Gene Maps, Brain Scans, and Psychiatric Nosology

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Neuroethics to date has tended to focus on social and ethical implications of developments in brain science, especially in functional neuroimaging. Within clinical neuroethics, the emphasis has been on ethical issues in clinical neuroscience practice, including informed consent to neuroimaging; the development of ethical research protocols for functional magnetic resonance imaging especially, and especially in children; and the ethical clinical management of incidental findings. Within normative neuroethics, we have witnessed the more philosophical and/or social scientific study of the meanings of developments in neuroscience, including concerns about the impact of neuroimaging on privacy, freedom of thought, moral culpability, and sense of self. In this piece, I argue for an expansion of neuroethical attention to the interface of neuroscience and psychiatry, where brain science meets the clinical sciences of the mind. My particular focus is the development of psychiatric classification systems.

Some psychiatrists have claimed that the application of technologies from such domains as neuroscience, genetics, and genomics promise revolutionary advances in diagnosis, classification, and patient care. Such promises include the identification of “genes for” all kinds of psychiatric disease from bipolar disorder to schizophrenia and the construction of a new taxonomy of disease based on the underlying etiology of illness. Whether these putative advances are worth realizing remains to be determined on a case-by-case basis, given a certain skepticism about the likelihood that they in fact can be realized. Having elsewhere interrogated the genetics of psychiatric disease, and leaving aside at this time the vexing question of the relationship between psychiatry and neurology, in this essay I restrict my attention to psychiatric classification—in particular, to whether and how genomics data and neuroimaging data may be used to define a new taxonomy of psychiatric disease.

My guiding concern is for appropriate patient care (an ethical consideration), and my discussion is premised on a systems approach to understanding development, and so to understanding the role of genes in development (a conceptual concern in the philosophy of biology). Accordingly, my analysis of these issues is as much conceptual as ethical, as is increasingly common in the philosophy of psychiatry. But this does not make it any less normative an analysis of developments in psychiatry and neuroscience.

I am grateful to Jenny Brian, Carl Craver, Thane Plantikow, Claire Pouncey, and Ken Schaffner for discussion of many of the themes presented here. Early research on which portions of this article are based was funded by the Canadian Institutes of Health Research in the form of an operating grant and salary award. My current research is supported by the Institute for Humanities Research, the Center for Biology and Society, and the School of Life Sciences, Arizona State University.
In what follows, I contend that whether a new taxonomy of psychiatric
disease is adequate to patient care will depend largely on the approach taken in
designing that taxonomy. Whether the approach is purely reductionistic (based
solely or largely on the underlying molecular etiology or molecular character-
ization,) or rather more integrative (based on not only molecular data but also
intermediate and macro-level information) will determine its value for patient
care. Given alternative visions of good psychiatry (as of good medicine more
generally), and given that these are open to evaluation on multiple fronts, I will
stake a claim for one alternative vision over the considerably more popular
view that a reductionistic taxonomy is good, worthwhile, and imminent in
psychiatry as elsewhere in medicine.

A Molecular Taxonomy of Disease?
The National Human Genome Research Institute’s “vision for the future of ge-
nomics research” includes the quest for “a new molecular taxonomy of illness,
which would replace our present, largely empirical, classification schemes and
advance both disease prevention and treatment” (p. 841). Along the same lines,
the Director of the National Institutes of Health has recently claimed that
“[t]he reclassification of disease based on specific molecular signatures is likely
to be one of the most original contributions to clinical science in the 21st century”
(p. 1355). Thus, the architects of the human genome sequence are predicting
a molecular reclassification of disease based on elucidating the underlying mo-
lecular etiology or identifying molecular markers. Psychiatric researchers have
joined in the hunt for particular genes associated with psychiatric conditions,
and many of them look forward to a more “scientific” psychiatric nosology based
on genetic markers and molecular signatures. But what might that mean?

Let us assume for the sake of argument that there are very likely a number of
genes involved in the etiology of schizophrenia. Now, what role should this mo-
lecular information play in psychiatric disease classification? The leading ap-
proach, a reductionistic one, is evidently motivated by a belief in the centrality
and primacy of genetic explanations of higher level phenomena, and so instances
of this approach are characterized by a certain optimism about the prospects of
molecular genetics in psychiatry. Indeed, there almost seems to be an imperative
to recreate psychiatric classifications on the basis of genomics data.

A recent review suggests that genomics can help to eliminate (some) social
and political factors from the nosology, thereby generating a more objective,
scientific nosology. Regarding the movement toward “a more biological basis
for psychiatric diagnosis,” Harris and Schaffner anticipated “that molecular
genetics will make a very substantial contribution to this movement. As genetic
markers play an increasing role in diagnosis, new disease classes may emerge
that replace or significantly modify old ones” (pp. 128–9). Similarly, Tsuang
et al. enthusiastically claimed that “the new tools of molecular and statistical
 genetics promise to build an enduring theoretical and empirical structure that
 will house solutions to many questions of aetiology, pathophysiology, diagnosis
 and treatment” (p. 131).

Tsuang’s work is especially instructive. He endorses the creation of a psychiatric genetic nosology that “seeks to classify patients into categories that corre-
respond to distinct genetic entities” (p. 4). In other words, “instead of using

Jason Scott Robert
predefined categories, these methods attempt to define new phenotypes that maximally correspond to the genetic component of psychiatric illnesses” (p. 136).14 This approach obviously presumes of “genes for” psychiatric disorders, a presumption that is increasingly seen as unwarranted.15 Moreover, the notion of tailoring clinical diagnoses to suit genetic data simply does not establish the reality—or even the validity—of the disorder. Additionally, there is an even deeper concern here, based on the presuppositions that, first, the most genetic phenotype is the most clinically relevant phenotype, and second, that a genetic account of schizophrenia should be any more stable or real than a neurobiological or even a phenomenological account. It has often been suggested that a psychiatry built on a scientific nosology would enjoy increased prestige and credibility and would be objective in precisely the way that mere clinical judgments—the target of resounding criticism—fail to be.16 So psychiatric diagnoses, based in science and ideally in genetics, would ostensibly be just as scientific, objective, nonnormative, and value neutral as any other biomedical diagnosis. Except that biomedical diagnosis is not as scientific, objective, nonnormative, and value neutral as some would pretend.17

Indeed, the move toward a psychiatric genetic nosology does not do away with preconceptions. Insofar as knowledge of the normal follows upon knowledge of the pathological, any values (e.g., about normalcy, health, and illness) that are present at the level of phenotypes are imported to the level of the genome. Because those same values abound in the genetic realm, the process of identifying the genotype of a psychiatric condition simply is no less value-laden than the process of identifying the phenotype of a psychiatric condition. (In fact, the process of identifying the genotype may be even more value-laden than the process of identifying the phenotype, in assuming that the condition is a genetic disorder rather than something else.) Genetic normality is no more value neutral than phenotypic normality. To “go genomic” is just to push the matter down a level. Thus, whether a scientific psychiatric nosology grounded in molecular data is more credible than earlier nosologies remains to be demonstrated.

There is little doubt that some molecular taxonomy of disease is eminently achievable. Insofar as genes are involved in pathways of disease (psychiatric or otherwise), they will eventually be identified. This is a function of the immense efforts expended searching for such genes, as facilitated by whole genome scans and other technical innovations. But whether these immense efforts are worthwhile remains unclear. It is plainly evident that there is no necessary link between knowing the genes associated with a disease and developing therapies for that disease; there are plenty of instances of therapies in the absence of detailed knowledge about etiology and of detailed knowledge about etiology in the absence of therapies. Granted, a molecular characterization of a disease may be, even if it need not be, enormously therapeutically useful. For instance, in the presence of other data, genetic data may support novel treatment strategies for conditions that are apparently distinct, such as autism and catatonia,18 and molecular signatures may help distinguish disease subtypes. So a molecular taxonomy of disease may be generally achievable and locally useful. But will it be generally useful?

Fiona Miller and colleagues have recently studied in detail how new genetic knowledge may contribute to lumping, splitting, or otherwise refining diagnostic categories, focusing on hemophilia, Rett syndrome, and cystic fibrosis.19
On the basis of their work, it is possible to distinguish between some of the
different senses in which a diagnostic classification system may be adequate: It
may be “metaphysically” adequate, adequate for research purposes, adequate
for treatment purposes, adequate for the purposes of health services organiza-
tion, and adequate for the purposes of patient self-perception. From Miller
et al.’s case studies and interviews with genetic counselors, it is apparent that
these domains of adequacy, rather than converging nicely, may instead come
into conflict. So a taxonomy that cuts the world at its metaphysical joints may
be inadequate for the organization of health services, or one that is helpful for
research purposes may be a therapeutic dead-end.

It is not clear that a single taxonomy, or a single approach to generating
taxonomies, will ever be completely adequate. So the promise of a revolution-
ary new molecular taxonomy of disease is probably too strong a promise,
potentially collapsing or otherwise eliding the differences between these vari-
ous senses of adequacy. Moreover, that we have genomics data at hand says
nothing about whether those data should be used to revolutionize or even to
refine diagnostic categories—such changes are optional.

Because it is not in dispute that genetics should play some role in psychiatric
classification, clarifying this more limited role is important. An approach
whereby the impact of molecular data on disease classification is negotiated
locally, on a case-by-case basis, may be more promising than any more reduc-
tionistic approach to classification. Less reductionistic approaches are not
committed to the ultimacy or primacy of genetic explanations. Genetic data
may or may not prove useful in delimiting diagnostic categories; this will
depend on many factors, include how we define “useful” in particular cases.
As this approach implies, a psychiatric genetic nosology is not forced on us by
the nature of psychiatric disease; rather, we may choose, when appropriate, to
integrate with other psychiatric data the results of methodologically sound and
genuinely informative genetic research. These are pragmatic considerations not
to be decided a priori but rather empirically, with appropriate attention to
biological, psychological, social, and cultural dimensions of disease. Here, as
elsewhere, the overriding emphasis should be on whether changes in diagnos-
tic classification systems tend toward improvements in patient care.

**Integrating Neuroscience into Nosology**

There is more to biology than genetics, and it should come as no surprise that
the human brain might prove inimical to genetic reduction, even though
genetic information is critical to understanding the brain. Human brains are
among the most complex of all biological systems; the heterogeneity, net-
worked connectivity, and complexity of the brain (not to mention its relative
inaccessibility) have rendered it an exceedingly difficult organ to study. To
genuinely understand (and alter) brain function requires coordinated, sus-
tained efforts across traditional disciplinary boundaries. This is why neuro-
sience is not a traditional discipline and, indeed, why we usually refer to the
neurosciences.

For present purposes, it is important to underscore several features of the
relationship between genetics and neuroscience both for understanding psychi-
atic and neurological disease, but also for understanding how to approach the
process of classifying such diseases. Research on the genetics of behavior and of psychiatric disorders has proceeded through two distinct stages: During the first stage, the techniques used were those of quantitative genetics; during the second stage (roughly, the past 15 years), molecular genetic techniques have been appropriated to supplement quantitative approaches. Despite some research successes with these techniques, widespread and rigorous results have not been achieved. Psychiatric and behavior geneticists now anticipate significant advances as quantitative and molecular strategies are enhanced by techniques developed through functional genomics. Advocates of psychiatric and behavioral genomics envision the consilience of bottom-up and top-down research approaches in the ‘omics era. Such hopes will be bolstered by the emerging science of neurogenomics, which comprises “the study of how the genome as a whole contributes to the evolution, development, structure and function of the nervous system” at the interface of neuroscience and genomics (p. 429). Such a vision calls for an integrative, systems approach to brain science, whereby advances in neuroimaging, brain mapping, genetics and genomics, and molecular and cell biology should allow us to better understand intricate details of the more than 100 billion neurons and supporting cells in the human brain, and to thereby achieve a more integrative, systems approach to brain research.

This sort of systems approach is only partly reductionistic—meaningful reductions are permitted, but where reduction limits rather than enhances understanding, integration is the norm. An integrative, systems approach to the brain depends jointly on gene maps and brain scans and a whole suite of observational and experimental techniques at all levels of analysis from the molecular to the behavioral and back again. Psychiatric illness is itself complex, requiring attention not just to genes and neurons but also what is clinically observable in the prime matériel of the psychiatrist: unhappy and often ill people who behave bizarrely. The person, her/his behavior, context, and life circumstances, must all be part of our analysis.

And yet the clinic has been removed from psychiatric nosology, and concurrently patients have been replaced by their blood, sweat, urine—and DNA. German Berrios objects that such a turn in psychiatry has “effectively condemned clinicians as fuddy-duddies” (p. 457). Consequently, psychiatric nosologists have tended to overlook a rich and important phenotypic feature of psychiatric patients—their own narrative of the disorder, their own experience of its various, variable symptoms—as well as clinicians’ experiences and observations, while presuming that the “true disease” (p. 136) is at the level of genes or brains and not of persons.

An integrative, systems approach to the brain recommends an alternative approach to psychiatric classification, one that reflects input from all relevant sources, incorporating multidirectional feedback between genes and larger phenotypic and environmental elements. This integrative approach to nosology requires that the nature of psychiatric classifications be decided by interlevel, interdisciplinary negotiation rather than reductionistic revelation.

To be sure, the point of the foregoing is not to deny the importance of biological aspects of psychiatric disease; it is instead to begin to understand such disease at an appropriate level of complexity. But clinical phenomenology is of absolute necessity. Whether we are justified in either lumping together...
discrete phenotypes on the basis of (presumably) shared genotype or splitting homogeneous phenotypes on the basis of discrete genotypes cannot be decided a priori. But neither can it be decided empirically on either a strictly genetic or a strictly clinical basis. Hence the need for a dialectical, integrative approach between good phenomenology, scientific but nonmolecular aspects of nosology (such as biometric and neurobiological approaches), and molecular genetics, in an effort to accurately describe the clinical, personal, and biological reality of psychiatric disease—and, eventually, to understand its etiology, its variability, and its tractability to treatment. Without sustained attention to clinical descriptions of psychological phenomena, and without adequate funding for this sort of research, Berrios predicts that “current investigative techniques” in both neurobiology and genetics—“however powerful,” and however well funded—“will draw the proverbial blank” (p. 458).32

Endophenotypes and an Integrative Approach to Taxonomy

As we recognize the limits of genetic reductionism in psychiatry and in psychiatric nosology, an increasingly critical concept is the notion of an endophenotype. Endophenotypes are “measurable components along the patho-physiological pathway between aetiology and psychopathology” (p. 204).33 They are traits or sets of traits that mediate the gap between underlying neuropathology and observable phenotypic manifestation: “An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, neuropsychological or a personality trait, and represents simpler clues to the genetic and environmental underpinnings than the disease syndrome itself” (p. 204).34

In general, in the context of behavioral development, the description of an endophenotype may require attention at least to clinical phenomenology, various biological and biochemical assays, neuroanatomy, and neurocognitive processing—the latter being typically accessed clinically and then mapped through neuroscientific techniques such as positron emission tomography scans and (functional) magnetic resonance imaging. Clinically relevant endophenotypes may prove useful in the establishment of robust psychiatric diagnostic categories that integrate data from various levels of analysis—clinical observations, patient narratives, molecular biomarkers, and neuroimages, for instance. These endophenotypes may also serve to facilitate integrative research of the sort envisioned above.

The notion of an endophenotype was initially devised in relation to schizophrenia in 1972,35 and has experienced a renaissance in the past decade. We know that schizophrenia is both clinically diverse and diagnostically ambiguous, confounding research at two levels of investigation, the micro-level of etiology and the macro-level of observed symptoms. Research into the etiology of particular symptoms has tended, unfortunately, “to focus on one aspect of the disorder while ignoring others (e.g., accounting for hallucinations by invoking the temporal lobe but failing to explain why delusions or various negative symptoms are also present)” (p. 908).36 Meanwhile, the lack of agreement about the nature of the schizophrenic phenotype37 has held back the quest for schizophrenia genes.38

Recent work on endophenotypes may help to redress these concerns. Nancy Andreasen’s group, focusing at intermediate levels between genes and observ-
able symptoms, have proposed that the endophenotype of schizophrenia is a neurodevelopmental cognitive abnormality—a timing aberration in a fundamental feedback loop that is highly sensitive during development. If this endophenotype is in fact the underlying type uniting phenotypic manifestations of schizophrenia, it may well be able to refocus genetic research in productive ways. But even if this particular endophenotype turns out to be not well supported, it remains illustrative of the basic point.

This defect in timing affects a basic neurodevelopmental process upon which memory, attention, and language are based. The result of disrupting this process is the severe heterogeneous symptoms characteristic of schizophrenia. Andreasen et al. develop their model of cognitive development and function/malfunction on an analogy with the development of motor activity. An alteration in the timing of these processes—motor dysmetria—leads to lack of motor coordination and consequently, “abnormalities such as dysdiakokinesia or inability to perform tandem gait.” Drawing on research in neuroanatomy and neuroimaging, Andreasen et al. have proposed that a cognitive equivalent of motor dysmetria—cognitive dysmetria—underlies a variety of symptoms of schizophrenia. “The hallmark of normal cognition,” they argue is “the fluid coordination of mental activity” as governed by the cortico-cerebellar-thalamic-cortical circuit (CCTCC); cognitive dysmetria results from a disruption of the CCTCC, manifesting in the clinical presentation of schizophrenia (p. 911).

To explain this consequence, Andreasen et al. argue that

[an] individual with mistimed information transfer may incorrectly connect perceptions and associations and misinterpret both external and internal processes, leading in turn to delusions or hallucinations (e.g., a neutral perception will be associated with a frightening affective association, internal thoughts or vocalizations may be attributed to others). Defects in coordinating language production will lead to “thought disorder”. In addition, the flow of information through the system may become paralyzed, leading to “negative symptoms” such as alogia or affective blunting (p. 916).

So, Andreasen and her colleagues speculate that the clinical variability of schizophrenia might be interpreted as a function of various perturbations in the CCTCC, whereas a disturbed CCTCC “represents a basic neural phenomenon common to patients suffering from schizophrenia” (p. 391).

Setting aside whether Andreasen et al. are right about cognitive dysmetria as the schizophrenia endophenotype, two key observations are in order. First, notice that though the focus of inquiry is not the genetic level, it is inappropriate to thereby infer that the genetics of cognitive dysmetria are unimportant or irrelevant. Cognitive dysmetria is worth investigating on its own terms, from all relevant perspectives, using all appropriate methods, for the reinterpretation of the symptoms of schizophrenia, as sharing an underlying neuro-phenotypic substrate opens up the possibility of more phenotypically well-grounded genetic research. Indeed, numerous researchers have expressly argued that focusing on endophenotypes can facilitate genetic investigation.

Additionally, notice that endophenotypes such as this one—identified on the basis of the integration of multiple indicators accessed through clinical observation, theoretical neurobiology and neuropathology, and neuroimaging techniques—
could help to delimit a robust disease category that may put to rest long-standing debates over the appropriate interpretation of the schizophrenia construct.

An integrative approach to disease classification, facilitated by but not reducible to molecular data, is a tractable research strategy for advancing taxonomy along multiple lines of adequacy. I reiterate that no single taxonomy is likely to be useful for all purposes, but the open-ended, integrative approach advocated here is more amenable to pragmatic negotiation than reductionistic, nonempirical alternatives.

Conclusion

What is most important about psychiatric nosology is whether it serves patients well and whether it is amenable to therapeutic ends for patients and their healthcare providers. There is no reason to believe that a reductionistic taxonomy, whether based on gene maps or brain scans, will achieve this end in all cases, or even very often. Just the opposite may prove true; hence my advocacy for an integrative approach based on the notion of the endophenotype, within which the boundaries of psychiatric classifications may be determined by appeal to relevant knowledge including but not limited to molecular knowledge. Though the adequacy of any classification system must be demonstrated and not assumed, the integrative approach to taxonomy takes seriously the clinical phenomenology of psychiatric conditions and thus is predisposed to clinical adequacy for patient care. Given everything we know about the brain and about the complexity of psychiatric classification, an a priori commitment to a new molecular taxonomy in psychiatry is unjustified.

As neuroethics develops, and as it attends both to medicine and also to the many social contexts into which brain science flows, such as education, law, and national security, psychiatry and psychiatric ethics will increasingly demand sustained attention. The relationships between neuroscience and psychiatry, brain and mind, are complex and worthy of both conceptual and ethical investigation. In this paper, I have raised some preliminary considerations about psychiatric classification. But psychiatric diagnosis is also of central clinical concern, raising important questions about the appropriate use of genetic and neuroscientific data in diagnosing patients. Determining the relationship between classification and diagnosis, and assessing whether and how molecular, neuroscientific, and neurological markers should be used in diagnosis, must await future analysis in neuroethics and the philosophy of psychiatry.

Notes


Gene Maps, Brain Scans, and Psychiatric Nosology

10. Krishnan KR. Psychiatric disease in the genomic era: Rational approach. Molecular Psychiatry 2005;10:978–84. Whether it is possible to eliminate these putatively extraneous factors is entirely debatable. But whether it is desirable to do so is equally open to dispute. Increasingly, the literature seems to suggest that it is only by embracing the social and political (and cultural and ecological) embeddedness of medical conditions that clinicians will be able to grasp the complexity of illness and to offer suitable treatment regimes to their patients. Of course, the latter approach is not developed in ignorance of science, but neither is it based in an overly reductionistic approach to science: Molecular markers, brain images, and biochemical assays are indeed meaningful, but not on their own; they acquire meaning only in an appropriate bio-psycho-social context.
12. Tsuang MT, Faraone SV, Lyons MJ. Identification of the phenotype in psychiatric genetics. European Archives of Psychiatry and Clinical Neuroscience 1993;243:131–42. Note that this usage of “empirical” implies the philosophical sense of validated through systematic investigation and observation, rather than the pejorative sense in which Collins and colleagues use it in the passage cited above; see note 7, Collins et al. 2003.
15. See, for example, note 3, Kendler 2005 and note 4, Robert 2000.
17. Philosophers of science have long contended that no scientific theories are perfectly value free; this is certainly the case with biomedical theories, insofar as diagnoses of illness inherently make value judgments about the state of the patient’s body as compared to a normal body. Psychiatry could perhaps be rendered less (ostensibly) subjective by appeal to biological markers—that is the point of using, for example, neurological testing as a means of determining from what sort of disorder a particular patient suffers. But insofar as biological markers are themselves normative, the hope of value freedom in psychiatric diagnosis is a false hope, in the same way that such a hope is false also in the case of other biomedical diagnoses—none of which is to say that biomedical diagnoses are subjective or otherwise unscientific.
24. See, for example, note 3, Kendler 2005 and note 4, Robert 2000.
32. See note 29, Berrios 1999.
34. See note 33, Weiser et al. 2005.
38. See note 4, Robert 2000.
39. For a skeptical view, see Kaprinis GS, Fountoulakis KN, Kaprinis SG. Arguments against the cognitive dysmetria hypothesis of schizophrenia. *Perceptual and Motor Skills* 2002;94:975–84.
41. See note 36, Andreasen et al. 1999.
42. See note 36, Andreasen et al. 1999.
43. See note 40, Crespo-Facorro et al. 1999.