Chapter 2
Applications of Nanotechnology to the Brain and Central Nervous System

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> [Leo Zonneveld]: '*US and European governments are introducing programmes for the convergence of nanobio-and cognitive technologies all aiming to improve human performance (Roco and Bainbridge 2003). How do you feel about these new trends, which connect studies in neuroscience to technological aims*?'
> "Professor the Lord Winston: 'Well, I don't think we should necessarily trouble ourselves with nanotechnology in this regard. Its possible impact is probably not yet relevant to mainstream neuroscience and therefore difficult to judge.'" – *Reshaping the Human Condition*

2.1 Introduction

In *Reshaping the Human Condition: Exploring Human Enhancement*, a recent report by the Rathenau Institute, in collaboration with the British Embassy in the Hague and the UK Parliamentary Office of Science and Technology, Professor the Lord Winston, Professor of Science and Society at Imperial College dismisses any concern about the application of nanotechnology research to the field of neuroscience as too nascent and inconclusive (Zonneveld et al. 2008). No other mention of nanotechnology occurs in the report. This view is common. In informal conversations with a number of leading researchers in the field of neural prosthetics, our colleague found little knowledge of nanotechnology or expectation that it would have any significant impact on the field for the near future. Current neural prosthetics technologies operate at the micrometer scale range, at the smallest, and this was deemed as sufficient for the design of neural implant devices (Robert, personal communication). Imagine

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our surprise, then, when a search of Web of Science generated over 10,000 research articles at the intersection of nanotechnology and neuroscience.

The theory of anticipatory governance is built on the idea of integrating deliberations about the social and ethical dimensions of science and technology upstream in the innovation process (Barben 2008). By grappling with the possible meanings of new and emerging technologies for society as early as possible in their design and development, this theoretical framework suggests that societies can position themselves both to anticipate potential risks and benefits of new technologies and to help shape their design and application (Wilsdon and Willis 2004). Ultimately, such work aims to help build the necessary capacity throughout society to reflexively and democratically govern the fashioning of future technological societies (Voss et al. 2006; Sclove 1995).

One key capacity required for such work is the ability to detect emerging trends in new and emerging technologies. The Center for Nanotechnology in Society at Arizona State University (CNS-ASU) has built one such technology, in collaboration with researchers at Georgia Institute of Technology, designed to facilitate the detection, mapping, and potentially even forecasting of new and emerging science and technology in the field of nanotechnology. At the core of this technology is an extensive database of over one million research articles from 1990 to 2008 captured by a detailed definition of the emerging field of nanotechnology (Porter et al. 2008). With this tool, researchers are able to develop nuanced and sophisticated analyses of emerging domains of nanotechnology research, helping to facilitate more systematic deliberations of the possible societal and ethical outcomes of nanotechnology research and innovation.

In this chapter, we used the Georgia Tech/CNS-ASU database to identify and explore the main concepts, trends, and trajectories of nanotechnology research applied to neuroscience, the brain, and the central nervous system. In distinct contrast to commentators who have downplayed the importance of such work, we found extensive research being carried out in this rapidly expanding field. Indeed, we found work occurring with potentially transformative implications for the ability of scientists to: (a) understand the human brain; (b) identify, diagnose, and repair brain and nerve disease and damage; (c) provide effective interfaces between the brain and the central nervous system and human technologies; and (d) enhance human cognitive and nerve function. Our findings thus agree with Silva, who conducted a more limited review of the field:

> Applications of nanotechnology to neuroscience are already having significant effects, which will continue in the near future. Short-term progress has benefited in vitro and ex vivo studies of neural cells, often supporting or augmenting standard technologies. These advances contribute to both our basic understanding of cellular neurobiology and neurophysiology, and to our understanding and interpretation of neuropathology. Although the development of nanotechnologies designed to interact with the nervous system in vivo is slow and challenging, they will have significant, direct clinical implications. Nanotechnologies targeted at supporting cellular or pharmacological therapies or facilitating direct physiological effects in vivo will make significant contributions to clinical care and prevention. (Silva 2006)

However, we would also go further. Now is the time to begin a serious dialogue among neuroscientists, nanotechnology researchers, ethicists, social scientists, regulators, policymakers, and the public about this burgeoning field of work and the social and ethical dilemmas that are likely to accompany its growing technological accomplishments.

2.2 Overview of Nano-Neuro Research

To analyze research trends in the application of nanotechnology to neuroscience, (which we term nano-neuro research), we began with a database of Science Citation Index (SCI) records for all nanotechnology publications from 1990 to mid-2008 contained in the Web of Science (WOS). Our search based on an algorithm developed at Georgia Institute of Technology in collaboration with CNS-ASU (Porter et al. 2008). We subsequently applied specific search terms to extract from this database those articles that focused on the brain or central nervous system. To do this, we used the following search terms:

> brain, neur*, fmri, "functional mri", synap*, myelin, axon*, serotonin, spinal, paralysis, paralyzed, prosthe*, nerv*, plexus, gangli*, olfact*, cortex, cornea*, cerebell*, cerebr*, parietal, broca, parkinson*, alzheimer*, blind*, deaf*, parapleg*, quadripleg*, glial*, glioblastoma, retin*, epilep*, aneurysm, stroke, amnesia, middle ear, visual, vision, cortic*

This search yielded 10,763 records of journal article/presentation abstracts, which form the basis for the following analysis. This database was cleaned and analyzed using VantagePoint text-mining software.[1]

We begin this chapter with an overview of the nano-neuro material. We observe in Fig. 2.1 that the number of nanotechnology publications identified by our nano-neuro search terms has grown substantially in absolute annual publication numbers

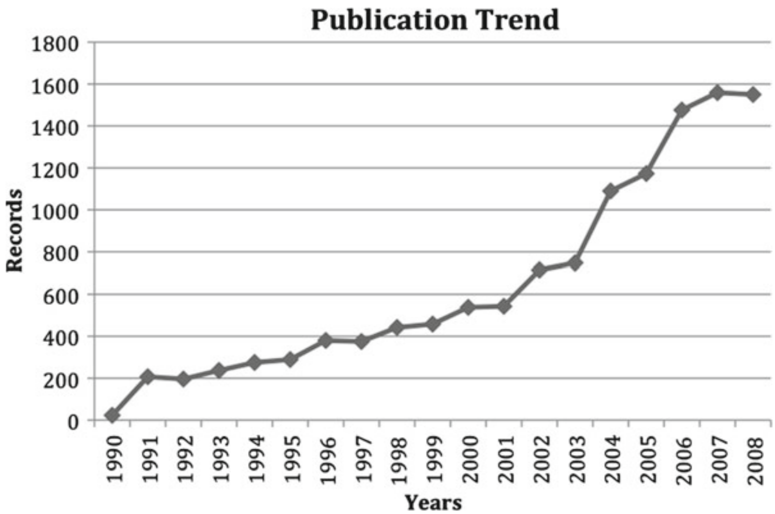

Fig. 2.1 Publication trend of nano-neuro articles (2008 records are adjusted to reflect end-of-year projections)

[1] http://www.thevantagepoint.com/

Table 2.1 Top publication countries

Rank	Countries	Records	Percent (%)
1	US	4,570	42.46
2	Germany	1,234	11.47
3	Japan	985	9.15
4	UK	823	7.65
5	France	586	5.44
6	China	496	4.61
7	Italy	483	4.49
8	Canada	450	4.18
9	Spain	261	2.42
10	Switzerland	259	2.41
11	Sweden	253	2.35
12	Australia	215	2.00
13	S. Korea	198	1.84
14	Netherlands	188	1.75
15	India	180	1.67
16	Taiwan	157	1.46
17	Israel	153	1.42
18	Brazil	148	1.38
19	Russia	146	1.36
20	Belgium	143	1.33
21	Austria	122	1.13
22	Poland	119	1.11
23	Denmark	108	1.00
24	Singapore	76	0.71
25	Turkey	66	0.61
	All Europe	4,660	43.30

from 1990 through 2007 (full data for 2008 were not yet available). Overall, from 1991 to 2007, the field grew almost eightfold, from approximately 200 publications per year in 1991–1992 to just under 1,600 publications per year in 2007. Growth was steady but relatively slow during the first decade however, up until 2001, after which the number of publications per year began to expand much more rapidly. Indeed, the number of publications per year triples between 2001 and 2007. Additionally, as a percentage of all SCI publications in the overall nanotechnology database, the share of articles published in the field of nano-neuro research also increased significantly between 1990 and 2007.

Following these overall trends, Table 2.1 displays the top 25 countries by number of published nano-neuro articles. Note that this table involves multiple counts for some articles, as researchers from multiple countries may be included as authors on a single article. In cases such as these, each article has been counted once for each country involved. Among the top 25 countries, European countries account for 4,660 articles, or almost exactly the same number as the United States. Nonetheless, while the total number of articles published outside of the United States and Europe is relatively small, it is significant that over 100 articles have been published in nano-neuro research by authors in 23 separate countries including China, South

Table 2.2 Top 25 Universities pursuing nano-neuro research

Rank	University	Number of records
1	Harvard University	177
2	University of Illinois	104
3	University of Texas	104
4	Johns Hopkins University	98
5	University of Wisconsin	97
6	University of Tokyo	90
7	University of Michigan	89
8	UC San Diego	88
9	UC Los Angeles	83
10	UC San Francisco	82
11	Stanford University	79
12	University of Southern California	76
13	Chinese Academy of Science	75
14	Northwestern University	73
15	University of Pennsylvania	72
16	University of Toronto	72
17	CNRS	71
18	MIT	71
19	University of Washington	70
20	University of California, Berkeley	68
21	Duke University	67
22	University of Frankfurt	61
23	Cornell University	60
24	University of Cambridge	59
25	University of Munich	58

Korea, India, Taiwan, Israel, Brazil, Russia, and Poland, and authors in Turkey have published an additional 66 articles. Nano-neuro research is thus expanding globally and is increasingly widely distributed.

The global distribution of nano-neuro research is also apparent among both the top universities and top researchers in the field. Table 2.2 displays the top 25 institutional affiliations of the publications captured in the database. While 18 are in the United States, including the top five, two are in Germany, and one each are in Japan, China, Canada, France, and England.

It is also interesting to examine the distribution of nano-neuro research across scientific fields. Here, too, we observe a very broad distribution of research across a wide range of basic scientific fields, ranging from the neurosciences (17%), to biochemistry (13.5%), chemistry (11.5%), and engineering and materials (10%). Clinical applications include pharmacology (7%), neurology (5.5%), ophthamology (5%), surgery (2.5%), radiology (1.75%), and pathology (1.67%). We present subject category data in Fig. 2.2 as an overlay map of subject categories in nano-neuro research, in comparison to the full range of subject categories found in World of

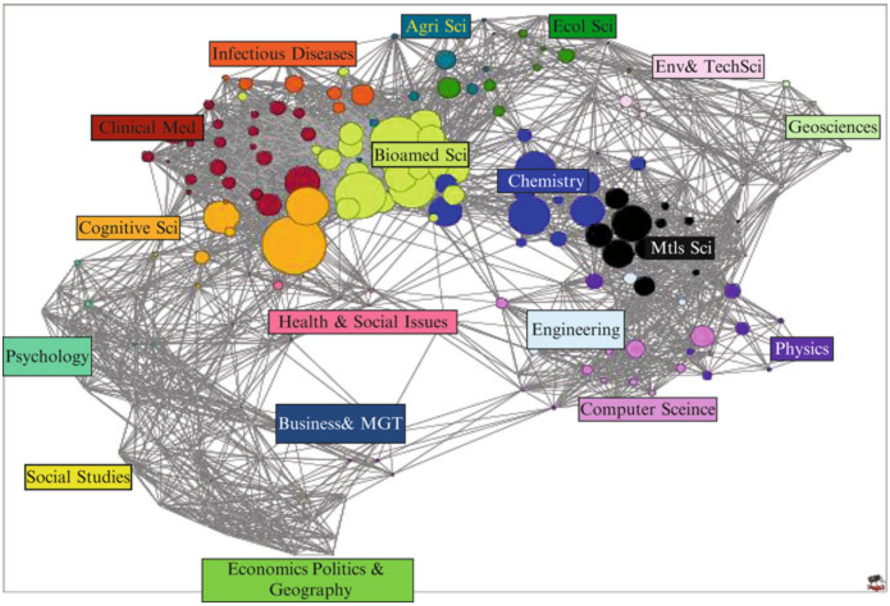

Fig. 2.2 Nano-neuro subject category overlay map (By contrast, the map indicates little or no work being done in areas that might examine the potential implications for nano-neuro research in fields such as psychology, health and social issues, social studies, business and management, or economics)

Science. This map was generated following the methods of Porter and Youtie (2009). The map shows circles for subsets of subject categories, with larger circles indicating more articles citing that subject category. Colors indicate general domains of scientific research, as indicated in the color labels on the map. Consistent with Silva (2006), the map indicates that the bulk of work remains in core areas of basic research. The bulk of nano-neuro research is found, not surprisingly, in cognitive science and the biomedical sciences, indicating its focus in neuroscience, and in chemistry and material sciences, from its nanotechnology elements. At the next level down, the map indicates work in clinical medicine, computer science, physics, and infectious diseases. An unexpected element of this work was the intersection of infectious diseases with nano-neuro, which we explore later in this chapter.

2.3 Thematic Breakdown of Nano-Neuro Research

In this section, we begin to analyze the content of nano-neuro research. Overall, the top 10% of data suggests the major keywords in nano-neuro are microscopy, biosensors, neurodegenerative diseases, biological techniques, biocompatibility, Parkinson's disease, in vitro/in vivo, neurite outgrowth, drug delivery, polymers, endothelial

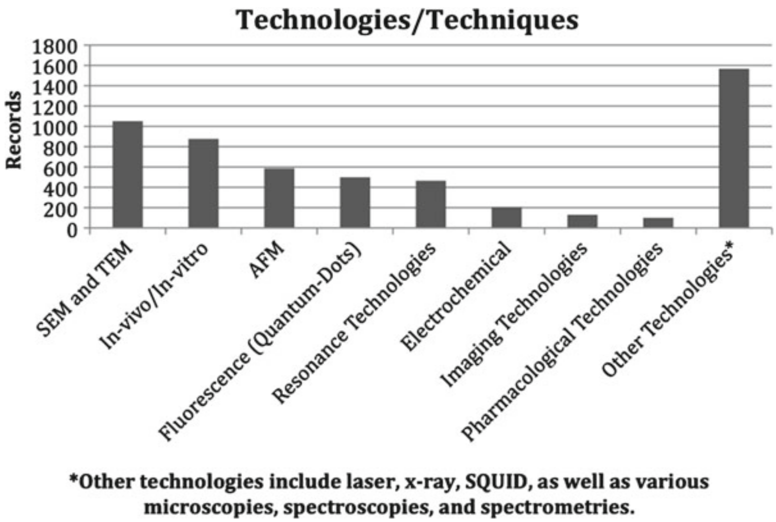

Fig. 2.3 Distribution of articles mentioning each technology or technique

cells, gene expression, apoptosis, Alzheimer's disease, microtubules, dopamine, calcium, and microspheres. Based on these keywords and the overview analyses above, we decided to focus on three overarching themes. The first examines the technologies and techniques used in nano-neuro research. The second examines diseases under investigation in nano-neuro research. The third examines applications targeted in nano-neuro research.

2.3.1 Technologies and Techniques

Our research identified 5,692 records citing various technologies and techniques used in nano-neuro research. Figure 2.3 offers the breakdown of the top eight technologies identified in the database. In-vitro and in-vivo are, we recognize, not precisely techniques; nonetheless, we included them to show the relative distribution of in-vitro and in-vivo research in comparison to other research approaches.

Perhaps most obvious from Fig. 2.3 is the broad dominance of microscopy and spectroscopy technologies such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic-force microscopy (AFM) as well as other imaging technologies such as fluorescence, x-ray, and laser technologies. As in other areas of nanotechnology research, the capacity image at molecular scales not only forms a substantial fraction of the research, but is also opening up broad new research horizons in visualizing the basic structural foundations of materials and their properties. Other technologies identified indicate research focusing on biosensors; superconducting quantum interface devices (SQUID); pharmacokinetic

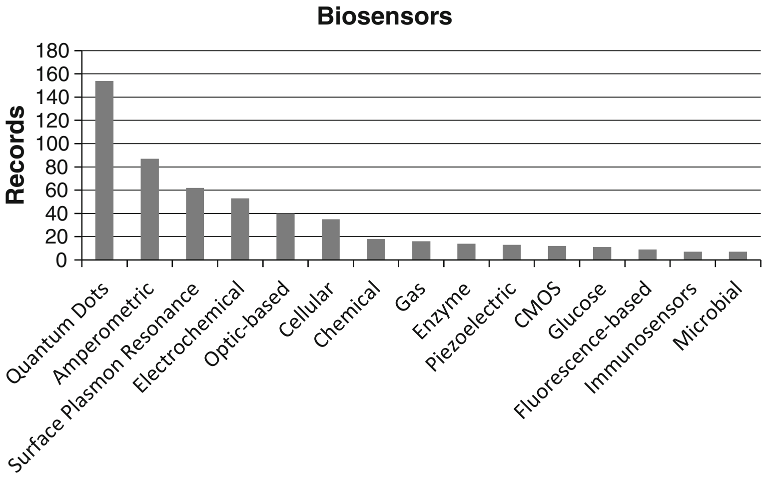

Fig. 2.4 Top 15 areas of biosensors research in nano-neuro

technologies; gold nanoparticles; drug targeting; and in situ hybridization, which involve evaluations and manipulations on the chromosomal level.

Biosensors incorporate at least one biological component in the process of detecting or analyzing the materials sensed. Our search yielded approximately 800 records referring to biosensors, 50% of which represent the top five biosensors in Fig. 2.4, which displays the top 15 biosensor related keywords in the database.

Most of the biosensors discovered in the database fall into the main categories of either electrochemical or optical, but there are of course various others such as piezoelectric biosensors. Optical sensors are the most common of these main divisions and total nearly half of all biosensors in the database. Within optical sensors, the most common are surface plasmon resonance (SPR) and quantum dots. SPR sensors have been used as "lab-on-a-chip" technologies and are mentioned in conjunction with self-assembled monolayers, Alzheimer's disease, gold nanoparticles, and to a lesser extent silver nanoparticles. SPR sensors are also referenced as a tool for dual detection, for instance of highly toxic nerve-agent analogs, as well as for their monitoring and recording capabilities. Quantum dot sensors are growing in popularity due to the breadth of their capabilities. For instance, quantum dots are mentioned as being a better alternative to organic dyes in providing contrast in imaging. Additionally, they are used for optical detection, tagging brain tumor cells, and labeling cell surface proteins. Quantum dots are also mentioned in conjunction with in-vivo, nanocrystals, fluorescence, brain cancer/tumor, Alzheimer's disease, and to a lesser extent, cytotoxicity and glycine receptors.

Electrochemical sensors are the next most prominent biosensor in the literature and seem to aid more in brain injuries and strokes and in Alzheimer's disease detection. These sensors are mentioned in conjunction with voltammetry, nerve agents, brain tissue, electropolymerized films, glucose, and organophosphate pesticides. Amperometric biosensors are used in tandem with an electrochemical element and

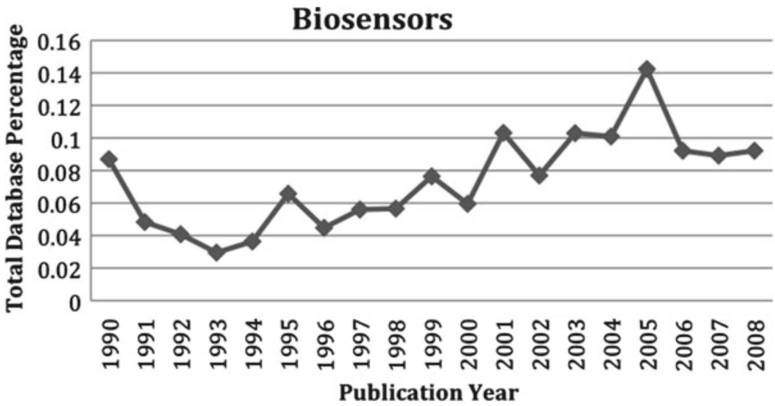

Fig. 2.5 Percentage of articles pursuing research with biosensors

are mentioned in reference to Alzheimer's disease, brain injury, epilepsy, stroke, and vascular disease. Other keywords associated with amperometric sensors include enzyme immobilization, liquid-chromatography, carbon nanotubes, choline, dopamine, glutamate, pesticides, and voltammetry.

The line graph above magnifies the research activity in biosensors, allowing us to see the growing significance of biosensor research from 1990 to 2008, with biosensors accounting for 10% of all nano-neuro research after 2001 (Fig. 2.5).

2.3.2 *Diseases*

Our search identified 3,776 records citing various diseases. We expressly searched for over 300 diseases, and of those, we found hits on over 200 diseases and ailments searched for within the database. Figure 2.6 shows the breakdown of the top ten diseases. In addition to those diseases represented in the graph, we found research focusing on a variety of mental health conditions, cancers (breast and prostate), retinopathy, deafness, spiral atrophy, seizures, epilepsy, and a large number of infectious diseases, among others.

Figure 2.6 offers interesting insight into nano-neuro research. First, it is useful to note that nano-neuro research covers the full spectrum of brain and nervous system diseases, including Alzheimer's and Parkinson's, epilepsy and seizure, stroke, spinal cord injury, schizophrenia, and brain cancer. Particularly striking is the broad appearance of infectious diseases in nano-neuro research. Cumulatively, infectious diseases comprised 14% of the articles relating to diseases, which is both significant and unexpected.

Our research identified 75 infectious diseases out of 115 such diseases searched for within the database. The references are inclusive of the five main divisions of

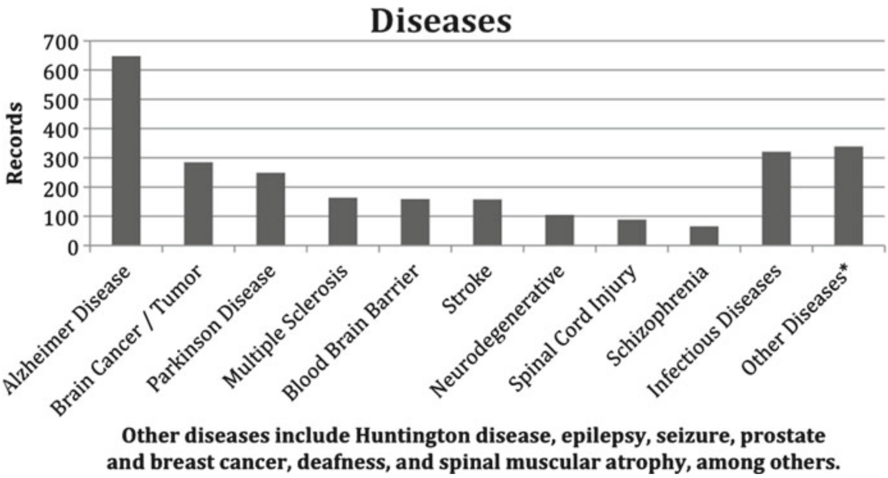

Fig. 2.6 Diseases involved in nano-neuro research

infectious diseases: viral, bacterial, parasitic, fungal, and prion diseases, totaling 533 records in each of the 75 infectious diseases identified. Overall, infectious disease research nearly consistently averaged 5% over the 19 years represented in this study.

In general, infectious disease research on the nano-neuro level appears to focus on cellular and molecular recognition and reconstruction. Infectious diseases offer an opportunity to study, observe, and even manipulate how organisms and toxins bind to the cell surface and potentially reach the brain. Observing allows researchers to test various techniques and technologies such as in-vitro/in-vivo or imaging techniques on the molecular level to determine effectiveness, to improve delivery of natural or synthetic elements, or to develop receptors for new therapies. In most cases, research in this area appears to concentrate on observing molecular changes, with or without manipulation, that have potential to affect the brain or nervous system, or that mimic conditions that do.

Table 2.3 shows the infectious diseases identified that appeared in five or more records within the database. In addition to the 29 infectious diseases represented in the table below, we found research focusing on 44 other infectious diseases, including anthrax.

2.4 Applications

Our research identified 1,707 records referring to anticipated applications of nano-neuro research. Figure 2.7 shows the breakdown of the top ten applications:

The top three categories (drug delivery, prosthetics/implants, and transplants) each have specialties of focus. In drug delivery, the primary application foci are for

Table 2.3 Distribution of nano-neuro research across infectious diseases

Infectious disease	Number of records	Infection type
HIV/AIDS	87	Viral
Encephalitis	49	Viral
Herpes	44	Viral
Creutzfeldt-Jakob disease	39	Prion
Cholera	37	Bacterial
Pneumonia	34	Viral
Meningitis	29	Viral
Influenza	23	Viral
Tetanus	23	Viral
Cytomegalovirus	22	Viral
Toxoplasmosis	21	Parasitic
Hepatitis	15	Viral
Aspergillosis	14	Fungal
Enterobacteria	13	Parasitic
Malaria	13	Viral
Rabies	13	Viral
Urinary tract	10	Bacterial
Leishmaniasis	9	Parasitic
Schistosomiasis	9	Parasitic
Ascariasis	8	Parasitic
Candida	8	Fungal
Taeniasis	7	Parasitic
Trypanosomiasis	7	Parasitic
Tuberculosis	7	Viral
Leukoenephalopathy	6	Viral
Polio	5	Viral
Campylobacter	5	Bacterial
Pertussis (whooping cough)	5	Bacterial
Gerstmann-Straussler-Scheinker Syndrome	5	Prion

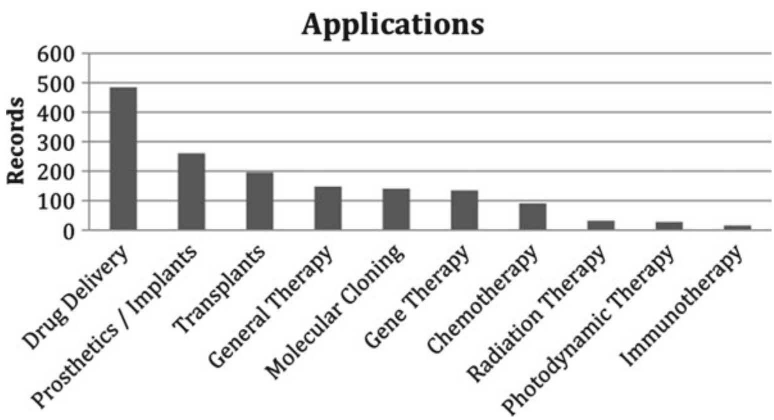

Fig. 2.7 Nano-neuro research applications

ocular and gene therapy. For prosthetics, the primary applications deal with neural, hand, and abdominal prosthetics; within transplants, the primary applications are for neural, brain, cell, and corneal transplants; and in the category of implants, primary uses are for cochlear, brain, and neural implants.

2.4.1 Domains of Nanotechnology Application in Neuroscience

In the first two-thirds of this paper, we offered an overview of research in nanotechnology applied to neuroscience and neurotechnology. In this second part of the paper, we offer a somewhat more detailed analysis of specific areas of application, identifying with greater focus and insight the rapidly growing impact of nanotechnology on our ability to understand, create interfaces with, and manipulate neural and cognitive systems. We focus, in particular, on the six fields: quantum dots, paralysis, epilepsy, stroke, brain-machine interface, and cochlear research. Collectively, these areas reflect approximately 600 total records or 6% of the overall research abstracts collected in the database. These six fields were selected to provide a reasonable cross-section of fields categorized by diverse orientations, including nanotechnology-related terms, (especially quantum dots), diseases, (paralysis, epilepsy), and applications, (brain-machine interfaces and cochlear research).

For this portion of the study, we examined in detail bibliographic records drawn from the larger database of nano-neuro publications. Within each record, qualitative textual analysis was carried out on the title, abstract, and keywords to identify the specific research represented by the record. Individual research studies were then sorted into an emergent classification to identify six broad categories of nano-neuro research. These categories are not exhaustive, but rather represent major domains of research. For each, we describe below the broad research area and offer a few examples of interesting research projects.

2.4.1.1 Visualizing Brain and Nerve Structure and Dynamics at the Nanoscale

One of the central contributions of nanotechnology to many fields of science has been improved visualization tools, such as electron microscopes and atomic force microscopes that enable materials to be visualized on the scale of nanometers, thousands of times smaller than the best light microscopes. Indeed, these instruments have become so ubiquitous in many fields that they are taken for granted as the necessary tools for modern scientific research. It is not particularly surprising, therefore, that a very large fraction of the nanotechnology work being done in neuroscience involves nanoscale microscopy (see Fig. 2.3 above).

In addition to nanoscale microscopy and quantum dots, other nanoparticles, like nano-diamond crystals, are also increasingly being used as tools for visualizing and probing the biological structure and functioning of the brain (Liu et al. 2008).

Quantum dots are nanoscale structures that fluoresce and offer flexible chemical structures that can be used to target the attachment of quantum dots to specific molecules. Quantum dots can thus be used as valuable contrast agents for enabling the visualization of biological structures and processes and can be designed to bind to specific molecular binding sites, allowing them to tag particular biological reactions or locations within complex molecules (Wang et al. 2005).

Finally, nanoelectric arrays are also being designed that allow for measurement of electrical signals from individual neurons within a group of cells and from different locations within a single nerve cell. In this case, cells are cultured on top of arrays of nanofibers that are individually addressed, allowing for detection and monitoring of signals at each point in the array. These arrays can be used to develop a better understanding of cell signaling and transmission pathways, providing new insights into cell behavior and functioning (Wickramanayake et al. 2005; Mazzatenta et al. 2007; Greve et al. 2007).

Collectively, these and other new approaches to visualization are opening up significant new capacities for understanding the brain and nervous system at molecular scales and rapidly altering the capacity of neuroscience research to examine and understand cellular structures and dynamics. One illustration of the potential impacts of nanotechnology for scientific understanding of normal brain and nerve functioning, the causes of disease, and possibilities for clinical therapies for nerve and brain repair and regeneration, comes from a review of potential applications of nanotechnology in Alzheimer's research:

> In this report, we present the promises that nanotechnology brings in research on the AD diagnosis and therapy. They include its potential for the better understanding of the AD root cause molecular mechanisms, AD's early diagnoses, and effective treatment. The advances in AD research offered by the atomic force microscopy, single molecule fluorescence microscopy and NanoSIMS microscopy are examined here. In addition, the recently proposed applications of nanotechnology for the early diagnosis of AD including bio-barcode assay, localized surface plasmon resonance nanosensor, quantum dot, and nanomechanical cantilever arrays are analyzed. Applications of nanotechnology in AD therapy including neuroprotections against oxidative stress and anti-amyloid therapeutics, neuroregeneration, and drug delivery beyond the blood brain barrier (BBB) are discussed and analyzed. All of these applications could improve the treatment approach of AD and other neurodegenerative diseases (Nazem and Mansoori 2008).

More broadly, both quantum dots and electron microscopy analyses have been used to examine detailed aspects of cellular structure and behavior in nerve cells. Examples of the use of quantum dots as imaging include studies of ion channels, protein receptor sites, neurochemical flows, molecular morphology, RNA, cell tracking, clinical pathology of degenerative eye diseases, and many other applications (O'Connell et al. 2006; Howarth et al. 2008; Chapman et al. 2008; Liang et al. 2005; Ji et al. 2006; Tomlinson 2006; Tsai et al. 2008; Yamamoto et al. 2007). Examples of electron microscopy use included examinations of: the molecular and cellular level processes that contribute to damage to nerve cells after spinal cord injuries or in hereditary spinal cord diseases, enabling a better understanding of the full effects of spinal cord degeneration and helping explain certain observed therapeutic outcomes (Werner et al. 2007; Tator 1995); and the molecular basis of nerve degeneration in paraplegia and muscle degeneration from denervation (Biral et al. 2008). In addition to imaging, quantum dots are also being tested for use in disease therapies, such as degenerative eye diseases (Christie and Kompella 2008).

2.4.1.2 Visualizing Nerve Growth and Regeneration

One specific area of nanoscale visualization research is that of nerve growth and regeneration. Nerve regeneration is crucial to efforts to find new therapies for both nerve damage, (e.g., due to spinal cord injury or other trauma that impacts the nervous system), and degenerative nerve diseases, especially in the brain, (e.g., Parkinson's, Alzheimer's, and many others). A wide array of medical research is seeking to promote nerve regeneration, either through pharmaceutical development or, for example, the use of stem cells to regrow damaged sections of nerves or the brain. Efforts using stem cells include implanting neural stem cells to act as progenitor cells for regrowth or as producers of neurotrophic factors that encourage other cells to grow and replicate.

Nano-imaging techniques can be used to visualize the process of nerve growth and regeneration at molecular scales, thus significantly enhancing researchers' ability to both understand and manipulate molecular level processes involved. There are several potential goals here. Nano-imaging can help researchers understand underlying biological processes of nerve growth and can also help evaluate the success of experimental or clinical efforts to use nerve regeneration in therapeutic applications. One study using electron microscopy, for example, examined neurite growth on dorsal root ganglia when cultured on different surfaces, using microscopy to study the detailed growth patterns observed (Chakrabortty et al. 2000). Other studies used quantum dot imaging to study how growing nerve cells respond to external stimuli that direct their growth (Bouzigues et al. 2004, 2007; Rajan and Vu 2006; Cui et al. 2007; Echarte et al. 2007).

2.4.1.3 Developing Scaffolding for Nerve Regeneration Experiments

Beyond visualization of nanoscale phenomena, nanotechnology is also emerging as a potentially valuable tool for enhancing the outcomes of clinical applications of tissue engineering and cell transplantation therapies by enabling understanding, visualization, and control of cellular interactions at nanoscales. One important area where this work is going on is in the field of spinal cord injuries and other neurodegenerative diseases. Here, in addition to improving scientific understanding of nerve growth and regeneration through novel nano-imaging technologies, nanotechnologies are also emerging as potentially important elements in the design of scaffolding to help facilitate nerve regeneration.

Work in this area has focused on experimental assessments of the potential for nanomaterials to help structure and guide nerve growth and regeneration, such as the use of nanotechnology substrates for nerve regeneration and growth, including single-walled carbon nanotubes. Research has shown that carbon nanotubes have good electrical conductivity, corrosion resistance, and strength, as well as chemical functionalization, cell adhesion, and biocompatibility characteristics that make them promising materials on which to grow cells. Experiments have shown, in particular, that nerve growth on carbon nanotube-based materials is similar in terms of cell growth and differentiation, neurite growth, and biocompatibility to other commonly used materials (Liopo et al. 2006; Rochkind et al. 2006). The use of various tools capable of developing nanoscale patterns on solid materials is also being explored as a potential approach to nerve regeneration, where axonal growth can be encouraged to follow certain scalar patterns (Johansson et al. 2006).

Building on these results, a mouse model was used to test the use of nanomaterials to help fashion viable scaffolding for nerve regeneration in the case of spinal cord injury. Nanofibers were placed inside a tubular scaffold that was then used to culture human embryonic spinal cord stem cells and subsequently sutured into a 4 mm gap cut in the spinal cord. After 3 months, the results showed partial recovery of function in one or two limbs of all of the mice using human embryonic stem cells within the scaffold, highlighting the potential value of such scaffolds in clinical cell transplantation for spinal cord injury and paraplegia (Rochkind et al. 2006).

Like the discussion of Alzheimer's above, researchers see nerve injury as a key site where nanotechnology may have enormous implications:

> Cell transplantation to treat diseases characterized by tissue and cell dysfunction, ranging from diabetes to spinal cord injury, has made great strides preclinically and towards clinical efficacy. In order to enhance clinical outcomes, research needs to continue in areas including the development of a universal cell source that can be differentiated into specific cellular phenotypes, methods to protect the transplanted allogeneic or xenogeneic cells from rejection by the host immune system, techniques to enhance cellular integration of the transplant within the host tissue, strategies for in vivo detection and monitoring of the cellular implants, and new techniques to deliver genes to cells without eliciting a host immune response. Overcoming these obstacles will be of considerable benefit, as it allows understanding, visualizing, and controlling cellular interactions at a submicron level. Nanotechnology is a multidisciplinary field that allows us to manipulate materials, tissues, cells, and DNA at the level of and within the individual cell. As such, nanotechnology may be well suited to optimize the generally encouraging results already achieved in cell transplantation (Halberstadt et al. 2006).

2.4.1.4 Visualizing and Structuring Neural Prosthetic Interfaces

As we noted in the introduction to this chapter, a series of informal conversations with leading researchers in the field of neural prosthetics revealed little interest in, or engagement with, work in nanotechnology. It was with significant surprise therefore, that we discovered in the database a growing number of studies applying nanotechnology research to the design and analysis of neural prosthetics. This work can be divided into two major domains, consistent with other fields of nano-neuro research: visualization and imaging studies, and active application of nanotechnology to prosthetic design. Overall, nanotechnology research is being applied in numerous ways to the field of brain-machine interfaces and neural prosthetics in two areas. First, by enhancing both the capacity to visualize and therefore study the behavior of interfaces between biological and implant materials (Wrobel et al. 2008). Second, by enhancing the ability of researchers to create highly functional and optimized interfaces between electronic and biological systems (Sarje and Thakor 2004; Hu et al. 2006).

In the field of imaging, studies have used electron microscopy tools to explore nanoscale features of nerve growth and attachment and rates of bacterial growth on both diverse implant materials and diversely structured implant interfaces (Brors et al. 2002; Selvakumaran et al. 2002; Pawlowki et al. 2005). Other studies have explored the degradation of implant materials over time, examining rates of degradation and affect on signal transmission between nerve and implant (Mlynski et al. 2007; Trabandt et al. 2005). A final study examined the nanostructuring of the biological environment, (and potential damage to it), within which the implant is placed, to determine optimal approaches to placing the implant device (Glueckert et al. 2005).

Nanoscale techniques also offer unique capacities to create structure at the interface between biological systems and implanted devices. Three primary approaches have been adopted. First, the use of single-walled nanotubes, quantum dots, and tethered nanopolymers as extensions from conventional microelectrodes into the nerve cell to improve conductivity and signal transmission (Wickramanayake et al. 2005). Second, the patterning of implant surfaces at nanoscales to improve either biocompatibility, (e.g., by reducing microbial growth or implant surface degradation), or electrical conductivity (Pawlowki et al. 2005; Johansson et al. 2006). Third, the development of nanocoatings, again to improve various aspects of implant functioning (Turck et al. 2007). The most ambitious research efforts use arrays of nanofiber electrodes to allow simultaneous sampling either from multiple neurons or from multiple parts of the same neuron. This last could be used to improve implant conductivity and signal transmission quality (McKnight et al. 2006).

Illustrative examples of work in these areas include:

- Efforts to enhance the electrical contact between biological and electrical systems through the design of new nanoscale molecules, (e.g., polymer coatings, polymer molecules, quantum dots, and carbon nanotubes), with the goal of ultimately designing interfaces capable of high-bandwidth transmission between nerves and either biosensors or robotic devices that might be controlled by the nervous system (Widge et al. 2004).
- The use of high precision machining tools, such as focused ion beams, to modify surface patterns at nanoscales in ways that influence cell adhesion and other interface characteristics. Scales approximately tens of nanometers to 100 nm, which is the typical scale of cellular interaction in biological systems, seem to generate optimum results (Raffa et al. 2007; Johansson et al. 2006).
- The design and characterization of nanoelectronic arrays out of functionalized carbon nanotubes and quantum dot layer-by-layer assemblies that allow for facilitation of neuron growth and development and multi-site communication between

electronic systems and multi-cellular matrices (Mazzatenta et al. 2007; Greve et al. 2007).

- Visual studies of the cytotoxicity of diverse materials that might be used in implant devices to assess their biocompatibility for long-term implantation in the human body (Liopo et al. 2006; Gomez et al. 2005).
- Efforts to evaluate and optimize the nanostructural characteristics of materials for brain-machine interfaces, including pore size, material composition, geometrical features, surface chemistry, etc. (Johansson et al. 2005; Moxon et al. 2004).

2.4.1.5 Improved Cancer Detection and Identification

Among their many applications in neuroscience, one interesting emerging area of research is in the use of quantum dots to detect and identify cancer cells in the brain. Research has demonstrated that brain tumor cells do take up quantum dots that can then be used to tag cancer cells using fluorescent imaging techniques. Quantum dots were functionalized to target epidermal growth factor receptors, which are believed to be involved in a number of brain cancer types. Consequently, quantum dot tagging may be usable as a tool for not only detecting cancer cells, but also for diagnosing specific cancers. Following up this work, other research has found that the fluorescent brightness varies between healthy and cancerous brain cells labeled with quantum dots, with the result that quantum dot imaging tools can potentially also be used to help make clearer differentiations between healthy and tumor tissues (Cai et al. 2006; Farias et al. 2006, 2008). Still other research has suggested quantum dot imaging can help identify radiation damage to tissues in cancer treatments, assess tissue viability, and potentially provide other valuable insights into cancer diagnosis and therapy in the brain and central nervous system (Toms et al. 2006).

Recent reviews of nanotechnology applications to brain cancer suggest the value of nanotechnology may be even bigger in the future:

> Recent developments in nanotechnology have provided researchers with new tools for cancer imaging and treatment. This technology has enabled the development of nanoscale devices that can be conjugated with several functional molecules simultaneously, including tumor-specific ligands, antibodies, anticancer drugs, and imaging probes. Since these nanodevices are 100–1,000-fold smaller than cancer cells, they can be easily transferred through leaky blood vessels and interact with targeted tumor-specific proteins both on the surface of and inside cancer cells. Therefore, their application as cancer cell-specific delivery vehicles will be a significant addition to the currently available armory for cancer therapeutics and imaging. (Wang et al. 2008)

> Nanotechnology is a multidisciplinary field, which covers a vast and diverse array of devices derived from engineering, biology, physics, and chemistry. These devices include nanovectors for the targeted delivery of anticancer drugs and imaging contrast agents. Nanowires and nanocantilever arrays are among the leading approaches under development for the early detection of precancerous and malignant lesions from biological fluids. These and other nanodevices can provide essential breakthroughs in the fight against cancer (Ferrari 2005).

2.5 Conclusion

The application of nanotechnology research in the field of neuroscience is growing rapidly and suggesting a wide range of applications. Like most other fields of nanotechnology research, the primary applications to neuroscience include imaging of nanoscale structures, the design of nanoscale materials, and the development of new nano-sensors and devices. Given this rapid growth of research activity, assessments of these new technologies, their potential applications, and their long-term social and ethical dimensions, is essential and timely. Many of the long-term ambitions of neuroscientists, with regard to understanding the brain and nervous system, assessing disease, creating new therapies, designing highly capable neuroprosthetics, and even manipulating and enhancing brain function through new drugs and devices, are likely to depend on nanotechnology and to be shaped by the capabilities of nanoscale science and engineering. Understanding this kind of dynamic interaction between two fields of scientific research is thus critical to assessing future technological applications and their ethics.

As nano-neuro research experiences rapid growth, there is a need to balance applied research with the various fields of study responsible for critically examining nano-neuro research and assessing how nanotechnology should be used in neuroscience, as well as creating a policy by which nanotechnology will be used. Introducing nano-neuro discussions into critical fields of study early on may help to safeguard the use of such new and emerging nanotechnologies, limiting abuse or misuse. An absence of this focus may signal a lack of foundational framework by which to systematically implement and regulate nanotechnologies in neuroscience.

Overall, the research summarized above makes something of a mockery of both the claim that the application of nanotechnology to neuroscience is speculative and the claim that ethical analysis of this field can be put off until some unspecified date in the future. The application of nanotechnology to research on the human brain is here, today, and the transition from research to clinical application is imminent if not already occurring. It is essential that ethical analyses of this research and its potential applications go forward in conjunction with broader work in nano-ethics and neuro-ethics.

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