Neuroscience 164 (2009) 7–15

REVIEW

IMAGING GENETICS AND THE POWER OF COMBINED TECHNOLOGIES: A PERSPECTIVE FROM NEUROETHICS

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Abstract—Imaging genetics has emerged as a powerful and sensitive approach to the study of functional genetic variations and brain responses in psychiatric and neurologic disorders. Ethics issues in contemporary neuroscience as they apply separately to genetics and neuroimaging have been a growing focus for research but, to date, there has not yet been a rigorous exploration of the ethical dimensions of the territory in which they overlap. Here we propose that the ethics challenges associated with the combination of these methods call for an expanded "neuro-space" in which societal and ethical values are closely and explicitly integrated with the new science. We build specifically on the model delivered by Roffman et al. [Roffman JL, Weiss AP, Goff DC, Rauch SL, Weinberger DR (2006) Neuroimaging-genetic paradigms: a new approach to investigate the pathophysiology and treatment of cognitive deficits in schizophrenia. Harv Rev Psychiatry 14:78–91] for neuroimaging, and develop the argument that the ethics issues parallel the heightened discriminative and cumulative power of imaging genetics. In the new combined space, features of discriminative power concern better differentiation of disease, sometimes by ethnicity, and incidental findings. Clinical utility, prediction and intervention, and stigma and labeling reflect a common ground between discriminative and cumulative power. Privacy, autonomy, response sensitivity and attitudes, resource allocation for research and for health care, and commercialization, are features of cumulative power. Parallel to the clinical features highlighted in the Roffman et al. map, the combined space yields additional neuroethics features. These are characterized by new knowledge and new implications for health care, justice, and policy. We conclude by examining these features in the context of public health at the interface of emerging new neurotechnologies.

Keywords: neuroethics, imaging genetics, genetics, neuroimaging, public health.

Contents

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E-mail address: jilles@interchange.ubc.ca (J. Illes).
Abbreviations: AD, Alzheimer's disease; COMT, catechol-*O*-methyltransferase; fMRI, functional magnetic resonance imaging.

In 2003, Hariri and Weinberger wrote that the enhanced power and sensitivity of imaging genomics places this technology at the forefront of available tools for the *in vivo* study of brain responses and functional genetic variation (Hariri and Weinberger, 2003). Three years later, in 2005, Congdon and Canli wrote, ". . . an advantage of the imaging genomics approach is that it is significantly more powerful and more sensitive than association studies looking at self-reported traits, psychiatric diagnosis, and even behavioral performance" (Congdon and Canli, 2005).

What qualifies a neuroscience tool as powerful, very powerful, or even "significantly more powerful"? Reliability, sensitivity and specificity are key scientific factors certainly, as they are based on empiric data and reproducibility. Utility, cultural ubiquity, and individual and societal acceptability are major ethical–societal and human variables that have yet to be explored. In this paper we consider the scientific factors as a backdrop to our major focus on the latter variables. We focus on the major applications of imaging and genetics —"imaging genetics"—today in Alzheimer's disease (AD) and neuropsychiatry, and explore past discussions of genethics as it is differentiated from neuroethics. (The terms "imaging genetics" and "imaging genomics" are used interchangeably in the published literature, the former being used more frequently than the latter; we observed 40/18 ratio of these two terms in the published literature and therefore adopt the more prevalent term "imaging genetics" for our discussion here.) While ethics issues in genetics and in imaging have been discussed separately in recent years, both in scientific and non-scientific communities, we propose that ethics challenges in a combination approach such as imaging genetics call for an expanded "neuro-space" in which societal ethical values are closely and explicitly integrated with the technical capabilities of the emerging technology. In the

0306-4522/09 $ - see front matter
doi:10.1016/j.neuroscience.2009.01.052

context of this paper we define the ethics "neuro-space" as the ethics environment generated by the complex interaction of genetics, neural systems, and behavior. We build specifically on the model proposed by Roffman et al. (2006) and develop the argument that while the ethics issues for imaging genetics are not necessarily more numerous than those that have been described for brain imaging alone (Illes and Racine, 2005), they are qualitatively different, closely paralleling the heightened discriminative and cumulative power of the dual technology itself.

To our knowledge, this is the first analysis of the ethics dimensions of imaging genetics. Our goal through this exploration is to provide a foundation for discussion, and seed further examination of the issues. We conclude with a look beyond ethics paradigms to public health and health systems at the interface of emerging neurotechnologies.

APPLICATIONS OF IMAGING GENETICS IN NEUROLOGY AND PSYCHIATRY

One of the earliest imaging genetics studies was published on AD by Bookheimer and colleagues (2000) in the *New England Journal of Medicine*. In this longitudinal study, the authors observed that patterns of brain activation as measured by functional magnetic resonance imaging (fMRI) vary depending on the genetic risk of AD, and suggested that they may predict the course of cognitive decline. In 2001 and again later in 2007, Reiman and colleagues (Reiman et al., 2001; Reiman, 2007) also reported on the use of MRI as well as positron emission tomography (PET) to study brain changes associated with aging in persons with and without the apolipoprotein E (APOE) 4 allele—the common AD susceptibility gene. They described how imaging combined with subsequent genomic studies can provide early biomarkers for the disease even before the onset of plaques and tangles in persons at risk, and improve disease tracking. These studies and others (Ringman, 2005; van Berckel and Scheltens, 2007; Ryu and Chen, 2008) have served not only to better characterize AD risk factors and brain abnormalities, but to advance the possibility of cost-effective prevention strategies and potentially remarkable, albeit still future public health impact.

The promise of a new combined capability in the early part of the decade for AD quickly unleashed a series of studies such as those on apolipoprotein E and memory systems, catechol-o-methyltransferase (COMT) and the prefrontal cortex, and 5-HTT and the amygdala (Mattay and Goldberg, 2004). There were several prominent studies focusing both on common gene variants known to affect cognitive and behavioral processes within the normal range, as well as on various diseases and conditions such as attention deficit hyperactivity disorder (ADHD) (Mitterschiffthaler et al., 2006), depression (Mitterschiffthaler et al., 2006), obsessive-compulsive disorder (OCD) (Mitterschiffthaler et al., 2006), anxiety and stress (Xu et al., 2006), and schizophrenia (Meyer-Lindenberg and Weinberger, 2006; Blasi and Bertolino, 2006). Egan et al., for example, examined the relationship between functional polymorphisms of the COMT gene and regulation of prefrontal dopamine that is associated with the genetic risk of schizophrenia. They examined the effect of COMT genotype on prefrontal physiology during a working memory task and found that the low activity Met allele load consistently predicted a more efficient physiological response in prefrontal cortex (Egan et al., 2001). Hariri et al. (2005, 2006) used fMRI to study emotional behavior (anxiety, response to fear) in healthy volunteers with different 5-HTT genotypes, as well as the susceptibility gene for affective disorders. They found that subjects carrying the less efficient *s* allele of the 5-HTT promoter gene had an increased amygdala response to fearful stimuli in comparison to subjects homozygous for the *l* allele. More recent meta-analyses of the association between 5-HT transporter genotype and amygdala activation provide supportive data for this association, although the limited statistical power of the studies conducted to date is an acknowledged limitation (Munafo et al., 2008).

The alignment of results from imaging genetics on neurodegenerative disease and neuropsychiatric disorders supports the suggestion that the combined method may have an unprecedented power to predict effectively and, by extension, lead to the prevention of certain diseases and risky behaviors (Mattay and Goldberg, 2004). Imaging genetics provides a unique opportunity to explore the functional impact of brain-relevant genetic polymorphisms more rapidly and with greater sensitivity than existing behavioral assays. With continually increasing methodological power, the approach of imaging genetics now allows for complex behaviors and predispositions to psychiatric syndromes to be linked to functional brain differences and to be explained from a biological prospective (Hariri and Weinberger, 2003). Already today these methods are widely recognized as effective *in vivo* tools to measure the gene effects on different parts of the brain involved in specific moral, emotional, cognitive functions resulting in certain behaviors. Combining genetic studies with non-invasive imaging technologies such as fMRI has the potential to reduce the participation time required of subjects and the overall number of subjects needed for group-averaging of the neuroimaging data (Hariri and Weinberger, 2003). While this could be viewed as an asset to neuroimaging methods, the potential ethics concerns brought forward by the ability to examine subtle gene effects on brain function with relatively small numbers of subjects require ongoing and careful analysis. In addition, by virtue of their technical non-invasiveness, combined imaging and genetic methods are considered by some to be ideal for the study of development in children (Viding et al., 2006; Brocki et al., 2008), again with both benefit and risk at play.

While there still remains much to be learned, one point seems certain: like other successful innovations in genetics and neuroscience, there will be an increased use of imaging genetics in the years to come (Mitterschiffthaler et al., 2006; Annas, 2007). Will the anticipated surge in scientific activity be accompanied by a similar surge in ethics-based challenges? We explore this question next.

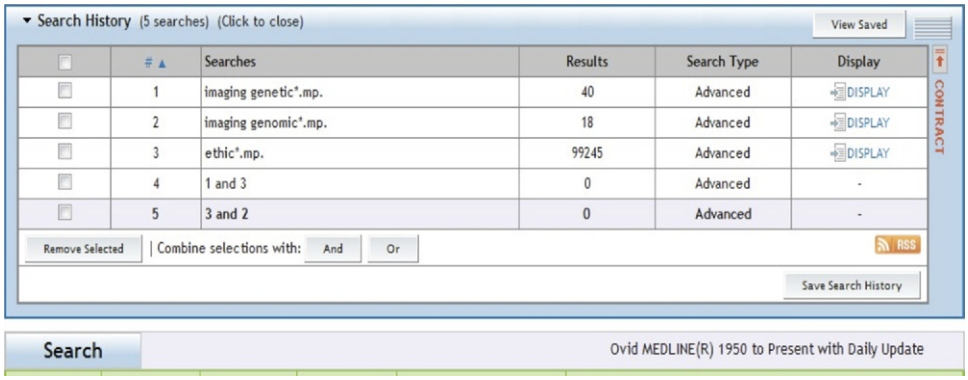

Fig. 1. Snapshot of MEDLINE search results (August–September 2008) for imaging genetics and ethics.

AN ETHICS NEURO-SPACE FOR IMAGING GENETICS

Foster et al. (2006) wrote "As medical researchers and clinicians increasingly combine genetic information with a range of non-genetic information in the study and clinical management of patients with common diseases, the unique ethical challenges attributed to genetics must be re-examined" (p. 635). They argued, in fact, that little consideration has been given to the ethical implications of working with multiple kinds of information at once (Foster et al., 2006). In the past, we and others with interest in the intersection between ethics and neuroscience, broadly defined as "neuroethics," have discussed the converging and diverging ethical dimensions of genetics compared to other approaches to understanding brain health and disease (Illes, 2003; Illes et al., 2003, 2006; Morley et al., 2004; Fuchs, 2006; Fins and Shapiro, 2007; Fukushi et al., 2007). Concepts of self and personhood clearly add a new layer of ethics especially, for example, to brain imaging (Racine and Illes, 2006). As Roskies (2007) highlighted, "despite the overlap between the ethics of neuroscience and genetics, there are important areas where the two diverge." For instance, the ethics issues associated with manipulating the genome lie in the domain of genethics, whereas consciousness, decision-making, free will and moral cognition as distinguishing features of neuroscience and neuroimaging are apart from genetics. Neuroscience, and especially brain imaging, might shed light on the state of consciousness of patients, even those whose verbal and physical response capabilities are impaired (Roskies, 2007). As Roskies further states, "our genes are causally far removed from our behaviors," making free will and decision-making a domain for neuroscience and neuroethics inquiry apart from genetics. Prompted in part by Foster et al. (2006), the question now is what is known about ethics in the combination of neuroimaging and genetics?

To gain an initial understanding as to how ethics has been treated in research involving genetics and imaging concurrently, we conducted a literature search using the subheading and keyword search functions of the Ovid MEDLINE (R) database (search conducted on September 25, 2008). The search revealed a sample of 40 articles containing the search string "imaging genetic*" and 18 articles containing "imaging genomic*." Ninety-five percent of original and review articles found were published from 2000 onward. The highest year-to-year increase in number of papers was from 2005 to 2006 (17 papers in 2006, two papers in 2005; 750% increase).

When we added the term "ethic*" to either of the two search configurations, there were no matching articles found in this comprehensive database (see Fig. 1). Therefore, even if ethics issues in contemporary neuroscience, in neuroimaging and in genomics continue to be a growing focus for research, there would not yet appear to be any rigorous exploration of the ethical dimensions in this overlapping territory. The topic of ethics challenges borne on the frontier of imaging and genomics has not yet been developed.

As a starting point to fill this gap, we build directly on the work published by Roffman et al. (2006). The authors presented neuroimaging–genetics paradigms to elucidate the relationship between genes and cognitive dysfunction in schizophrenia. They focused on criteria guiding the selection of genes, imaging techniques, and subjects in imaging genetics studies, including: the identification of the appropriate candidate genes, gene–illness association, variability effects among ethnic groups, disease targets, subject selection, and consistency of findings (both imaging and pathophysiology). The potential clinical utility of the imaging genetics paradigm, according to the authors, is the predictive power of imaging genetics in determining certain clinical outcomes and treatment responses. The findings in turn will help identify individuals at risk of disease and suggest individual treatment plans (Roffman et al., 2006).

We have reproduced their illustration (Fig. 2, top) showing a continuum from genes to clinical features, with neuroimaging at the interface, but have extended it to include an ethics framework (Fig. 2, bottom). This frame includes what we see to be a discriminative and cumulative ethics power that parallels the power of the combined technologies. Discriminative power is defined as the capacity to differentiate phenomena and distinguish them based on objective criteria. It draws upon the improved specificity naturally afforded by combined techniques and, therefore, the possibility of reduced statistical error. Cumulative power is

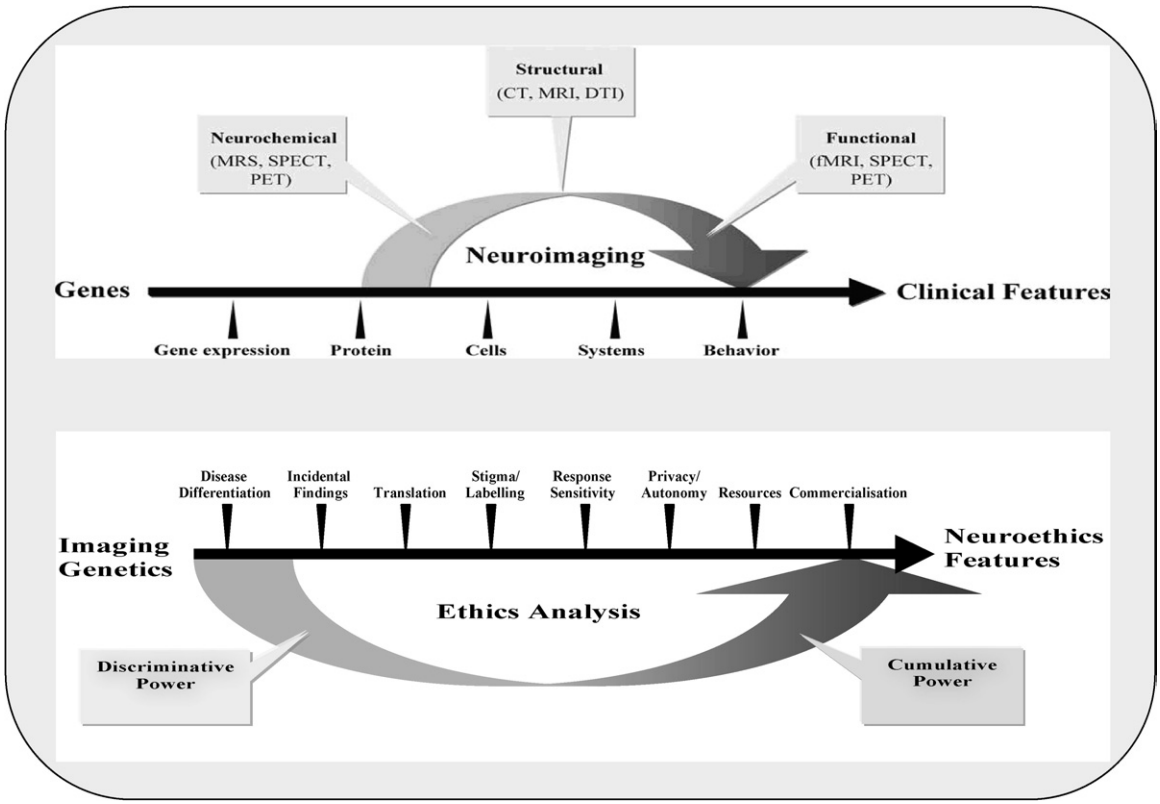

Fig. 2. The role of neuroimaging in investigating intermediate phenotypes expanded with ethics features to create a new "neuro-space." The features reflect a logical continuum but not necessarily a fixed temporal relationship. Embedded Roffman et al. (2006) figure reprinted by permission [Informa Healthcare USA, Inc.].

the ability to gain greater information about the discriminated phenomena and by extension, associated ethics challenges. In this new, combined "neuro-space," features reflect a logical continuum but not necessarily fixed temporal relationships. Features of discriminative power in this representation include better differentiation of disease, sometimes by ethnicity (collectively shown as "disease differentiation" on the figure), and incidental findings. Clinical utility, prediction and intervention (collectively termed "translation" in the figure), and stigma and labeling have fuzzier boundaries that reflect the greatest common ground between discriminative and cumulative power. Viewed as a two-tailed problem, the discriminative power of imaging genetics may, on the one hand, amplify stigma and labeling of people with brain diseases by reducing them into subgroups while, on the other, the cumulative power may provide evidence-based information that reduces stigma associated with these conditions. Privacy (right not to reveal or disclose any personal, identifiable information), autonomy (self-governance and the capacity to make an informed, uncoerced decision), "response sensitivity" (beliefs [hope, hype] and attitudes [trust, desirability, public perception]), resource allocation for research and health care, and commercialization are features of cumulative power. Like the output of the Roffman et al. (2006) continuum that yields clinical features, we propose that the ethics trajectory yields neuroethics features characterized by new knowledge and new considerations for health care, justice, and policy.

We stress both the early and unvetted nature of this framework and its characteristics described next, and our goal of stimulating further debate of the ethics issues in this domain.

Disease differentiation

New diseases and disease by ethnicity. As the sensitivity and specificity of both genetic and imaging technologies improve, the possibilities for better diagnostic measures come to light. Increasing numbers of patients may be diagnosed at ever-earlier stages of disease, allowing for, if not requiring new opportunities for refinement of disease nosology and taxonomies that may affect basic and translational research and ultimately even markers of well-being (Illes and Atlas, 2007). Findings of variations of genotypes by ethnicity may similarly open new arrays of discussion on determinants of brain disease. Studies have shown that ancestry and ethnicity are significant determinants of susceptibility to some complex diseases such as diabetes, cardiovascular disease, breast cancer, and response to treatments (Spielman et al., 2007; Storey et al., 2007; Zhang and Dolan, 2008). To discover similar effects in brain disease, subjects representing specific ethnic genetic backgrounds must be recruited. Besides artifacts of population stratification and issues surrounding the generalizability of results from ethnicity-centered studies, ethical consideration of justice and equity, among others must be

taken into account. Unless historical access barriers are attended to proactively, results of imaging genetics studies, like other emerging technologies with societal as well as medical impact, may become a new source of disparities among different socioeconomic, ethnic, and age groups (Sankar et al., 2004; Fleming et al., 2008; Miranda et al., 2008; Warnecke et al., 2008; Zhang and Dolan, 2008). How imaging genetics informs the understanding of brain diseases, how that information is shaped by race and ethnicity, and how societal forces and public policy will need to respond are questions well-suited to discovery in the expanded neuro-space.

Incidental findings

Combined technology will almost certainly yield more sensitivity to unexpected findings in research that may have clinical significance, but will not necessarily yield more specificity. The past 5 years of work on the subject of incidental findings in neuroimaging research specifically suggests, for example, an incidence of clinically significant findings of various degrees in 2%–8% of the population, with low incidence but high clinical significance in young participants presumed to be neurologically healthy, and the inverse in the elderly 65 years and older population (Illes et al., 2008a; Illes and Chin, 2008). Among the most common findings are arteriovenous malformations and aneurysms. Although the discriminative power to reveal such unexpected or unusual findings may be regarded as a positive attribute on the one hand, it may be obfuscating on the other if, for example, only one of the two (or even more) methods yields a suspicious finding or each reveals a finding that is discordant with the other. Nevertheless, the overarching challenge of handling these medical findings in research remains unchanged regardless of whether the conversation concerns a single or multiplex technology, or in original or archived data (Illes, 2006b; Illes et al., 2008a; Wolf et al., 2008): what do we do with these findings? What is the optimal timing for disclosure, if at all, and to whom? How do we manage the potential blurring of the boundaries of research and clinical medicine? Clearly, much empiric and consensus-generating work remains to be done on this subject.

Translation

Clinical validity, prediction and intervention. We see the enormous potential for the combination of genetic information with brain activation images to multiply the positive clinical validity of either method alone, mitigate statistical uncertainty about prediction effects, and lead to better interventions. In imaging genetics studies, the factors that help establish plausible gene–clinical symptom relationships are gene variations, changes in protein and cell function, and the consistency of findings with pathophysiological knowledge. The new ability to predict clinical outcomes based on gene polymorphism data coupled with neuroimaging information (Roffman et al., 2006) will be an added factor in the future, although more salient studies showing a strong relationship between gene variation and brain disease are still awaited (Borgwardt and Fusar-Poli, 2007; Meyer-Lindenberg et al., 2008). It is important to emphasize that neuroimaging studies currently generate plausible results primarily based on group-averaged data, and it is still too early to interpret individual brain imaging and genetic data combinations for diagnosis or even individual prognosis; there is a significant need to increase the scientific validity and reliability of imaging genetic methods before clinical utility can be maximized. Premature and off-label adoption of applications (Illes and Kirschen, 2003), and the routinization of medical technology, are well-documented phenomena (Koenig, 1988). Keeping these risks at bay is essential. Unrealistic or hasty release of information will invariably drive consumer and clinician expectations for information and treatment. Inequalities in health care will arise if access to information and prognosis about potential health risks or identifiable disease are uneven, allowing some to take action towards minimizing risks, acquiring education, adopting lifestyle changes, or seeking interventions, while disadvantaging others less able to gain access to their own health information.

Stigma and labeling

We may well expect “double trouble” with dual technology as the cumulative power of trusted genetic information combined with the visualized brain images (Dumit, 2004; Racine et al., 2006) amplifies stigma and labeling of people with brain diseases (Wolf et al., 2008; Milstein, 2008; Richardson, 2008). Accurate perceptions of heritability, family history, and, most importantly, projections of health outcomes on future generations are all at stake. The risks of stigma and discrimination of neuroprofiling children early in their lives alongside examination of the potential benefits will be significant if the promise of imaging genetics in this cohort is realized. With disorders of mental health affecting one in every three people in some developed countries (Demyttenaere et al., 2004), this particular feature of the ethics neuro-space for imaging genetics could easily be identified as a priority area for empiric elaboration.

Privacy and autonomy

Genetic testing and imaging together yield fundamentally new kinds of knowledge that require new approaches to data anonymization, storage, banking and retrieval. Further complicating necessary protections to human subjects are co-morbidities, pleiotropy (Wachbroit, 1998) and the implications of results for third parties (Fulda and Lykens, 2006; Romeo-Malanda and Nicol, 2007). Autonomy is a principle independent of privacy, and we raise it here with respect to the ability of a person to provide informed consent for participation in research. It is unequivocally linked with an informed understanding of what data can realistically be kept private and confidential. With recent reports of breaches of confidentiality in banked data at the National Human Genome Research Institute (Couzin, 2008; Kaiser, 2008), this new era of data collection necessarily brings new challenges to the concept of human subject’s protection. Even if current risk to human subject confidentiality is regarded to be minimal (Couzin, 2008), the proliferation of genetics information over the next 5 or 10 years

may change the risk–benefit equation both for privacy and for autonomy.

Response sensitivity

It is not unreasonable to expect that wishful beliefs for cures to currently incurable diseases, sometimes fueled by press coverage of exciting new results, will lead to even more hope from newly integrated capabilities. Like beliefs, attitudes in terms of public trust and acceptance may be adversely affected if not managed well and especially, we believe, if the ethics are left to the wayside. In recent history, the application of fMRI to patients in minimal conscious states (Schiff et al., 2005; Laureys and Boly, 2008) is one example of such a phenomenon. Press accounts represented laboratory results to be well beyond their real-world validity, and incited families to seek scans to assist with decisions, including those about end of life, for patients in vegetative states (Hirsch, 2005; Illes et al., 2008b). A positive response to such events is modeled in reports by Laureys and Boly (2008); Fins and Shapiro (2007), and Illes et al. (2008b) from a consensus meeting among principal investigators and other stakeholders from the neuroscience, ethics and legal communities. These reports delivered a set of ethics recommendations framed for future research, as well as educational products for professionals and consumers alike (Illes et al., 2008b). We would urge similar outreach for imaging genetics.

Resources

Our use of the term “resources” here encapsulates both resources for research and resource allocation for health care.

For research, the manner by which priorities and funding agendas are set is all but simplistic, and is influenced heavily by political, social and societal priorities and values (Fraser, 2000; Ashcroft, 2007). Research findings inform policy for resource allocation, collectively with the needs of society and stakeholders. As with any promising science tool at the cutting edge, the emergence of imaging genetics might prompt new strategies for allocation of resources. If this is the case, it is essential to ensure just re-allocation of scarce research funding, especially for those technologies and projects in which substantial investments have already been made and results achieved.

Allocation of resources to patients once clinical readiness has been demonstrated is no less complicated in today’s health care systems. Historically, new and high-cost technology is initially accessed by those who are privileged socioeconomically (Illes and Atlas, 2007; Illes and Kirschen, 2003). Long wait times characterize access to non-emergency imaging in Canada (Canadian Institute for Health Information, 2008). How will health care systems respond to new demands for expensive technology, especially as its application may be for screening as much as for diagnosis? How will uncertainty regarding the future treatment of presently untreatable diseases impact current decision making in the realm of novel technology funding?

Commercialization

In this modern era in which the commercialization of innovative neurotechnologies is a fast moving trend, imaging genetics has great potential to become an attractive product for emerging high technology medical markets. Guidance for considering the cumulative power of the combined technologies may well be learned from past lessons on commercialization. These include considerations of the sale of technology for uses for which the technology was not intended and potentially for which data do not exist, sustained validity, and aggressive marketing strategies that pose risks especially to some of the most vulnerable members of society who suffer from neurologic or mental health disorders and accompanying cognitive deficits (Illes et al., 2004).

The possible sale of this technology for forensic purposes is an area entirely untapped. Neuroscience databases, including those archiving neurologic and genomics data, have been created around the world. The resulting challenges for the commercial sector, as for researchers, are enormous. A range of legal authorities, and potential litigants such as insurers and employers, may seek this information. Individuals who are data sources may also try to access information about themselves. As the data can be banked indefinitely, these issues have an indeterminate lifetime for a source individual and family members.

BEYOND THE ETHICS PARADIGM: PUBLIC HEALTH CONSIDERATIONS AND CONCLUSIONS

Humans have an insatiable appetite for information and innovation. History has shown that when a new medical device or method is rolled out after proven validity in the laboratory, little abates the hunger for intended clinical and extended application. Imaging genetics, like other emerging technologies, holds tremendous benefit both in terms of long-term and short-term implications for translational outcomes (Viding et al., 2006). The rewards will be reaped from the ability to document possible predictive genetic, biological, environmental, and social markers for outcomes, and early identification of individuals with neurologic or psychiatric health risks. This will be significant not only on at the individual level but also for public health both in local and global communities.

From the public health point of view, the eventual application of imaging genetics for research and specifically for diagnostic and clinical purposes has the potential to impact many different determinants of population health, defined in the public health literature to include individual, environmental, behavior and lifestyle factors, as well as access to health services (Merson et al., 2006). Opportunities for better diagnosis with imaging genetics and other advanced technologies can lead to improved knowledge about health status and prognosis, and better informed consumers motivated to seek preventive, clinical and social services. Environmental factors, particularly socioeconomic status, will interact with imaging genetics as income will determine demand and social status and acceptance

determine paths of access. Lifestyle and behavioral determinants of health and health service–seeking behavior, as well as the overall perception of brain disorders may shift if imaging genetics becomes a choice for the population at large. For health systems eventually providing access to imaging genetics, this will raise questions about cost-effectiveness and clinical and public health benefits; for population health, questions can rightly be expected about motivators for accessing services including rights, cultural factors, eligibility, acceptance, time, distance, and social cost.

The World Health Organization defines the three main goals for health care systems to be good health, responsiveness to expectations (particularly non-medical expectations such as quality, safety, respect, confidentiality, autonomy, client orientation) and financial protection (World Health Organization, 2000). How will imaging genetics technology promote better health system performance, responsiveness and fairness and, therefore yield better individual health? Will the new technology provide daunting challenges for the health care systems or efficient solutions? The answers to these questions will depend on the how the core functions of health care systems such as resource generation, service provision, financing and stewardship (World Health Organization, 2000) are optimized to the new technology. Resource generation in terms of human resources (availability, education, training), knowledge, technology and investments will determine what kinds of services are generated, at which level of health care system, at what sector (private, public, non-governmental) and for whom (patients, families, providers). Stewardship will lead the assessment of metrics of performance and sustainable outcomes.

Even while we think about the future public health impact of imaging genetics, the absence of ethics consideration in today's environment remains as a significant gap. As we have discussed, defining that gap are the discriminative and cumulative power afforded by the combination of two or more technologies applied to frank, probable and even possible diseases of the central nervous system (CNS), and the ethics challenges brought to the foreground by this added power. This gap must be filled by interdisciplinary collaboration, attention to historical lessons and accomplishment, and a commitment to the challenges ahead. Indeed, the ethical, social, and legal challenges of imaging genetics will be best addressed through a well-balanced interdisciplinary approach (Racine and Illes, 2006; Racine, 2008). Responses to the challenges will derive from dialogue and ideally consensus among different professional and lay stakeholders about the complex ethical considerations that human subjects research and clinical translation entail: informed consent, safety, privacy and confidentiality, the social implications of different kinds of information, handling of probabilistic or statistical information about future health, the vexing question of how to differentiate borderline pathology from normality, and an expanded duty to communicate scientific results to individuals and to the public (Illes et al., 2008b; Racine et al., 2005).

The importance of effective communication and neuroscience literacy has been emphasized by the significant level of penetration of both genomics and imaging into non-academic spheres, namely press, courts, private business, and marketing (Illes, 2006b). In many cases, although certainly not all, the potential of the research is overstated, giving more power to its real-world potential use than has been realized in the laboratory (Racine, 2003; Hjorleifsson and Schei, 2006; Illes and Suchowersky, 2008). In the non-peer-reviewed literature indexed in MEDLINE for 1950 through 2008, there are more than 70 times more letters and press articles on ethics and genetics than on ethics and brain imaging (Tairyan and Illes, unpublished observations). One can only speculate what these data predict for coverage of the combination of the two disciplines in the future.

While analyses of the ethical, legal and social implications of other combined technologies such as those developed for preimplantation genetic diagnosis and stem cells have been developed in the past (Wolf et al., 2003), to our knowledge we have provided the first framework for the ethics discussion in imaging genetics. Our framework draws upon principalist thinking in bioethics (Beauchamp and Childress, 2001; Veatch, 2003) stressing beneficence, autonomy and justice, and pragmatism (McGee, 2003). We emphasize that our framework is intended to be a launch for discussion, is fluid, and is certainly not meant to represent any one or set of inflexible barriers that could become obstructive to the speed or promise of innovation at hand. On the contrary, we are committed to the idea that early exploration and strategies toward resolution of ethics challenges in neuroscience fosters, not hinders, the overall scientific goal (Illes, 2006a). To conclude then, we offer a final quote from Hariri and Weinberger (2003): "Genes are the biological toolbox with which one negotiates the environment" (p 260) (Hariri and Weinberger, 2003), and call for a close alignment of the ethics and social considerations to provide a necessary map, along with imaging, for that navigation.

Acknowledgments—Supported by CIHR/INMHA CNE #85117, NIH/NIMH #9R01MH84282-04A1, VCHRI, and the Foundation for Ethics and Technology. Special thanks to Daniel Buchman, Neil Chahal and the team at the National Core for Neuroethics at UBC for helpful discussions on the neuroethics of imaging genetics, and to anonymous reviewers for thoughtful comments on the manuscript.

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(Accepted 28 January 2009)
(Available online 3 February 2009)