**Toward an Operational Neuroethical Risk Analysis and Mitigation Paradigm for Emerging
Neuroscience and Technology (NeuroS/T)**

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Introduction.

Neuroscience and neurotechnology (neuroS/T) are developing at a rapid pace, fostered by an ever more convergent paradigm that has prompted and nurtured de-siloed, multi-disciplinary methods (Giordano, 2012a) that has afforded a systems'-based, integrative approach to the development and translational use of neuroscientific technologies and techniques (neuroS/T; Giordano, 2012a; Vaseashta, 2012).

Research and applications of neuroS/T are aimed at assessing and treating a number of neuropsychiatric disorders and conditions, yet are also being increasingly viewed as means of affecting neural substrates of cognition, emotion and behavior to modify aspects of human performance (if not personality).

The field - and its domains of application and use – is fast paced, engaged by multiple entries, each and all vying for defined outcomes (and “prizes” of innovation, discovery, recognition, and economic gain), and as such can be seen as a “neuroS/T speedway”. Reflective of the racing comparison, it is a highly competitive environment, which while offering definable benefits (to both stake and share-holders), is not without risk, if not frank dangers as neuroS/T is ever more broadly engaged in the social milieu (Giordano and Benedikter, 2012a; Hughes, 2006; Lynch, 2006). To be sure, neuroS/T evokes a variety of inherent and derivative neuroethico-legal and social issues (NELSI) generated by imperatives for innovation, novelty of approaches, limitations of knowledge, and resultant uncertainties of benefit, burdens, and harms.

In this paper, NELSI of current and near-term neuroS/T are defined, and an overview of our ongoing work toward establishing a preparatory paradigm for addressing, resolving and reducing NELSI is presented. Our approaches to querying, framing, and defining particular domains are offered, and our

aims and efforts in modeling patterns and trajectories of NELSI are discussed. To enable and sustain this preparatory stance, it will be important to harness existing resources, and to cultivate a cadre of multi-disciplinary and task agile subject matter experts that can operate on local to global levels. Toward such ends the need for neuroethics education and training are emphasized.

Key Neuroethico-legal and Social Issues

As depicted in Table I, NELSI can be generally categorized as: (1) those arising in/from the characteristics of neuroS/T, and (2) those fostered by the use, misuse, and/or distribution of neuroS/T in various domains of the social realm. Scientific and technical issues, questions, and problems are increasing as a result of the complexity and sophistication of the techniques and devices being developed, and the widening scope of their application (Giordano, 2014a,b). Social issues are becoming increasingly diverse and important given the pluralist nature of the twenty first century global stage and the rising prominence of international commercial entities and political support in neuroS/T research, development, and employment (Giordano and Benedikter, 2012a,b; Hughes, 2006; Lanzilao, Shook, Benedikter, Giordano, 2013; Lynch and McCann, 2010; NeuroInsights, 2015). In reality, these issues are not mutually exclusive; they are interactive and can often be reciprocal in effect, and therefore require an interfluent approach to their address and resolution (Giordano and Olds, 2010).

Table I about here

ON-RAMP: Addressing NELSI – and Managing Risks - on the NeuroS/T Speedway

The role of any ethics is not to be solely proscriptive, but to define facts, plot the terrain of effects, and inform guidance and governance toward achieving and sustaining a relative balance of benefit over burden and harm(s) (Khushf, 2006). Neuroethics is no different (Giordano, 2010a,b; 2012b; Racine, 2010). We have argued that adherence to a simple precautionary stance fails to account for the speed,

multiple entries, exigencies and contingencies of the neuroS/T speedway, and thus is poorly suited to ethically navigating its course and pace (Giordano, 2010; 2012b; Giordano and Benedikter, 2012a,b) . Instead, we call for a preparatory neuroethical approach that: (1) develops correlative models of neuroS/T innovation and translation, as well as the realistic benefits, burdens and risks such scientific, technical and social trajectories incur; (2) proactively and iteratively identifies and evaluates key risks that could constrain benefits; and (3) develops and proposes appropriate methods and measures to prevent, constrain and/or counter such risks as best possible by analyzing relative value-effects of risk domains and dimensions (Giordano, 2010;2012a,b; 2014a,b; 2015a,b; Giordano and Benedikter, 2012 a,b; Giordano and Olds, 2010; Giordano, Forsythe, Olds, 2010).

Toward this end, we have described an ***Operational Neuroethical Risk Analyses and Management Paradigm (ON-RAMP)***, as presented below, that entails (1) querying the type, goals, and utilization/applications of neuroS/T; (2) framing such applications to consider dimensions of effect; (3) defining key domains that will be (differentially) affected by neuroS/T, and (4) employing approaches to model and plot trajectories of effect (Giordano, 2015a,b; Giordano, Casebeer and Sanchez, 2014).

1. Querying NeuroS/T: Mining NELSI

A first step is to pose questions that define the patterns of employment, and depict targeted benefits, and discernible burdens and harms that are likely to be incurred by the use of any neuroS/T. These questions are:

- **What** neuroS/T approaches are being considered for use; and what are the benefits and identified and (realistically)potential burdens, risks and/or harms?
- **Why** are specific neuroS/T approaches being considered in light of their actual capabilities to affect pathology, cognition and/or behavior?
- **Who** will receive these neuroS/T approach(es) ?

- **When** will particular neuroS/T be considered and/or advocated for use (e.g.- within a treatment protocol; within certain occupational settings)?
- **Where** will neuroS/T be utilized/provided (e.g.- contexts; circumstances)?
- **Which** programs of subsidy will be used and/or developed to support both provision of neuroS/T as well as continuity of research and care necessary for sound translation of science in practice?

2. Framing NELS Questions

These neuroethical questions should be framed by/within a view that builds upon Casebeer's groundwork (Casebeer, 2013), to establish a **6-C concept** that characterizes – and examines - the possible development and use of any neuroS/T in reference to:

- **Capacities** – of the S/T
- **Consequences** – of the research and/or its translation;
- **Character** – of both the research, and how its outcomes/products might affect individual and/or community identity and ontology;
- **Continuity of Clinical Care and Research** – as necessary to address and manage any/all effects of novel interventions;
- **Consent** – with regard to the nature, and extent of information required to assure voluntary participation in research trials or clinical interventions in light of the relative nascence of techniques and technologies;
- **Contexts** - in which specific types of neuroS/T might be used within various situations, institutions, and socio-cultural contingencies that may affect the aforementioned variables.

3. Defining Key Domains.

It is vital to assess extant evidence from the international peer-reviewed literature, commercial trends, and public media and forums to map key NELSI domains generated by neuroS/T in global contexts, and identify those foci that are of primary concern and importance (Nuffield Council on Bioethics, 2013; Schnabel, Kohls, Sheppard, Giordano, 2014). Resulting maps reveal the extent and interactions of various domains of effect and influence, and can be employed to (1) propose statistical models of NELSI (domains) incurred by various uses of neuroS/T, and (2) develop quantitative metrics of the strength of interconnections between NELSI domains.

In some cases however, the patterns of neuroS/T use(s) and effect(s) will be entirely new. In such situations, a more casuistic approach may be required to provide prior exemplars that may serve as comparitors from which plots of near- to mid-term future trajectories can be developed. Toward such ends, we have proposed a method referred to by the acronym *HISTORY* - that addresses *historicity* and *implications* of *S/T*, and engages *ombudsmanship*, and *responsible yeomanry* in the pragmatic elucidation, and address of ethical-legal and social issues and problems generated by *S/T* in specific contexts (Giordano and Benedikter, 2013; Tractenberg, FitzGerald, Giordano, 2014). Historical analysis of the influence and implications of *S/T* is an important step toward *ombudsmanship*: revealing and depicting ethico-legal and social issues and problems evoked by *S/T* and its various applications in a given social milieu. From this arises *responsible yeomanry*: to identify and analyze the actual capabilities and limitations of *S/T* and the needs, values, and mores of individuals and communities that will utilize and be affected by such *S/T*.

4. Simulating and Plotting Trajectories of Effect

Whether assessed by depiction of extant progress, or via casuistic evaluation of previous relevant trends, the modeling of social effects of neuroS/T characteristically entails extrapolations of concept-to-construct articulation. Prior work by our group has shown that modeling neuroS/T progress and effects beyond a 10 year future horizon becomes difficult due to fractal growth of S/T, reciprocal interaction of S/T and social forces, and resulting diversity of potential (known and unknown) effects (Schnabel, Kohls, Shepard and Giordano, 2014). While this impacts modeling and address of long-term effects and NELSI of any neuroS/T, it is particularly problematic for any consideration and guidance of dual-use neuroS/T, especially given “world stage” scenarios, inclusive of economic and political, as well as military applications and capabilities (Albers, Lin, and Mehlman, 2014; Benanti, 2014; Dando, 2015; Giordano, 2014c; Giordano, Forsythe and Olds, 2010; Nagel, 2010; Tabery, 2014).

Force-planning techniques may be useful - if not essential - for enabling preparation for post-10 year circumstances and effects of neuroS/T development and articulation. Force planning employs a multi-disciplinary/multi-faceted approach to appraise strategic needs set forth in strategy, establishes requirements to meet these needs, and selects capabilities that will optimally suit operational requirements as projected over a defined time frame (10+ years). This process entails analyzing resource constraints, changing environments, and risks (e.g. - uncertainty and negative outcomes associated with mismatches among essential factors) to discern key variables so as to optimize modeling and planning for NELSI and their effects in and upon given socio-cultural settings.

If and when used within an integrative, convergent approach to neuroS/T assessment, the engagement and adaptation of extant force planning methods could provide a valid and valuable approach to neuroS/T and NELSI modeling (Vaseashta, 2012). Such methods can: (1) enable a more flexible and responsive orientation to predicting and describing likely public health, socio-economic, political and

military scenarios that can shape if, why, what, and how neuroS/T may progress within international ecologies; (2) define key NELSI arising in and from these trajectories and scenarios, and in these ways (3) inform proximate and mid-term future guidance and governance of neuroS/T.

At present, we are developing modeling and gaming-simulation protocols that identify domains and plot trajectories of effect generated by uses/applications of neuroS/T in fields of influence at varying timepoints of extrapolation, and under multi-variate conditions (Schnabel, Kohls, Shepard and Giordano, 2014). This approach:

- Hedges strategies for future uncertainties in use/misuse and effects of neuroS/T
- Addresses second, third and fourth order effects of decisions
- Provides a force-planning pathway for the preferred future(s) of neuroS/T research and applications that is responsive to managing risk and uncertainty
- Reveals likely outcomes and enables participants to challenge assumptions by allowing stakeholder interactions to foster new insights to NELSI.
- Addresses differing ways of handling critical NELSI
- Examines unique regional regulatory challenges and how can they be managed
- Affords understanding of the NELSI from tactical to strategic levels

Neuroethics Engaged: Prudently – and Successfully - Navigating the NeuroS/T Super-Speedway

Recent recommendations, such as those offered by the Presidential Commission for the Study of Bioethical Issues (2015) and federal guidelines and regulations (e.g. - ICH E-6, ISO 14155; 2011; and 21 CFR 812.43) provide important parameters for research and use of neuroS/T. However, a number of

neuroethical challenges remain, as the breadth, pace, and distribution of neuroS/T, and the demand for such techniques and technologies expand (Shook and Giordano, in press). In light of this, an adaptation of the *Heilmeier Catechism* - seven key questions based upon those originally proposed by George Heilmeier to discern and direct the need, importance, and success of S/T research and development undertaken by the Defense Advanced Research Projects Agency (DARPA) - may be of value to explicating and engaging NELSI arising in and from neuroS/T research and its applications in various forums. These are:

1. What is the problem, and why is it difficult?
2. How is it being approached at present?
3. What is the new approach?
4. What is the impact if successful?
5. How will success be measured?
6. How would this be organized?
7. To whom will this matter?

In posing the first of these questions, it becomes apparent that neuroS/T can and will affect and be affected by socio-cultural needs, values and views. Although some needs and values may be common to many if not all cultures, others will differ. This complicates NELSI, and their address. The second question reveals that existing ethical precepts and principles, while viable in some cases, will likely not be sufficient or adequate to address and guide the specific situations and contingencies posed by the varied (socio-cultural) contexts in which neurotechnologies are being developed and/or employed (Levy; 2010; Giordano, 2010; Giordano and Benedikter, 2012a,b; Shook and Giordano, 2014). We have argued that to be internationally relevant, neuroethical deliberation and engagement may require consideration of the viability and utility of extant ethical concepts, revision of certain current principles and the formulation of others anew (Shook and Giordano, 2014). If successful, this would enable both a

broad cosmopolitan palette of constructs and approaches that is leverageable upon the twenty-first century world stage, as well as the ability to employ this neuroethical toolkit in more focused, community-sensitive and responsive ways (Giordano, Lanzilao, Shook, Benedikter 2015; Avram and Giordano, 2014; Lanzilao, Shook, Benedikter, Giordano, 2013).

The organization of infrastructures dedicated to the type and extent of deliberation necessary for resolving neuroethico-legal and social issues would require participatory commitment of individuals from multiple disciplines that possess both subject matter expertise and task agility (i.e. - knowledge of the contingencies and exigencies inherent to different circumstances of neuroS/T utilization).

Fundamental to such expertise – and the process of neuroethical address - are awareness of, and responsiveness to: (1) the actual capabilities and limitations of neuroS/T, (2) the unquities of neuroS/T research and its translation in particular contexts, and (3) the ways that these unique circumstances are related to and affect neuroS/T use and NELSI more generally (Tractenberg, FitzGerald, Giordano, 2014).

Organizations currently devoted to addressing NELSI (e.g. - the Presidential Commission for the Study of Bioethical Issues, intramural advisory groups at DARPA and the National Institutes of Health in the United States; recent work of the Nuffield Council on Bioethics in the UK, et al.) are significant in their composition and activities. But in order for this be sustained, and therefore to “matter” to neuroS/T users, stake- and share-holders beyond the immediate future, investment must be dedicated to neuroethics education and training.

Conclusions

Apropos these considerations, we have called for “no new neuroS/T without neuroethics”, and have offered steps toward targeting and initiating focal NELSI projects and programs that may create tractionable opportunities for collaborative engagement of governmental agencies, commercial enterprise(s) and academia (Giordano, 2015c; Shook and Giordano, in press). When engaged within a

general paradigm for NELSI deliberation, the proposed ON-RAMP may afford viable and valuable methods and measures to address, identify, prevent, constrain and/or counter the attendant risks of neuroS/T, and maximize the benefits, gains and “prizes” that such research, development and their translation can provide to global health. Clearly, this task is formidable, and thus neuroethics – and our efforts - remain a work in progress.

Acknowledgments.

This work was supported in part by funding from the Children’s Hospital and Clinics Foundation, William H. and Ruth Crane Schaefer Endowment, and through an unrestricted research grant provided by Thync Biotechnologies. JG serves as an appointed member of the Neuroethics, Legal and Social Issues Advisory Panel of the Defense Advanced Research Projects Agency (DARPA). The views expressed in this paper do not necessarily reflect those of DARPA, the United States Department of Defense, or the United States federal government.

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Table I

General Categories of Neuroethico-legal Issues (NELSI)

Issues arising from Neuro S/T

- Uncertainties of new, “frontier” developments
- Safety and effectiveness
- Constraints upon/limits of informed consent

Derivative/Responsive Social Issues

- Definitions of treatment, enablement and/or enhancement
- Neural “norming”
- “Mind control”/altered autonomy
- Distributive justice
- Legal concerns