Loose ends of psychiatric research

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"We learn from history that we never learn from history."
Paraphrased from G.W.F. Hegel, *The Philosophy of History*

Reading psychiatric research literature of the last several decades frequently gives the impression of fragmentation, where old research topics are abandoned for newer ones without proper follow-up that would place the existing data into a coherent structure. Such perspective is increasingly relevant though, as medical research draws more and more on methods that allow exploratory analyses of large amounts of data without having to specify a priori hypotheses. As in most medical research, methods of genome-wide association analyses, gene expression and proteomic profiling studies, and voxel-based morphometry and functional brain imaging studies have been prominent tools in psychiatry. They frequently end up with barely significant findings, and the validity of their results is often claimed post hoc on biological or pathophysiological grounds. Sometimes such claims are rather tenuous (e.g., relevance of a genetic polymorphism based on the fact that the specific gene is also expressed in the brain). It is well established that genetic findings in complex traits are hard to validate and to show conclusively how they contribute to disease susceptibility. Brain imaging findings are often based on small and clinically heterogeneous samples with similar consequences for interpretation of any findings.¹ Thus, it is even more imperative that new psychiatric findings be put into a pathophysiological framework built on earlier results. In psychiatry, such knowledge is fairly limited, putting the field at a disadvantage compared with other areas of medicine.

For instance, Alzheimer disease, diabetes mellitus, inflammatory bowel disease, multiple sclerosis or Parkinson disease are all complex traits, typically less heritable than major psychiatric disorders, but their genetic research has advanced faster, benefiting from prior knowledge of their pathology and pathophysiology. Although the mechanisms of these disorders are far from completely understood, the available information has helped to select candidate genes and/or interpret the genetic findings.

Slow progress of research can be attributed to various causes. They are not exclusive to, but are often more prominent in psychiatry. First, research moves along trends that tend

to leave behind inconclusive and partial results that are not easy to fit together. Yet, we believe that many of the now abandoned studies reported real findings in real patients, and if interpreted in proper context they could contribute to the modern understanding of psychiatric illness. For instance, electrolyte changes have been postulated as a possible pathophysiological mechanism of bipolar disorder since the 1960s, and shifts in ion balance have been documented repeatedly as being associated with transitions in the clinical course (from mania to euthymia to depression). With the wider application of lithium (Li), the hypothesis became even more compelling. Abnormalities of membrane ion transport have been proposed as the mechanism of bipolar disorder, and some authors have suggested that abnormalities of Li membrane transport could be used as a diagnostic test. Few years later, this research was abandoned, perhaps prematurely, following reports of unreliable laboratory methods, poor intraindividual reproducibility of some of the measures² and unsatisfactory correlation of peripheral (red blood cell) and brain transport mechanism. And yet, similar investigations in hypertension have generated intriguing findings potentially relevant for psychiatry. Patients with bipolar disorder are known to have increased rates of hypertension and higher cardiovascular mortality, and reproducible abnormalities of Li-sodium countertransport are among well-established biological markers of essential hypertension. A number of examples just in the area of mood disorders can be found in studies of sleep deprivation effects on depression, cholinergic REM sleep induction³ or once trendy neuroendocrinological research. The dexamethasone suppression test (DST) has been one of the most studied abnormalities in mood disorders and was considered a candidate for a diagnostic test of depression. Yet, hundreds of papers later, we can only acknowledge that the hypothalamo-pituitary-adrenal (HPA) axis dysregulation is associated with several serious psychiatric disorders, but the actual mechanisms and their relation to other neurobiological findings are just barely being uncovered.⁴ More recently, the neuroprotective effect of Li has attracted much attention. It is well supported by animal and human studies that Li increases expression of multiple molecules known to be neuroprotective and that it does increase hippocampal volume and concentration of *N*-acetylaspartate in

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imaging studies. Both effects are considered to be indirect evidence of neuroprotection, but the key question — whether and to what extent neuroprotection is relevant for mood stabilization in bipolar disorder — remains open.⁵ Very few studies have attempted to answer it, with a consequent risk that researchers will lose interest, give up and move to the next promising theme.

A second factor particularly applicable to psychiatry is the concern about diagnostic classification. Research results obtained in the same area with the same or similar methods a few years apart may differ simply because the research participants' diagnoses have been based on changed criteria. Psychiatric classification is based on phenomenological description that is typically cross-sectional. The difficulty matching artificial diagnostic categories with biological findings has been raised by a number of authors (see van Praag⁶ for a review). Also, the fact that most disorders manifest as phenotypic spectra rather than clear-cut diagnostic entities suggests that the biological dysregulations do not follow classification categories. This argument has been recently strengthened by findings from longitudinal studies suggesting that severe psychiatric disorders develop in stages characterized by varying clinical presentation.⁷ More than 40 years ago, Robins and Guze⁸ proposed 5 main requirements for validating a disease category (nosological entity) in psychiatry: clinical presentation, laboratory study, differentiation from other conditions, follow-up (temporary stability) and family study. To this day, there are practically no diagnoses in psychiatry meeting all these criteria. At the same time, perhaps unexpectedly in light of the criticisms of psychiatric classification, the current diagnostic systems of DSM and ICD define conditions that are highly heritable and have a considerable impact on population health in terms of their mortality, physical comorbidities and disability rates. All this contrasts with weak findings and small effect sizes of neurobiological and especially genetic findings, raising doubts about their clinical utility.

Ultimately, psychiatrists diagnose and treat disorders, and the role of research is to generate knowledge and applications to improve clinical care. There is an increasing push toward such clinically directed research. Some of the latest examples in Canada are the recent Canadian Institutes of Health Research initiative for patient-oriented research or the 2012 Genome Canada Large-Scale Applied Research Project Competition focusing on personalized health. Research discoveries have transformed the practice of many areas of medicine. Biomarkers in areas such as oncology have helped rationalize clinical care, and there is hope that psychiatry will benefit from research discoveries as well. Yet, to date in psychiatry, the use of biological tests is limited to exclusions of other "organic" diagnoses⁹ and/or for monitoring of treatment either by drug blood levels or testing for adverse effects of treatment on liver, kidney or hematological parameters.

As with neurobiological studies, research of clinical tests and biomarkers seems to be abandoned perhaps prematurely. The DST seemed promising, but it never became a true biological test in psychiatry for reasons summarized by Nierenberg and Feinstein.¹⁰ But, it is also worth remembering that the peak of interest in DST (150 references in PubMed in 1985) fol-

lowed only a few years after the introduction of DSM III classification in 1980, which redefined depression substantially, and thus newer studies are based on different patient populations than the earlier reports. Subsequent studies of DST and its modifications support the view that HPA axis abnormalities can be used as a marker of activity of the illness¹¹ or as a measure of quality of antidepressant response and the risk of relapse. Neuropsychological or neuroimaging findings in schizophrenia or bipolar illness may not help diagnose these disorders, but may serve as useful measures of prognosis or progress of rehabilitation. And recent magnetic resonance spectroscopy studies revived interest in Li membrane transport and intracellular concentrations that could be a useful monitoring measure in patients with therapeutic levels, but unexplained side effects or poor treatment outcome.¹²

In conclusion, we do not think that psychiatry suffers from a lack of research findings. In many ways, psychiatric disorders are not substantially different from other common medical conditions, such as hypertension, diabetes or arthritis. These are all disorders that are multifactorial with some degree of genetic predisposition; their treatment is often symptomatic rather than curative and typically multimodal, combining medication with patient education and life style changes. What we need is a better integration of research across multiple domains and linking neurobiological discoveries to clinical dimensions. To this end, it may be relevant to revisit earlier findings, especially the promising ones that have not been tested in relation to modern data.

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References

1. Bennett C, Miller M, Wolford G. Neural correlates of interspecies perspective taking in the post-mortem Atlantic salmon: an argument for multiple comparisons correction. *Neuroimage* 2009;47(Suppl 1):S125.
2. Werstliuk ES, Rathbone MP, Grof P. Erythrocyte lithium efflux in bipolar patients and control subjects: the question of reproducibility. *Psychiatry Res* 1984;13:175-85.
3. Sitaram N, Nurnberger JI Jr, Gershon ES, et al. Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. *Science* 1980;208:200-2.
4. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009;12:342-8.
5. Bauer M, Alda M, Priller J, et al. Implications of the neuroprotective effects of lithium for the treatment of bipolar and neurodegenerative disorders. *Pharmacopsychiatry* 2003;36(Suppl 3):S250-4.
6. van Praag HM. Diagnosis, the rate-limiting factor of biological depression research. *Neuropsychobiology* 1993;28:197-206.
7. Duffy A, Alda M, Hajek T, et al. Early stages in the development of bipolar disorder. *J Affect Disord* 2010;121:127-35.
8. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* 1970;126:983-7.
9. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry* 2012 Aug. 7. [Epub ahead of print]
10. Nierenberg AA, Feinstein AR. How to evaluate a diagnostic marker test. Lessons from the rise and fall of dexamethasone suppression test. *JAMA* 1988;259:1699-702.
11. Deshauer D, Grof E, Alda M, et al. Patterns of DST positivity in remitted affective disorders. *Biol Psychiatry* 1999;45:1023-9.
12. Kato T, Takahashi S, Inubushi T. Brain lithium concentration by 7Li- and 1H-magnetic resonance spectroscopy in bipolar disorder. *Psychiatry Res* 1992;45:53-63.