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Nanotechnologies for the study of the central nervous system

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ABSTRACT

The impact of central nervous system (CNS) disorders on the human population is significant, contributing almost €800 billion in annual European healthcare costs. These disorders not only have a disabling social impact but also a crippling economic drain on resources. Developing novel therapeutic strategies for these disorders requires a better understanding of events that underlie mechanisms of neural circuit physiology. Studying the relationship between genetic expression, synapse development and circuit physiology in CNS function is a challenging task, involving simultaneous analysis of multiple parameters and the convergence of several disciplines and technological approaches. However, current gold-standard techniques used to study the CNS have limitations that pose unique challenges to furthering our understanding of functional CNS development.

The recent advancement in nanotechnologies for biomedical applications has seen the emergence of nanoscience as a key enabling technology for delivering a translational bridge between basic and clinical research. In particular, the development of neuroimaging and electrophysiology tools to identify the aetiology and progression of CNS disorders have led to new insights in our understanding of CNS physiology and the development of novel diagnostic modalities for therapeutic intervention. This review focuses on the latest applications of these nanotechnologies for investigating CNS function and the improved diagnosis of CNS disorders.

Contents

Abbreviations: Aβ1-42, amyloid-β peptide; AD, Alzheimer's disease; anti-IGFBP7, anti-insulin-like growth factor antibody; BAM10, amyloid-β monoclonal antibody clone; BBB, blood–brain barrier; BRAIN, brain research through advancing innovative neurotechnologies; Cd^{2+}, cadmium heavy metal ions; CdSe:Mn/ZnS, cadmium selenide:manganese/zinc sulphide; CLIONs, cross-linked iron oxide nanoparticles; CNS, central nervous system; CNT, carbon nanotube; CT, computer tomography; CVD, chemical vapour deposition; DAQ, data acquisition card; DOX, doxorubicin; DSC-CBV, dynamic susceptibility contrast perfusion imaging of cerebral blood volume; EAE, experimental autoimmune encephalomyelitis; Gd, gadolinium; GWAS, genome wide association studies; MB, microbubbles; MEA, microelectrode array; MEP, magnetoelectroporation; MNPs, magnetic nanoparticles; MNP-PBP, iron oxide nanoparticle contrast agent targeted towards p-selectin; MRI, magnetic resonance imaging; NIR, near-infra red; PAMAM, polyamidoamine; PBCA, poly(n-butyl cyanoacrylate); PEG, polyethylene glycol; PET, positron emission tomography; PLGA, polylactide-co-glycolide; PMMA, polymethylmethacrylate; QD, quantum dots; SCINEs, solid-conductor intracellular nanoelectrodes; Si-NWFET, silicon nanowire field-effect transistor; SiO_2, silicon dioxide; SPIONs, superparamagnetic iron oxide nanoparticles; SS-CBV, steady-state cerebral blood volume maps; TAT, trans-activator of transcription; Tf, transferrin; USPIONs, ultra-small superparamagnetic iron oxide nanoparticles; VCAM, vascular cell adhesion molecule; VSPIONs, very-small superparamagnetic iron oxide nanoparticles.

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1. Introduction

The impact of central nervous system (CNS) disorders on the human population is significant, covering hundreds of diseases with profoundly debilitating behavioural, social and cognitive deficits. Disorders in brain function are particularly insidious because they affect emotion, learning ability, and memory which unfold and regress as an individual gets older. The limited capacity of self-repair mechanisms in the brain can result in irreversible functionality, establishing disorders that not only have a major impact on individual lives, but also place a severe strain on healthcare resources. An extensive study by the European Brain Council estimated the total cost of disorders of the brain across Europe at €798 billion in 2010 (Gustavsson et al., 2011). Direct healthcare costs were shown to account for 60% of the total cost, while the remaining 40% was associated with loss in production. The breakdown in costs for brain disorders detailing number of persons, cost per person and total costs is summarised in Table 1.

Despite the significant impact of these disorders on society, advances in drug development remain limited, with treatments for diseases such as depression and schizophrenia still largely based on substances identified in the 1950s (Brandon and Sawa, 2011). Most currently available drugs merely delay disease onset or alleviate symptoms, and the lack of progress in the development of blockbuster drugs has led to several big pharmaceutical companies dropping or shrinking research for neural diseases (Abbott, 2011). The length of time for clinical trial and approval phases of CNS drugs is longer than for any other therapeutic area; 10 years for CNS *vs.* 7.8 and 7.6 years for cardiovascular and antineoplastic therapies respectively (Kaitin, 2010). Across the board, CNS drug discovery and development is associated with a longer and riskier development process and given the high rate of attrition for pharmaceutical research into neural disorders, there is a clear and present need to identify innovative approaches for more sensitive diagnosis and efficacious treatment (Muglia, 2011).

Table 1
Number of persons, cost per person and total cost of brain disorders.

Brain disorders	No. of subjects (Millions)	Total cost per patient (€PPP 2010)	Total costs (million €PPP 2010)
Mood disorders	33.3	3406	113,405
Dementia	6.3	16,584	105,163
Psychotic disorders	5	18,796	93,927
Anxiety disorders	69.1	1077	74,380
Addiction	15.5	4227	65,684
Stroke	8.2	7775	64,053
Headache	152.8	285	43,514
Mental retardation	4.2	10,334	43,301
Sleep disorders	44.9	790	35,425
Traumatic brain injury	3.7	8809	33,013
Personality disorders	4.3	6328	27,345
Child/adolescent disorders	5.9	3595	21,326
Somatoform disorder	20.4	1037	21,169
Multiple sclerosis	0.5	26,974	14,599
Parkinson's disease	1.2	11,153	13,933
Epilepsy	2.6	5221	13,800
Neuromuscular Disorders	0.3	30,052	7726
Brain tumour	0.2	21,590	5174
Eating disorders	1.5	559	827
Europe	379.9		797,764

Adapted from Gustavsson et al. (2011).

Due to the substantial heritability of many CNS disorders, research has intensified on identifying targets involved in disease aetiology rather than symptomology and choosing to pursue genetic risk factors as targets for diagnostic intervention. The ability to sequence the human genome and characterise patterns of variation among populations and subpopulations has made it possible to conduct high resolution and large scale genome-wide association studies (GWAS) (Hall et al., 2010), and more recently whole genome sequencing studies. Such hypothesis-free approaches have generated novel insights into the underlying molecular aetiology of neuropsychiatric and neurodegenerative disorders (Engle, 2010; Lin et al., 2009; Mitchell, 2011); for example, identifying shared genes involved in both circuit dysfunction of neurodegenerative disorders and calcium-channel dysfunction in psychotic disorders (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). While such genetic analysis data has redirected efforts in the research community to develop novel targets for future drug developments, these studies have also revealed that genetic data alone cannot build a functional model of disease pathology, as there are further layers of complexity caused by the interaction of functional gene expression with environmental stimuli. Thus, the key challenge for modern medicine is to further identify mechanisms behind brain function, from gene expression to physiological behaviour, and determine their implications in the aetiology and progression of CNS disorders (Stoeckli, 2012). The purpose of this review is to discuss how existing approaches presently limit our ability to meet these challenges effectively and highlight how modern nanotechnological advances could provide the keys to unlocking the complex nature of our brains for clinical intervention.

Current methods for characterising brain development and maturation involve the convergence of several diverse diagnostic methods, ranging from single-neuron observation at the intracellular level, to monitoring the principal activity of millions of neurons in synchrony. One fundamental modality for characterising brain development and activity has been the use of *in vivo* neuroimaging, a powerful technique for observing structural, biochemical, and functional changes within the brain. Significant advances in our ability to image the CNS at increasingly higher resolutions have elucidated several functional components of neuronal activity (Tropea et al., 2010). In addition, the aetiology of disease pathologies has been better characterised, improving our understanding of these disorders and highlighting novel pathways for targeted treatment (Corvin et al., 2012). Nonetheless, there are limitations in current approaches to neuroimaging such as artefact interference, lack of sensitivity, reduced half-life after intravenous administration, and decreased permeation across the endothelial barrier surrounding the brain (Nunes et al., 2012). In parallel, electrophysiological studies have also been critically important for understanding the functional connectivity of neuronal populations (Brown and Hestrin, 2009), combining several layers of CNS