) [66–71].

Magnetothermal heating is the result of rapid oscillations of an alternating current (AC) magnetic field in the presence of magnetic materials. Upon successive reorientations of the magnetic moment along the field's direction, there is an hysteretic energy loss between the magnetic moment and the magnetic particle's lattice (for a more thorough explanation see Ref. [72]). In order to produce IONPs with an appropriate hysteretic-loss profile, synthesis protocols must control the magnetic anisotropy of the nanoparticles, which is size-dependent. This can be achieved by combining materials with both soft and hard magnetic properties in core-shell configurations. These can be produced with monodisperse sizes while still maximizing their hysteretic-loss profile. Such IONPs can be produced by thermal decomposition at high temperatures in organic solvents [73].

Magnetomechanical energy transduction can also be employed via mechanical realignment of a material's magnetic axis with an applied magnetic field. Magnetic particles can be coupled to a mechanosensitive ion channel, and an applied magnetic field can exert torque sufficient to activate the channel [71]. Other mechanisms have also been proposed involving the interactions between the nanoparticles and weakly diamagnetic substances (e.g., biological molecules such as ferritin) within an aqueous solution. However, the extent of the biological effects achievable with magnetosensitive biomolecules has been previously disputed [74,75] as there are fundamental objections that can be made regarding the physical assumptions required for these effects to occur. Particularly, the magnetism values suggested for paramagnetic proteins are too weak to account for the reported measurements by huge margins: from 5 to 10 log units.

2.4. Multiferroic materials

A boron nitride nanotube (BNNT) is a structural equivalent of a CNT with a portion of its C atoms substituted by alternating B and N atoms to provide superior mechanical, chemical and electrical properties. Common synthesis protocols which yield BNNTs use arc discharge (high energy electrical ablation of reactive electrodes in an inert-gas chamber), and ball-milling (nanomaterial powder is milled by grinding balls), and chemical vapor deposition methods (for further details, see Ref. [76]). These materials are piezoelectric in nature, which means that their crystalline configuration can discharge electric current upon application of a mechanical deformation. Consequently, they are frequently used in combination with ultrasounds, and the resulting electric effects can stimulate neuronal cell growth. They have been also reported to show low toxicity to cells when dispersed in glycol-chitosan or comparable polymers (Fig. 1D) [77,78]. Importantly, this BNNT activity occurred within the cytoplasm in contrast to outside the cell membrane,

with important implications to the feasibility of the approach for other stimulatory nanomaterials.

Like BNNTs, piezoelectric ceramics such as $BaTiO_3$ nanoparticles (BTNPs) can transduce applied ultrasound signals into electric signals. Electric stimulation via BTNPs *in vitro* has been shown for neuronal cell stimulation, alteration of neurite growth, and treatment of glioblastoma multiforme [79,80]. In composite with $BaTiO_3$ as a piezoelectric transducer, magnetostrictive $CoFe_2O_4$ nanoparticles present magnetoelectric behavior at room temperature via strain-coupling of the two phases [81]. As magnetoelectric materials undergo electric polarization in the presence of a magnetic field [82], magnetoelectric nanoparticles (MENPs) can be used to electrically stimulate neurons. Synthesis can be achieved by a two-step chemical procedure which combines co-precipitation and sol-gel techniques [83]. Administration of MENPs to the brain has been demonstrated via stereotactic injections, and magnetic gradient targeting to the brain after intravenous delivery has been suggested. Application of an external AC and DC magnetic field to MENPs has demonstrated local and network neurostimulation in mice [17]. Like other magnetically-stimulated materials, MENPs provide localized stimulation via the material under application of a global magnetic field.

2.5. Quantum dots

Quantum dots (QDs) are composite nanocrystals with a semiconductor core. While most synthesis protocols normally yield QDs in organic solvents, there are alternatives to produce them in water. A synthesis protocol by Winter et al. yields mercaptoacetic-capped CdS nanocrystals via arrested precipitation in aqueous solution [84]. Their light absorbing and emitting features can be tuned by selecting their size, shape, and core-shell compositions. QDs are widely used as fluorescent probes in biology, with high quantum efficiency and photostability. Furthermore, electrons or 'holes' may escape the quantum confinement of the QDs under certain conditions, generating an electric current, enabling their use as nanoscale photoelectric stimulators [64,85–87]. While *in vitro* results seem promising [88], some issues limit their clinical applicability. Difficulties have been reported regarding high clearance via endocytosis and non-specific binding to neurons in physiological conditions when used as free standing devices [85]. This is due to the particularly small size of QDs, which in some cases can get below 5 nm [87]. Several groups have explored the use of QD films to address some of these issues for *in vitro* setups, and have reported different mechanisms of interaction (Fig. 1B) [86,87,89]. Other nanocrystal variants such as up-conversion nanoparticles (UCNPs) [30], or holographically patterned photo-absorbers known as PAINTS [90], while not strictly QDs, are also optical devices apt for neurostimulation strategies which, due to their excitation using light, are similarly designed to QD setups. It should be noted that QDs and other light-stimulated particles will carry similar drawbacks to optogenetic approaches, requiring localized stimulation via an implanted light source.

3. Nanomaterial surface modification methods

While the choice of a particular nanomaterial-energy field pairing will be done according to their fundamental physical interactions as presented above (e.g., intensity, depth, side effects), the final modulatory capabilities of the system will also depend on its biological interactions. Such concerns include tissue targeting, concentration, clearance, cell distance, etc. Thus, to elucidate how the structural layout of a certain nanoscale neurostimulator will condition the *in vivo* stimulatory possibilities, a thorough exploration of surface chemistries and conjugation ligands is required for the abovementioned transducing materials. Many reviews of nanomaterial surface chemistries already exist for *in vivo* applications such as cancer theranostics [41,91–93] and provide possible avenues for surface modification of neurostimulatory nanomaterials. As such, this section will now discuss the surface modifications which have currently been applied to energy-transducing nanomaterials for use in the nervous system.

While surface modification and bioconjugation of nanomaterials is a thoroughly studied field [19,93–95] [96], many conjugation approaches are incompatible with materials used for neurostimulation. Thus, this section will provide a brief summary of the surface modifications which can be used on the nanomaterials of interest (Fig. 2). The relevant surface modifications will be discussed in terms of the stage of functionalization in which they are employed (primary and secondary coatings) and the nature of the chemical bond formed (covalent or non-covalent).

3.1. Primary and secondary surface modification

As nanoscale neurostimulators are frequently synthesized in non-aqueous solutions, a primary coating is provided to solubilize them and avoid toxicity or precipitation issues. Later, either by substituting this primary layer or by adding a secondary chemistry, additional ligands can be added, frequently aiming to provide more bioactive functionalities. The first consideration in any conjugation protocol will be the type of chemical residues present in the surface of the nanomaterial. AuNPs and carbon nanomaterials present elemental surfaces of pure atoms (gold, carbon) which may adopt different physical topologies, but with generally the same chemical reactivity. Other materials are formulated with oxygen atoms in the form of oxides alongside their metallic elements (e.g., IONPs) or mixtures of different elements (e.g., BNNTs, QDs) increasing the options for primary surface modifications.

3.2. Covalent versus non-covalent surface modification

Nanomaterial surface modifications can be covalently or non-covalently linked. Covalent linkages can provide more stable modification, but limit the types of chemical interactions possible with the transducing nanomaterial. This is the case, for example, using silane chemistry on an oxygen-containing surface, on top of which many additional well-known conjugation techniques can be applied. Other covalent modifications include conjugating bioactive ligands such as proteins (e.g., antibodies) via nucleophilic substitutions, often achieved through standardized crosslinking protocols with (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS) chemistry, or the widespread gold-thiol chemistry strategies for AuNPs. Conversely, non-covalent modifications require less precise matching of the material surface with an appropriate chemistry. Hydrophilic, hydrophobic, and amphipathic polymers (e.g., PEG, PAA, chitosan) or some surfactants (phospholipids, CTAB) are commonly used both for colloidal stability and as substrates for additional conjugations. Given how non-covalent ligands form low-energy but high-number chemical interactions (via hydrogen bonds, Van der Waals forces, etc.) their stoichiometry and orientation in the final material is harder to control, but they require milder reaction conditions than most covalent modifications. Below, we will discuss covalent and non-covalent surface modification methods used for neurostimulatory nanomaterials.

3.3. Gold nanoparticles

Several protocols exist for the synthesis of both AuNRs [42] and AuNSs [43]. Regarding cell toxicity, common protocols yield AuNPs

which are stabilized in aqueous solutions by surfactants such as the cationic cetyltrimethylammonium bromide (CTAB), which is known to be toxic both *in vitro* and *in vivo* when solubilized [97]. To avoid such issues, AuNPs can be readily modified via covalent reaction with sulfur-containing molecules. Common toxicity issues have been substantially solved by further modification/substitution of the CTAB layer with thiolated polyethylene glycol, (SH-PEG), phospholipids, silica shells, polyelectrolytes such as poly(4-styrenesulfonic acid) (PSS) [98], polyacrylic acid (PAA) [99] or oligo-ethylene glycol (OEG) [100] with silica coating by use of tetraethyl orthosilicate (TEOS) being a frequent choice for *in vitro* neurostimulation [46,51].

3.4. Carbon nanomaterials

CNTs are the main type of carbon nanomaterial researched for biomedical purposes, including neuroscience [56,65]. Regardless, it should be noted that given their mostly carbon composition, surface modification options which can be used for most carbon nanomaterials are quite similar, and usually involve the use of a strong oxidant acid (e.g., nitric acid) to yield carboxyl residues on top of which conjugate additional passive and/or bioactive moieties [61,101,102] commonly by EDC/NHS chemistry.

On the other hand, BNNTs have been modified non-covalently via organic polymers such as glycol-chitosan [77], amphiphatic dendrimers [103], poly-ethyleneimine (PEI) or poly-L-lysine (PLL) [104].

3.5. Magnetic and multiferroic materials

In order to obtain monodisperse core-shell structured IONPs, thermal decomposition at high temperatures (200-300 °C) from their metallic precursors (i.e. mix of iron (III), cobalt (II) and manganese (II)) is performed in organic solvents. Transfer of the resulting IONPs to an aqueous phase is often done by non-covalent coating with an amphiphilic polymer such as dodecyl-grafted-poly(isobutylene-*alt*-maleic anhydride/PMA) or PMA-shell for short [69,70,73] which seems to perform well *in vivo* and can be

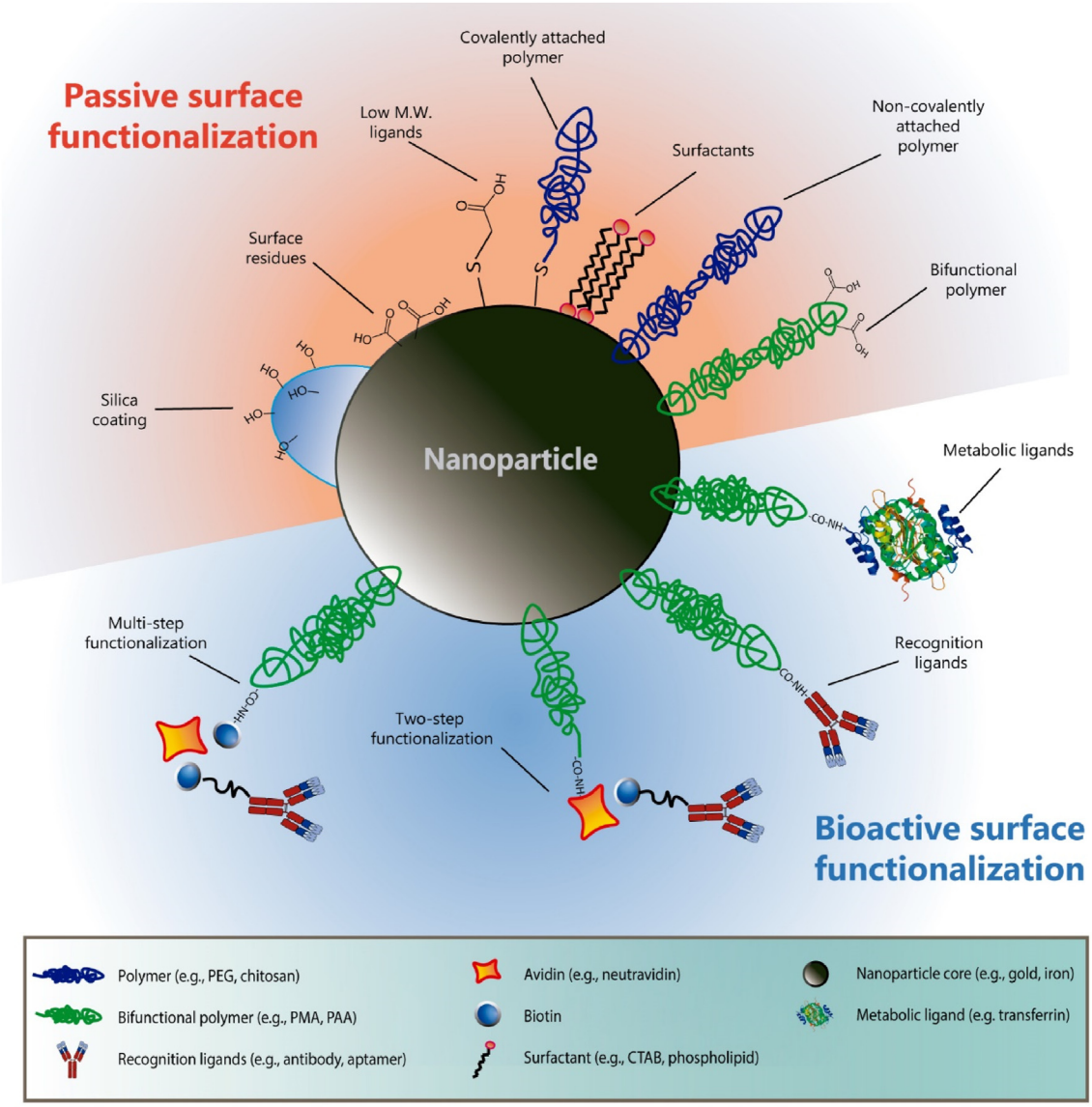

Fig. 2. Summary of surface functionalizations in neural stimulation nanomaterials. Schematic summarizing possible passive and bioactive ligands used for nanomaterial surface modification.

further functionalized by its peripheral carboxyl residues. A different approach was used by Gregurec et al. for their hematite nanodiscs, where they initially covalently reduced them with a surface of oleic acid, and later functionalized this surface non-covalently with poly(maleic anhydride-alt-1-octadecene) (PMAO) [71]. Noncovalent PEG coatings using PEG-oleic acid are also commonly used to functionalize magnetic nanoparticles (Fig. 3E and F) [105].

Surface modification of BTNPs has been done non-covalently in aqueous solution by several dispersing agents such as 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(poly-ethylene glycol)-5000] (DSPE-PEG) [79].

3.6. Quantum dots and up-conversion nanoparticles

QD use for neurostimulation has still primarily only been explored *in vitro* [64,85,86,88,89]. Two main modalities of interfacing the QDs to neurons have been explored so far. The first consists of directly attaching the QDs to the cellular membrane (i.e., as free-standing particles) either by their bare carboxylic residues produced after their synthesis with mercaptoacetic acid (MAA), or by conjugating antibodies or peptides to these carboxyl groups [85,88] by EDC/NHS chemistry. As discussed in the previous section, several issues have been encountered regarding the final fate of the QDs in physiological conditions when used as free-standing devices. Hence, the second way of modifying the QD interface with the neurons involves the layer-by-layer (LBL) formation of a QD substrate, on top of which neurons are cultured in a variety of forms [86,89] in an attempt to solve some of the issues. A schematic visualization of these LBL-QD constructs can be found in Bareket-Keren et al. [64]. It should be noted that this second method requires neurons to exist as a cell culture and will have limited application in *in vivo* situations.

4. Biological barriers and tissue targeting

As exemplified by the previously listed literature, which surface modifications and additional ligands are added onto the initial transducing nanomaterial will highly depend on what type of experimental application is being pursued. Therefore, classifying the many types of ligands may be challenging, as they will probably be appropriate for several design considerations. Conversely, many design issues often could be solved by more than one type of ligand. As such, the following classification of ligands with potential for *in vivo* use is discussed below, categorized by their primary purpose.

4.1. Colloidal stability

Nanoscale neurostimulators in a biological environment need to interact adequately with one another and with the environment, particularly to avoid aggregation and undesired protein corona effects [106]. Depending on the delivery method, the nanostimulators will need to be stable both in blood and the brain parenchyma, with only the latter being necessary for intracranially injected nanostimulators. Many comprehensive reviews already discuss strategies for stabilizing nanomaterials both in blood [107,108] and the CNS [109,110]. Particularly for neurostimulatory applications, and as highlighted by Champagne et al. [109], these stabilizing coatings often must offer the ability to further conjugate other bioactive molecules. This is represented by the numerous silica-shell [30,46,51] or PMA-shell [69,70,73] plus EDC/NHS chemistry approaches used especially *in vivo* (Fig. 3A,B**).** Many of the organic polymers discussed in the previous surface chemistry section also provide this double functionality by simultaneously improving colloidal stability and acting as a substrate for other ligands. Interestingly, organically-modified silica nanoparticles have already shown good interfacing properties with neurons *in vivo* [111] which further suggests the use of silica as a stabilizing coating in neurostimulation devices.

4.2. Immune clearance

Once inside the body, the fate of a given nanostimulator design will be determined by physico-chemical phenomena such as solubility, size, superficial charge, etc. (i.e., parameters which can reasonably be controlled at the synthesis stage). Another important interactive consideration, as introduced above, is the formation of a protein corona around the nanostimulators and how its dynamic profile across biological barriers and environments will determine the nanomaterial's functionality, biodistribution and therapeutic (or in this case, stimulatory) effect [112,113]. Generally, the host's immune system will identify and clear these nanomaterial-protein moieties depending on how and which of the plasmatic proteins adhere to them. The numerous immunological interactions possible with protein-coated nanomaterials have been extensively explored in specialized reviews [114,115]. PEG coatings are frequently used to avoid immune recognition in constructs delivered systemically [116] but there have been reports of acquired immune response against these PEG coatings after repeated exposure [117]. While neurostimulatory nanomaterials can apply immune evading strategies from other nanomedicines, thorough studies of immune clearance of neurostimulatory nanomaterials are not currently available. Current literature either i) bypasses systemic delivery issues [30,46,51,69,70]; ii) explores coating alternatives to PEG to solve immunologic issues related to systemic delivery, but for non-stimulatory setups [118,119] or iii) explores passive coatings which may be immunologically active (e.g. PEG or poly (lactic-*co*-glycolic acid) (PLGA)) but in time-constrained setups where this immune response is negligible [120–122]. Future research will be needed to address how these and other coatings affect the nanomaterials properties (e.g., transducing power, distribution, or aggregation) for neurostimulation purposes in more depth [106].

4.3. BBB crossing and tissue penetration

Neurostimulatory applications in which nanomaterials are delivered systemically must consider BBB crossing. Two strategies can be considered here. The first is comprised of biochemically-assisted approaches, which includes osmotic disruption of the BBB [123] and surface functionalization via ligand-receptor interactions, which can themselves involve endogenous molecules (e.g., insulin, transferrin, antibodies, peptides) or chimeric molecules [124–128]. The second strategy consists of physicochemical interventions to transiently open the BBB, such as FUS in combination with microbubbles [129], or applied magnetic fields to force the nanostimulators across the intact BBB [130,131]. Regarding tissue penetration and diffusion, many specialized reviews have explored how all of these passive and bioactive ligand combinations, sizes and morphologies will condition the dynamic profile of the nanomaterials within a tissue over time [132,133], albeit most of the time this is studied in the context of tumors and cancer theranostics and not for healthy, intact CNS tissues.

Stimulation of neural tissue in the peripheral nervous system (PNS) is also possible with these nanomaterials, and numerous existing reports are available which address their different challenges and limitations for this purpose compared to the CNS [134,135]. For instance, engineering approaches are fundamentally different (particularly surface chemistry) if the stimulating

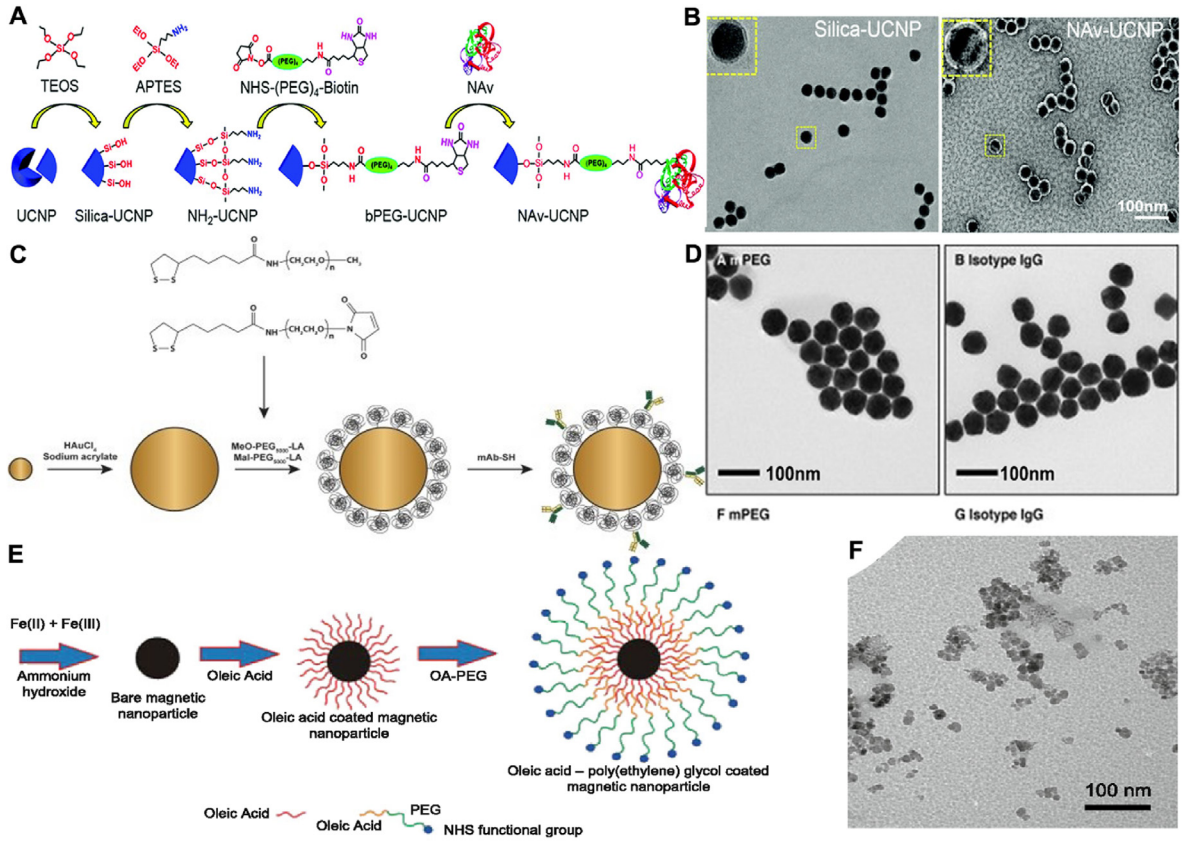

Fig. 3. Reaction schemes for nanomaterial functionalization. A–B: Multi-layer functionalization of UCNPs with neutravidin; C–D: Gold nanoparticle growth and functionalization with PEG and antibodies, reproduced with permission from Ref. [139]; *E*–F: Iron-oxide magnetic nanoparticle functionalization with a NHS-activated coat of PEG-oleic acid. Reproduced with permission [30,105,139]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

nanomaterial does not need to transit several biological barriers to reach their target tissue (i.e., from blood to brain parenchyma). Also, nanomaterials used to stimulate nerve activity in the PNS often include regenerative capabilities since they are often intended to restore damaged nerve function [136]. Additionally, due to the regenerative aim of these designs, studies in the PNS frequently measure neural activity as cell growth (e.g., neurite growth) instead of changes in action potentials per se [137]. However, successful neurostimulation approaches have been reported using retinal neurons, and since the retina can be considered both part of the CNS or the PNS depending on the pursued application, these type of studies can provide complementary insights to purely CNS and PNS studies, for instance by testing novel nanoengineered devices before using them in the CNS [138]. Overall, different challenges are present when designing nanomaterials to achieve neurostimulation in the CNS versus PNS tissues, and must be considered before designing experimental setups and while consulting published reports.

4.4. Cell/tissue-type specific targeting

The nanomaterial-cell interface is key to both application of the transducing signal, as well as avoidance of off-target effects. In general, two types of ligands can be considered. As described in the previous BBB-crossing section, several metabolic routes can be hijacked with either endogenous ligands (e.g., insulin, transferrin) [128] or antibodies which target their receptors (Fig. 3C and D) [125,139] in order to both cross the BBB and increase retention of the nanomaterials. While greatly useful to target vascularly-impaired tumors, or for the widespread delivery of neuroprotective drugs across the brain, this strategy lacks spatial selectivity required to enable precise, localized neurostimulation. Furthermore, in many neurostimulatory setups where there are no physiological differences between desired and off-target neural tissue, the bioactive ligands used to enable precise cell targeting usually involve gene editing. Generally, these experiments are performed either in transgenic animal models, or with wild-type animals with neural tissue transfected locally, which then allows the use of tailored antibodies that exclusively bind the nanomaterials to the transfected cells [15,30,67,69,70]. Regarding the bioactive ligands themselves, they functionally act as recognition ligands by epitope-paratope interactions (i.e., strong non-covalent 3-dimensional stereospecific interactions), and can be conventional antibodies, aptamers, short peptides, or chimeric molecules [140]. Another way to bypass the differential targeting of physiologically identical tissues and cells is the precise delivery of the nanostimulators by stereotactic injection [17,69,70].

Once the nanodevices are attached to their cellular target, the duration of this linkage will depend on a number of factors, including the rate of turnover for proteins in the neuronal membrane. If this turnover is too quick, only transient neurostimulation will be achievable and long-term setups will not be feasible. The main studies using antibody-conjugated nanomaterials presented in this review [30,49,51,69,70] report continued response to stimulation for up to a few days at most, and always less than a week. Eventually, clinical uses will likely require longer retention times to avoid repeated applications and off-site effects. The turnover rate of neuronal proteins has significant effects on neuronal excitability and plasticity, and these rates are known to change drastically depending on the stimuli and environment of the neurons

[141–143]. Neurostimulation unquestionably changes the physiology of neurons, and the anchoring effect of attached antibodies can also be expected to alter protein turnover rates. In summary, future studies will have to explore in depth how these turnover rates in neurostimulation setups are different to wild-type neurons and how to use this information to optimally target the most durable membrane molecules.

4.5. Tissue retention and clearance

A significant factor which will condition many aspects of any clinical neurostimulatory approach is the length of time that the nanostimulators remain at a functional concentration in the targeted tissue. Ideally, the nanostimulators should remain active as long as possible (thus avoiding repeated administrations) while inflicting the least amount of cellular damage. Glial cells and, in particular, microglia lead the response towards exogenous agents in the brain parenchyma, and consequently, orchestrate the clearance of any nanostimulators present. While the effects of some nanomaterials on mammalian cells *in vitro* and in animal models have been studied [144–146] there is currently a lack of research exploring the same mechanisms in humans due to logistic and ethical limitations. Models are in development to address this issue [106]. Albeit few, there are some preliminary studies on the clearance of other nanomaterials in the CNS of animal models. Superparamagnetic IONPs coated with dextran were injected into the rat striatum and were gradually cleared out from the brain parenchyma at the injection site in about two weeks (presumably with contribution of glial cells), with clearing times of up to 8 weeks depending on nanoparticle concentration [144]. The literature exploring how different nanomaterial ligands will condition this glial clearance is also scarce, with existing reviews exploring them in a case-by-case basis [147] for a myriad of different pathologies and applications frequently outside the CNS. However, there are some fundamental studies and reviews on the effects and clearance of heavy metals such as titanium [145], iron [120,148], and other metallic nanomaterials [146] in animal and *in vitro* models. Therefore, long-term clearance and toxicity of these nanomaterials, and especially how different surface ligands condition these phenomena remain to be assessed. A thorough review of key factors and limitations about this topic can be found in Ref. [146]. As a related side note, recent reports [149,150] have found that gadolinium-based contrast agents for MRI show retention and deposition in the brain (as well as other organs). Intriguingly, so far this has not shown to cause any neurological deficits, which suggests that these nanoscale compound particles (3–350 nm in size) must be somewhat well tolerated in the brain parenchyma, and that tissue clearance must be slow or absent. Considering this was an unexpected finding, it can be considered a valid reason to expect other types of nanomaterials to also show a comparable clearance and retention over time.

5. Conclusion, future perspectives, and pending issues

In this review, we have discussed current research avenues aimed at developing novel nanoscale neurostimulator interfaces for neurostimulatory purposes. While the field of neurostimulation via nanomaterials is in its infancy, future studies will lead to more innovative and translational technologies.

To achieve this, several technical challenges need to be adequately addressed before these designs can be applied to living human subjects. Namely, these challenges are the non-invasive delivery of the nanostimulators to the target area, cell-type/tissue-type specific modulation of neural elements, and external control of the nanostimulators to provoke excitatory and inhibitory changes in neuronal activity. As this is a nascent technology, no current nanostimulator design is able to meet these three requirements simultaneously.

Most of the published research in this field is performed with *in vitro* models [47,56,71,80], a practice which bypasses many biological constraints. In studies using *in vivo* models, gene editing and local nanoparticle administration also bypass some translational considerations [17,30,67,69,70]. Additionally, nanomedicine is a newly emerging field. Consequently, several of the discussed novel transducing nanomaterials (e.g., BNNTs and TBTNPs) and surface modifications are still relatively new and require further systematic characterization before clinical translation is possible. This review aims to provide a contextual background for these technical challenges, so that future studies about clinical neurostimulation can benefit from the use of nanomaterials. In contrast, more conventional nanomaterials have already proven their safety and effectiveness in clinical trials and FDA-approved nanomedicine formulations, albeit none of them (as of 2019) are capable of neurostimulation (for reviews on the state of clinically-approved materials, see Refs. [19,151]). The majority of neurostimulatory nanomaterial strategies presented in this review use more invasive, local delivery into the target tissue, with some examples [130] using systemic delivery. Local delivery may soon be replaced by systemic delivery of the nanoparticles via the blood stream as recent studies have shown that FUS or osmotic agents can transiently make the BBB permeable to nanoparticles [123,129,152]. In the future, these relatively non-invasive approaches will likely be preferred to a stereotactic injection, but more work with *in vivo* models will be needed to test the strengths and limitations of each technique before moving onto human subjects.

Regarding cell-type or tissue-type specificity, many of the studies listed have relied on the allocation of highly specific molecular constructs (e.g., exogenous ion channels) via gene editing and later binding of the nanoparticles to these constructs by matching antibodies. Ideally, more attempts should be made in the future to target molecular motifs already present in wild-type neurons. This will be a particularly challenging task since this binding selectivity will depend on the available molecular differences between desired and off-target tissues, which may be scarce. Future advancements in human gene editing may also help resolve this issue if the addition of selective constructs becomes more feasible and safe [33].

Cell-type specific neurostimulation is challenging when considering the use of endogenous responsive molecules to transduce the nanomaterial stimuli to the neurons. For thermally-induced stimulation, a common strategy is to introduce the heat-sensitive TRPV1 receptor via tissue genetic modification with viral tools [40,49,66,67,70], or other related ion channels such as TMEM16A [69]. For optogenetics and UCNP-based stimulation, gene editing is used to achieve expression of light-sensitive opsins [30,33]. Frequently, many of the reported gene editing interventions also introduce other useful constructs simultaneously. Among other uses, these help validate the causality of the neurostimulation achieved since they usually have well known response thresholds (e.g., the calcium indicator protein GCaMP6s). However, these approaches are also entirely dependent on first applying genetic engineering to human tissue. While wild-type neurons are responsive to small changes in temperature, pressure, and other cues from their environment, the magnitude of these responses might not be large enough as to provoke the intended stimulation only via intrinsic neuronal excitability. Consequently, more research will be needed to assess how to minimize reliance on transgenesis while still maintaining high responsiveness and spatial selectivity in the evoked responses.

It is worth mentioning that most examples of nanomaterials and production methods listed in this review are still at experimental stages, and few of them have been produced at large or under standardized guidelines. Eventually, as with all clinical products, nanostimulators will require Good Manufacturing Practices (GMP) to be made with appropriate quality standards. Different nanomaterial sizes, surface modifications, and morphologies carry different challenges and production costs. Thus, it remains to be determined which neurostimulating nanomaterials are not only effective in their design and transducing capabilities, but are also feasible to be produced under GMP guidelines. Once again, inspiration to tackle this problem can be drawn from existing reports evaluating challenges in GMP production of nanomedicines and other nanoscale products which are already closer to the clinic (for an introduction on the topic, see Refs. [153,154]).

This review has examined the current state of untethered, nanoscale neurostimulators with the intent of highlighting some of the key barriers to clinical translation. While additional work will be required to optimize nanomaterials for neurostimulation, parallel research in non-invasive delivery routes, toxicity, and tissue specificity will help move this technology closer towards patient use.

CRediT authorship contribution statement

David Dominguez-Paredes: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization. **Ali Jahanshahi:** Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition. **Kristen L. Kozielski:** Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition.

Declaration of competing interest

The authors declare that they have no competing interests.

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