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Perspective

# Mapping the Past, Present, and Future of Brain Research to Navigate Directions, Dangers, and Discourses of Dual-Use

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Tracking and evaluating prior publications of any scientific or technological field is essential to defining current trends, identifying and analyzing gaps in research methods, results and/or foci, and anticipating future research trajectories. Although neuroscience and neurotechnology (neuroS/T) have evolved from the nascent investigations of the early- to mid-twentieth century, recent developments in tools and techniques have fostered something of a renaissance of inquiry and innovation in the brain sciences. Understanding research trends, limitations, and directions is important to (1) assess contemporary knowledge and guide employment of extant and emerging technologies; (2) facilitate research translation from "bench-to-bedside"; (3) incorporate the most current information to the education and training of scientists; (4) inform relevant stake- and share-holders in professional and public domains; and (5) advise policymakers and research funding entities.

Arguably, benevolent intents are the motivating force propelling the vast majority of neuroS/T research. Yet, defining "the good" can - and often does - entail an examination of the needs, values, and philosophies of the agents and actors involved in any enterprise; and the brain sciences are no exception. The increasingly multi-national interest, investments, and engagement in brain science foster a culturally diverse palette that contributes varying views on what constitutes the relative "right" and "good" conduct and applications of research [1]. The capabilities of neuroS/T to assess and affect cognitive, emotional, and behavioral functions, while primarily directed toward medical aims, also prompt consideration, viability, and use for altering the performance of lifestyle and occupational activities, inclusive of those relevant to military, intelligence, and security operations. Indeed, there has been - and remains - interest, and increasing pursuit of dual- and/or direct-use of the brain sciences to optimize the performance of military personnel and to control and/or degrade neurobehavioral abilities and health of targeted adversaries [2].

Dual-use research of concern (DURC) is categorized by studies that employ substances and techniques that are deemed to pose defined risks to public health and safety. The Biological and Toxin Weapons Convention (BTWC) and Chemical Weapons Convention govern the development and use of weaponizable biological and chemical agents, respectively, which are additionally regulated by several international signatory treaties. However, several countries and groups have called for greater transparency and stringency of life science research (i.e. so-called confidence-building measures, CBMs) to ensure compliance with existing treaties [3]. During the 1990s, the disclosure of the (then) Soviet bioweapon program, coupled with growing concerns about biological and chemical terrorism, led to the establishment of programs of "biology-based threat assessment" (bioTA). BioTA entails laboratory development of biological weapons agents in order to (1) evaluate the capacity of an emerging science or technology, and (2) direct the design and creation of medical countermeasures [4].

In 2001, *The New York Times* reported that the United States (US) government was conducting three clandestine bioTA projects [5]. These included Project Jefferson (that reproduced a Russian genetically-modified strain of anthrax), Project Clear Vision (that reconstructed former Soviet biological weapons), and Project Bacchus (that created a mock biological weapons facility using easily obtainable biologicals and equipment). Although the US claimed that these research projects did not violate the BTWC, there was considerable speculation and debate about the utility of secret and/or undisclosed bioTA research projects. In counter, biosecurity experts have proposed options, other than conducting bioTA, which may be preferable [6]. For example, biosecurity operators may use analyses of research trends and other intelligence to identify dual- and/or direct use (i.e. for military or bellicose objectives) projects. Such analyses could be leveraged to generate international support for moratoria of those experiments and projects so identified.

One aim of this type of moratorium may be to limit the extent of novel methods and new products that at present are not (yet) guided or governed by regulatory treaties and conventions. For instance, emerging gene-editing techniques could be used to create unique microbes (and other agents) for disruptive purposes (e.g., development of "designer pathogens"; alteration of human structure and functions; modification of agricultural systems, etc.) [7]. Until very recently, it was believed that gene editing methods (such as those using CRISPR and related Cas enzymes) were not sufficiently mature for broad-scale use, and/or for human application(s). But in November 2018, a Chinese scientist used genetic editing to modify the genes of human embryos to generate an inherited resistance to HIV, smallpox, and cholera, as well as alter certain neurocognitive functions [8]. In March 2019, the World Health Organization determined that this type of change to human germlines is "irresponsible" and proposed the need for a "central registry" to facilitate greater oversight of potentially hazardous research. And while these measures were in reaction to an experiment, the intention is that by monitoring research trends, policy can be developed and articulated in preparation for dealing with (if not mitigating) any future activity of this kind. We believe this to be ever more important and necessary, as several recent scientific advancements have increased the plausibility and possibility of using the brain sciences (as well as other life sciences) for disruptive or destructive intent. During this past year alone, research studies have shown that novel nanoparticles can be engineered to gain exceptional access to the brain [9], nanodevices can enhance sensory capacities in mammals [10], optogenetics can augment/alter brain function [11,12] and gene editing can be used to increase the cognitive abilities of non-human primates [13].

Our ongoing work is devoted to fostering effective biosecurity strategies to include emerging fields like neuroS/T. Toward this goal, we identify two general approaches that can be used to monitor brain science research. First, is tracking, identifying, and comparing key features of research studies over a given interval of time and/or place(s) to assess patterns and directions. Yeung and colleagues recently examined the most prevalent research terms by comparing publication citations and shares from 2006 to 2015 [14]. Four term maps for the publications were produced over the selected period to illustrate the extent of co-occurrence and the impact of related publications. The researchers parsed the term maps into sections wherein one (i.e., the left) side related to cellular, molecular or genetic neuroscience, and the other (viz., the right) side was associated with brain imaging and neurological systems. Based upon map network analysis, it was clear that from the sampled time period, neuroS/T research shifted from a neurological systems to cellular neuroscience focus. Some recurring terms (e.g. cognitive control, decision-making, default mode network, diffusion tensor imaging, functional connectivity, insula, microglia, microRNA, neuroimaging, and orbitofrontal cortex) are considered relevant to biosecurity as possible directions for studies aimed at augmenting and/or degrading human performance or incurring destructive effects [15-17]. Also included were supplementary data analyses that depicted the relationship between specific fields and how often they appeared in academic literature during the ten-year sampling period. From 2006 to 2015, the US consistently produced substantially more research than any other country. Yet, and of note, there was a considerable increase in China's neuroS/T research output, moving from the 11$^{th}$ rank to the second-rank in just ten years, reflective if not due, in large part, to significant governmental interest, intent, and fiscal support toward establishing a broader and deeper footprint on global neuroS/T progress and markets [18,19].

As the authors noted, there were, to be expected, some limitations to their study. One is that such methods can only access and address published papers. While axiomatically viable for generating an overview of recent publications, the inherent lag in (1) getting the work that has been completed into press, and (2) time required for conducting the assessment of published work and its eventual publication, may incur a temporal gap in "pulsing" both research that has been concluded and published while the survey paper was being completed and put in-press, and those studies that are currently underway. Yeung., *et al.* published their work in 2017, and the most recent year the study tracked was 2015. Some research projects can take years to develop; and to re-iterate, the process of publishing a scientific, peer-reviewed paper can take months.

Thus, a second approach to evaluate current efforts and possible trajectories of neuroS/T research involves surveying subject matter experts (SMEs) to identify specific trends in research. Employing this method, a 2013 paper in *Nature Reviews Neuroscience* presented interviews of five leading neuroscientists to detail the aims and directions of the US' Brain Activity Map, the US' Brain Research through Advancing Innovative Neurotechnology (BRAIN) Initiative, and the European Union's Human Brain Project (EU-HBP) [20]. The SMEs interviewed detailed key activities of these programs and the challenges they must overcome and opportunities met in achieving their respectively stated goals (which can be vital to gauge what experiments researchers may undertake in the near and intermediate future). Additionally, the SMEs identified and discussed other issues facing neuroS/T research (e.g. sharing data, collaboration, and funding), which could influence - and be useful to forecast - what, where, and when near - and mid-term research projects may occur. Indubitably, this method also has limitations. Namely, it will reflect only the views of those SMEs queried. And while the individuals interviewed may represent different countries and fields of brain science, there may be bias(es) in their selection, and the chosen SMEs could overlook, misapprehend, or unintentionally (or purposively) over- or under-represent information about ongoing and forthcoming experiments. These factors can be particular problematic if/when attempting to gain insight to experiments, projects, and programs that have implications or indications for dual- or direct-use in ways that can affect public safety, health, and/or be employed in military/warfare applications.

Apropos these issues, we opine that it is - and will be increasingly - essential to assess and forecast current and near-to-intermediate future directions of neuroS/T research and its viable translation in varied applications [21]. However, current assessment and prediction models generally tend to focus upon and favor limited timescales and linear patterns of scientific and technological innovation and application. Further, when developing distal timescales, failure to appreciate the scope and diffusion of effects (i.e. multi-domain and -componential fractal diffusion) in and across the varied milieu of use can limit forecasting accuracy and predictive reliability.

To this point, we are in favor of improving forecasting to acknowledge and appreciate the "predictability horizon" to better define three future timeframes of neuroS/T research, development, and applications. As depicted in figure 1, these are the: (1) vista of probability (prior 5 years to 5 years in the future); (2) vista of possibility (6 to 15 years in the future); and (3) vista of potentiality (16 to 30 years in the future).

More near-term events and developments are simpler to define and probabilistically predict. When looking farther into the future, currently available and newly emerging neuroS/T tend to generate a broader range of possible uses and effects. As previously noted, potential long(er)-term uses and influences of neuroS/T are less easy to model and forecast in light of varied socio-political and economic forces (in culture and science) that can establish generative ecologies for viable applications of science and/or technology in and across domains of utility.

Nevertheless, given current trends and momentum in multi-national brain research, it is crucial to examine what is probable, and from such probabilities, what is thence possible. This is particularly true when considering, assessing, and forecasting the dual- and direct-use of neuroS/T by nations and non-state actors for bellicose or (non-combative) power-leveraging ends. Using only an induc-

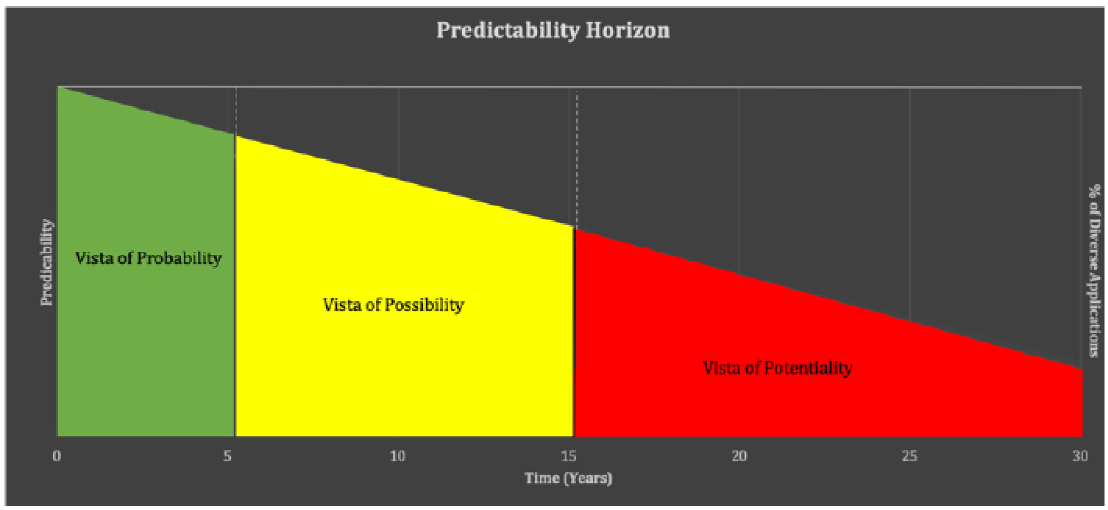


***Figure 1:*** *(1) Vista of probability (present to 5 years); (2) Vista of possibility (6 to 15 years); and (3) Vista of potentiality (16 to 30 years). As noted in text, and depicted on the left-hand ordinate axis, when looking farther into the future, predictability tends to decrease; while the likelihood of diffuse applications (as depicted on the right-hand ordinate axis) tends to increase.*

tive (i.e. prospective; i.e. "current-to-future") approach toward such purposes may not be effective, adequate, or of high value. Instead, we propose exercising combined inductive methods and deductive (i.e. retrospective; "potential future-to-present") analytics that work from the 16 - 30-year future timeframe backwards to define and model the possibilities and probabilities required to enable such long-term developments to be realized. Such an enterprise requires recognition and assessment of explicit and more tacit aspects of research and use activities of several countries that already have enterprises dedicated to dual- and/or direct- military/power-leveraging uses of neuroS/T [22,23]. Evaluation should focus on (1) activities and output of universities and research institutes/organizations; (2) vectors and investment loci of governmental, private and public support for neuroS/T; (3) recruitment of researchers; (4) commercialization efforts; (5) current and future neuroS/T markets; and (6) current and future military, intelligence and (multi-)national security intentions, postures, and activities.

Detecting dual and direct-use biological threats has always been difficult, and advancements in brain sciences are making this task ever more challenging. Nevertheless, effective and efficient tracking and forecasting of research in neuroS/T provide vital biosecurity insights to current and newly emerging risks and threats of weaponizable neuroS/T. In this light, we propose that current methods of tracking, modeling, and surveillance may require re-examination and, in some cases, revision. Still, questions remain as to which ethical approach(es) are best suited to guide multi-national neuroS/T research, and its use in specific contexts of application, particularly national security and defense [24,25]. The process and ethics must be discursive, dialectic, and sensitive as well as responsive to differing cultures, philosophies, needs, values, and interests [26,27]. To be sure, the task is not easy and is a work both in-progress and, hopefully, of progress. Our ongoing work remains dedicated to these collaborative efforts.

## Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the opinions of the US Department of Defense and/or the authors' supporting organizations and institutions.

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