Problems and Solutions in the Implementation of Integrative Pluralism in Psychiatric Genetics Research

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Integrative pluralism[1] is an attractive framework for psychiatric research because substantial bodies of high-quality research point to etiologic processes that impact on risk for psychiatric illness from many "levels" from molecular neuroscience on one hand to aspects of culture on the other. However, as recently shown, only a small proportion of publications in leading psychiatry and psychology journals instantiate this framework[2]. In this essay, I seek to address the question of why.

I divide this essay into two parts. The first is a general over-view of the three major themes: academic structure and training, funding and publication, and data collection. Then I will outline three "success" stories of pluralistic projects in psychiatric genetics. In this essay, I over-emphasize my own experiences because of their familiarity and apologize ahead of time for this parochial focus.

Part I

Academic Structure and Training

Academic departments in modern universities tend to focus knowledge into specialized areas. While often subtle, being a trainee or a faculty member in a department carries with it a geography of knowledge divided into "our space" and "outside space." In thinking about research ideas, trainees with expansive ideas are often told, sometimes subtly, sometimes not – "We don't do that kind of work here. That is done by xxx." The message is "Don't play off the reservation" if you want to get ahead. Inter-disciplinary work is possible and often "officially" encouraged, but in reality, it can be awkward. If I want to study both A and B, helpful advisors might raise concerns. What kind of job would you get with that background? You might be rejected by both fields as you don't fit easily into their requisite categories.

A case in point. Several eminent institutions including Cambridge University and University of Pittsburgh have Departments of the History and Philosophy of Science. I know people well enough at these places to know that a common concern of PhD graduates from these programs is difficulties getting jobs at more standard departments of Philosophy or History. They may not be seen as a real "Philosopher of Science" or a "Historian of Science," not fitting well into either niche. This is a problem because there are far more standard departments of Philosophy and History in US and European universities than there are in specialized programs in the History and Philosophy of Science.

One antidote to this problem of departmental silos is inter-disciplinary institutes or centers. Some of these institutes are established specifically to try to encourage multidisciplinary science. An example would be the Virginia Institute for Psychiatric and Behavioral Genetics (VIPBG) that I have directed since 1996. The goal of this institute has been to try to house, within one place, all the elements needed for high quality psychiatric genetics research. That means a lot of different kinds of expertise that represent different kinds of science. Examples would include i) human molecular genetics, ii) human post-mortem brain tissue studies, iii) statistical molecular genetics, iv) structural equation models that actively

incorporate environmental measures and developmental time, v) psychometrics (to try to develop better ways of measuring psychiatric disorders and their risk factors), vi) clinical psychology with substantive expertise in key phenotypes including anxiety disorders, PTSD, drug abuse and suicide and vii) psychiatry with an expertise in diagnostic assessments.

Without the traditional teaching mission and graduate programs of established departments with their typical revenue streams, the financial security of inter-disciplinary departments in modern universities can be precarious. But I won't go into that issue further here.

Funding and Publication

Extramural funding is the lifeblood of psychiatric science and in the US, the vast majority of those funds come from the NIH. To succeed as an academic researcher, NIH funding is vital. This means obtaining strong reviews from the existing NIH review panels. Often, albeit not always, the structure of these panels works against applications incorporating pluralistic aims. Many NIH review panels are rather specialized. A grant that incorporates three diverse methodological areas (A, B and C), would often be assigned to a committee that has lots of reviewers who are expert in A, only one or two in certain parts of B and no one who knows much about area C. Sometimes, the review just goes forward as is. That is risky for the applicant as the goals of the grant in area C might not be well understood or appreciated. Or, the review panel might call in an outside expert in C. That can work well but not always. The group process in many review panels is such that most reviewers will learn to trust their co-panelists. The committee's reaction to someone outside with whom they never have had contact is more variable. They might be more skeptical of a very favorable review and be less willing to change their views on the grant. It is certainly true that it is more difficult to obtain excellent scientific review of pluralist applications compared to those that fit well within a narrow area of expertise.

Then there is the related issue of "in-groups" of reviewers. Often these groups have decades of experience in their areas of expertise, know all the good researchers, and consciously or unconsciously see their tasks as helping their "sub-field" to prosper. If you come in as an outsider – say you are a geneticist who wants to study drug abuse – the died-in-the-wool drug abuse reviewers sometimes see you as an interloper. There is often justification in this. Your command of the literature and the methodology is not likely to be equal to that of a focused researcher with decades of experience. Little in the review process gives you "points" for trying to be inter-disciplinary. As a non-member of the "in-group" you are especially at risk of getting poor reviews in specific areas which will block you chances of funding. Some of this is fair, but it does tend to work against the pluralistic researcher.

Against this rather bleak picture, I do need to provide some balance. I have seen NIH reviews that were particularly praising of pluralistic proposals, arguing that this is the kind of research that has to be better supported. So, the NIH review process is not always biased against pluralistic proposals.

Most of the points raised about grant review applies to journal reviews. It is a more demanding task for an editor to find reviewers with sufficient expertise to review papers that contain several different methodologies. Some narrowly focused journals will be less enthusiastic about pluralistic papers. One practical problem is word length limits. They are getting shorter and shorter. If your study contains multiple methods, it takes more words to describe then and often to go over the findings in enough details. In total, I would see the bias against pluralistic research to be somewhat stronger at the level of grant review versus publication.

Data Collection

Focusing on human studies, if I want to study a large cohort and collect data that might allow me to address the questions of psychiatric illness from multiple levels, it is harder to recruit subjects and more expensive that if I want to just do one quick test or have them till out a series of questionnaires. Furthermore, it often takes a range of expertise to assess a wide variety of traits with few individual investigators having the time to obtain that. This results in some of the poor quality of multilevel studies in psychiatry.

Assume I am an expert in assessment of disorder X and I learn that it would be a good idea to assess risk factors A, B and C in my study. It is more common for the investigator to look up on the web or ask a few colleagues and find a convenient short questionnaire to assess the risk factors. Much less frequently will the investigator do an in-depth study to find the best assessments which might be a much lengthier interviewed based instrument. There is also a key pragmatic problem. Subjects have a limited attention span. As we crowd in more and more detailed assessments, we risk a degradation in quality of the assessments or the expensive option of spreading out assessments over days. So, collecting human data sets for high quality pluralistic science has multiple challenges.

Part II - Case Studies

To illustrate these more abstract points, I present 3 case studies of work in the area of psychiatric genetics that would meet, to varying degrees, the criteria of what I would call Integrative Pluralism.

Case 1 – Twin Study of Gene-Environment Interactions

When I shifted from my early career in neurochemistry to psychiatric genetics, my focus was on schizophrenia and especially clarifying the boundaries of the schizophrenia spectrum. I moved to MCV in 1983 in large part because of the presence of Lindon Eaves – a leader in biometrical genetics – and the high quality of the Virginia Twin study. Self-consciously, I switched to a focus on major depression (MD) because of evidence that I had only read about of a much more important environmental contribution to MD. I was especially interested in the question of Gene-Environment Interactions (GEI) as a result of my clinical training in psychiatry, having been so impressed at the wide variation of individuals response to the common stressors that life throws at most of us at one time or another.

There has been a long interest in the concept of GEI in psychiatry. Work with natural disasters or other high-stress exposures (prisoners of war, terrible industrial accidents) also document the extraordinary variability in how people react to severe stressors – where some people become psychiatrically ill and dysfunctional for years and others, while upset, quickly "shake it off" and get back to their lives. So institutively, it seems likely that genetic factors contribute to this variability but showing that has proven difficult.

There had been isolated small sample but very intriguing studies of GEI for alcohol abuse in Sweden[3] and for antisocial personality disorder in the US[4] both using adoption samples. I wanted to try to do this in a large twin sample using the great statistical power of studying pairs of monozygotic twins.

I dimly realized I needed five components to do a good study of this question. The first and only one that I was sufficiently expert in was the assessment of MD. I had learned structured psychiatric interviews in my Psychiatry Residency and felt confident in that ability. Second, I needed to find a large

number of twins that ideally would be representative of the general population so any results I would obtain would be generalizable. The Virginia Twin Registry would meet that demand. Third, I needed help from people with more statistical sophistication than I then possessed to learn the various ways to model GEI. Lindon Eaves and colleagues could do that. Fourth, I needed funding to do the study. Fifth, I needed help in learning how to assess stressful live events (SLE) carefully.

I knew a few colleagues in psychiatric epidemiology. I asked their advice about who to collaborate with who knew about SLE assessment. They all said Ron Kessler. Little did I know what fantastic advice I had been given. Over a three month period, I had repeated calls with Ron. He introduced me to George Browns rigorous SLE assessments. I read Brown's seminal book on the Social Origins of Depression – a new experience for a psychiatrist trained in a biological/psychopharmacological perspective. I read about other life event inventories by Paykel, Dohrenwend, etc. I visited Ron at the Social Research Institute at University of Michigan. We went over a huge array of instruments that he had. It took about a year.

We developed a multi-pronged approach to the problem in our longitudinal study design. At the initial interview wave, we would only assess occurrence and time of a key set of events. I trained the interviews about the boundaries of life events which took up a good percentage of time of our entire assessment.

But next, with further help from Ron, we upped our game and adopted a key refinement of Browns – the long-term contextual threat assessment. This took hours and hours of training. I recall creating all these training vignettes which we used for reliability trials of our interviewers. But it was critical because it would allow us to "dose" the SLE severity given us more power to understand the nature of the GEI. By the end of these several years, I knew a lot about SLE assessment and had a wide range of practical knowledge in training interviewers and supervising them in these assessments.

Two years after arriving at MCV, with help from Lindon and Ron, I wrote an NIMH grant seeking to fund the "Stress and Coping" study in the Virginia Twin Register. We asked for funds to assess twice over 1,000 pairs of female-female twin pairs. We proposed not only to look at a range of psychiatric disorders but assess carefully several key domains of environmental risk including SLEs. We were very fortunate to have a review panel with a number of broad minded psychiatric epidemiologists. They knew little about twin research but were excited about its promises. We got credit for the mastery we had of the diagnostic assessment and our measures of environmental adversity. We got funded on the first try.

The first paper on GEI, published in 1995[5], was based on early SLE assessments so only recorded the presence or absence of a SLE in female twins only. The measure of genetic risk was also simple but passed the soundness test of my statistical colleagues. The results were both simple and dramatic (figure 1). We saw a clear "fan-shaped" curve. Those at higher genetic risk for MD – assessed simply as a function of their zygosity (MZ vs DZ) and history of MD in their co-twin (Yes or No). We followed up with a more complex study in 2004 that utilized our LTCT rating and used neuroticism as an index of temperamental vulnerability to MD (figure 2)[6]. The LTCT scale performed exactly as Brown had predicted with an approximate doubling of MD risk with each increasing level of the 4 point scale[7]. Our results now replicated well across sexes. These studies have been widely cited.

Case 2 – Clarifying the Genetic Heterogeneity in Autism Spectrum Disorder

Anyone working in a clinical Autism program will be struck by the extraordinary clinical variation in patients meeting diagnostic criteria. Most striking is the difference between the most severely affected individuals, many of whom are non-verbal and spend many hours a day in highly ritualized motor behaviors (head-banging, spinning etc) and others who, though clearly suffering from an autistic syndrome, function at a relatively high intellectual level and sometimes display extraordinary cognitive capacities, often of a particularly focused kind.

One long-term hope of genetic research strategies for psychiatric disorders have been to use genetic findings to dissect psychiatric disorders, "carving" our broad syndromes into more specific entities. One example would be the very clear difference in patterns of family risks for illness in the relatives of unipolar versus bipolar affective disorder. These differences were among the stronger arguments for the division of Kraepelin's broad concept of manic-depressive illness into what we now call, in DSM-5, "bipolar and related disorders" and "depressive disorders." Despite an intense effort in the genetics of schizophrenia from several decades, no substantial widely-validated subtyping schema has emerged from genetic work.

Elise Robinson, now among the world leaders in the genetics of Autism Spectrum Disorders (ASD) came to the field not with a doctoral degree in genetics, molecular biology, or statistics, but rather in epidemiology. This was, in my view, crucial to the work that followed, as she understood the importance of careful phenotypic measures. As genotyping of cases of ASD began to accelerate in the early 2010, it became noted that, in aggregate, ASD cases had a marked increase of what is called "de novo loss of function (LOF) mutations." These are mutations in key areas of the genes coding proteins that occur in the parental gametes (egg or sperm) and are so severe that the protein is rendered non-functional. These kinds of mutations are typically quite rare in the population, in part because that are often associated with substantial brain dysfunction often of a non-specific form.

Dr. Robinson was studying a large sample of ASD cases from the Simons Collection that had undergone molecular genetic studies as well as rather careful phenotypic assessments. One simple measure available for nearly all of them was a full-scale IQ. Dr. Robinson's central insight, published in a 2014 PNAS paper[8] was to take 2,000 such cases of ASD and look at the rate of LOR as a function of their IQ. It was a simple but rather revolutionary idea the results of which are well captured in a latter summary figure reproduced here as figure 3. The Y-axis is the rate of De Novo LOF per gene. Four lines are provided showing the expected levels for cases of severe intellectual ability, ASD (on average), schizophrenia and the general population. As can be clearly seen, ASD cases with IQs below 75 have a marked excess of these LOF variants. ASD cases with IQs above 125 had low rates that roughly approximated the frequency found in the general population. This data had been available to other more molecularly oriented researchers, but it had apparently not occurred to them to conduct this kind of analyses. Dr. Robinson was, in this research, thinking "across levels."

This simple analysis suggested a striking genetic dissection of the ASD syndrome as a function of IQ. Lower IQ ASD cases were profoundly influenced by these LOF mutations. Higher IQ cases had no excess rate for this class of damaging mutations. Put another way, one class of genomic variants – rare de novo mutations – were critical in the etiology of low IQ ASD. An entirely different class of variants – common transmitted variants long in the human gene pool – were responsible for the higher IQ form of ASD. It came about by thinking across levels.

This work was done at the Stanley Center for Psychiatric Research at the Broad Institute. This center, funded largely by the Stanley Family by a $100 million commitment in 2010 and $650 million in 2014, is by design highly multidisciplinary. Led by Steven Hyman, this has become perhaps the most productive psychiatric genetics unit in the world with very high quality research groups in data collection, molecular genetics, statistical genetics, and a wide range of basic neurobiology. Faculty at the Stanley Center mostly have primary appointments at Harvard and/or MIT and work together on multidisciplinary teams focused on using genetic strategies to understand the etiology of three major psychiatric disorders: schizophrenia, bipolar illness and ASD. It is not an accident that 2/3 examples I outline here for pluralistic work occurred at the Stanley Ctr.

Story 3 – Complement C-4 and Schizophrenia

A front-page article in the New York Times on 1/27/16 started

> Scientists reported on Wednesday that they had taken a significant step toward understanding the cause of schizophrenia, in a landmark study that provides the first rigorously tested insight into the biology behind any common psychiatric disorder.

This work came out of the laboratory of Steve McCarroll at the Harvard Medical School and the Stanley Ctr at the Broad Institute. I can only touch the highlights of the science here, reported in Nature[9]. First, the project got started with a large dose of careful human molecular genetics, trying to disentangle genetic signals in the very complex region of the Human Genome known as the "HLA Region" on chromosome 6 (HLA stands for human leukocyte antigen). It had produced the strongest genetic signals for schizophrenia for years, but despite much effort, very limited progress had been made in disentangling the nature of that signal. The McCarroll team found evidence of a specific signal at one end of the large (multi-genic) HLA region that contained the locus for one gene in the complement cascade - complement component 4 or "C4." They identified haplotypes (short chromosomal segments that segregate together) that carried different copies of the C4 gene were relatively strongly related to risk of schizophrenia in a large genome-wide association case-control study of schizophrenia. Moving from genetics to normal human neurobiology, they then demonstrated that in normal human brain post-mortem samples, these same C4 variants impacted in a clear manner on the expression level of the C4 gene. Human C4 protein was found to be localized to neuronal synapses, dendrites, axons, and cell bodies. They then studied post-mortem samples of the brains of individuals suffering from schizophrenia, showing that they had significantly elevated levels of this high risk C4 variant.

Next came work from the mouse in the laboratory of the key-collaborator on this project, also working at Harvard University and the Stanley Center - Beth Stevens. Her lab had done the seminal work in mice showing the role of complement genes in synaptic pruning, trimming the dendritic spines of neurons, presumably of the unneeded excess. Stevens and her collaborators, in mouse models, then showed definitively that the C4 gene mediated synapse elimination during postnatal development. So, excess levels of the C4 gene – which was shown to exist in the brains of individuals with schizophrenia – would be expected to result in excess pruning in affected individuals. In prior work, not done at the Stanley center, this is exactly what has been found – that is reports of decreased synapse numbers in schizophrenia patients

This was highly multi-level work starting with large case-control GWAS studies of individuals with schizophrenia, then moving back and forth from statistical to population genetics to define a risk locus,

moving from there to post-mortem samples in normal and affected individuals and then to mouse brain. It required the collaboration of a host of experts across these various disciplines to produce what is perhaps the most integrated gene to phenotype story yet told in the genetics of schizophrenia. My contention is that this work would have been much less likely to occur without the collaborative environment set up at the Stanley center to encourage exactly this kind of work. This again shows the importance of institutional structure on the possibility of high quality pluralistic work in psychiatry.

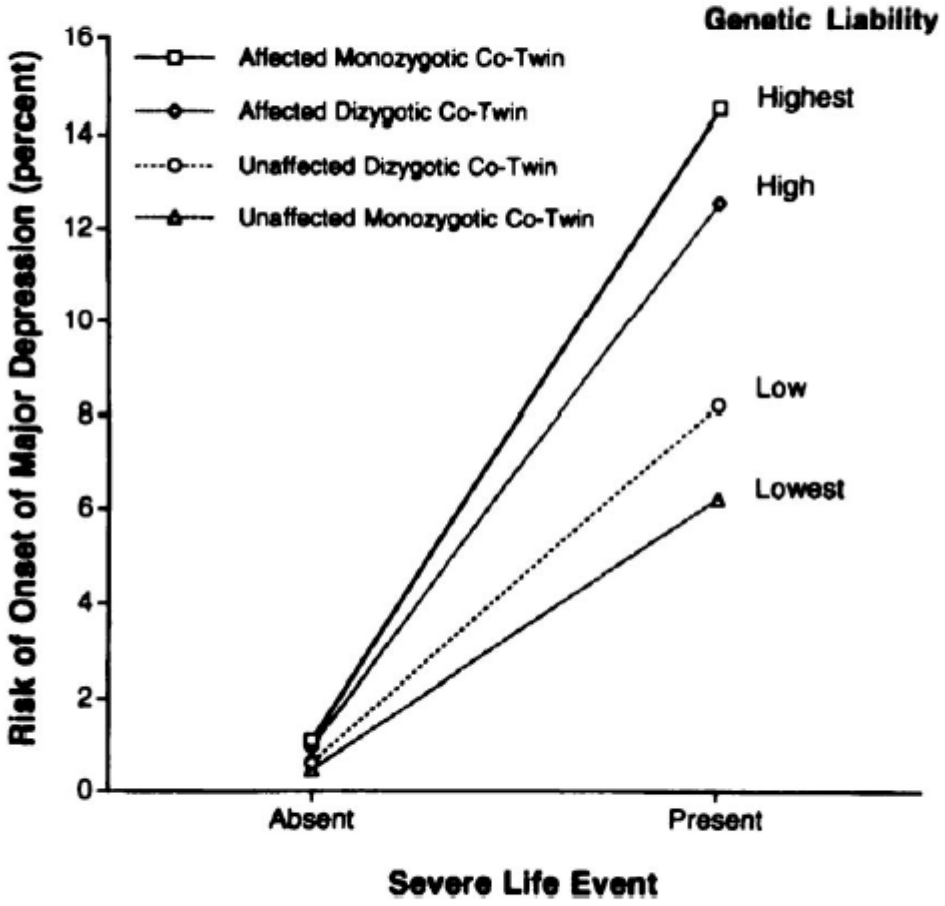
Conclusions

I have tried to address the question of the barriers to integrative pluralistic work in psychiatry from two perspectives – an over-view of a range of potential impediments and then three diverse "success-stories" of what I would judge to be meaningful multi-level research all in the area of my expertise – psychiatric genetics.

What would my major conclusions be from this self-reflective exercise? First, there are real structural impediments to pluralistic work in psychiatry in the way young researcher are trained, academic departments are organized, grants are funded, and papers published. Science is often easier for those who stay within pre-defined disciplinary boundaries. But these obstacles can be overcome, and two paths seem to be most important. One is old-fashioned investigator initiative. For researchers who want to "think outside the box" and are willing to be at least a bit "risk-taking" to reach their aspirations, success is clearly possible. Indeed, sometimes their efforts will be rewarded in the typical ways we have of doing that in academia, by prominent publications, funded grants, and promotions.

Second, local academic culture matters a lot. In my field, the Stanley Center at the Broad Institute stands out as a very well-funded program specifically established to encourage pluralistic inter-disciplinary research. I would like to think the Virginia Institute of Psychiatric and Behavioral Genetics has a similar structure. What these kinds of academic units can do is to promote a culture in which reaching across disciplines is actively encouraged. The leadership can make it clear that researchers are expected to make links outside their areas of expertise and provide, in their recruitment, that broad mix of faculty whose work together should be maximally inter-fertilizing. That is not always easy to do or to maintain over prolonged periods as sub-fields rapidly advance and shift. Personality matters here. Some very bright academics really want to define a small piece of academic "turf" and dig very carefully down for a 30 or 40 year career asking more and more refined but necessarily narrow questions. Great contributions to science can be made this way. But others enjoy living more on the edge, shifting back and forth across scientific perspectives. They are never quite as deeply expert in any one area, but they see the payback in the intellectual stimulation and excitement of trying to integrate across diverse perspectives. They too can make important contributions.

Figure 1. Risk of Onset of Major Depression per Person-Month as a Function of Genetic Liability and the Presence or Absence of a Severe Stressful Life Event in That Month Among 2,060 Female Twins[a]

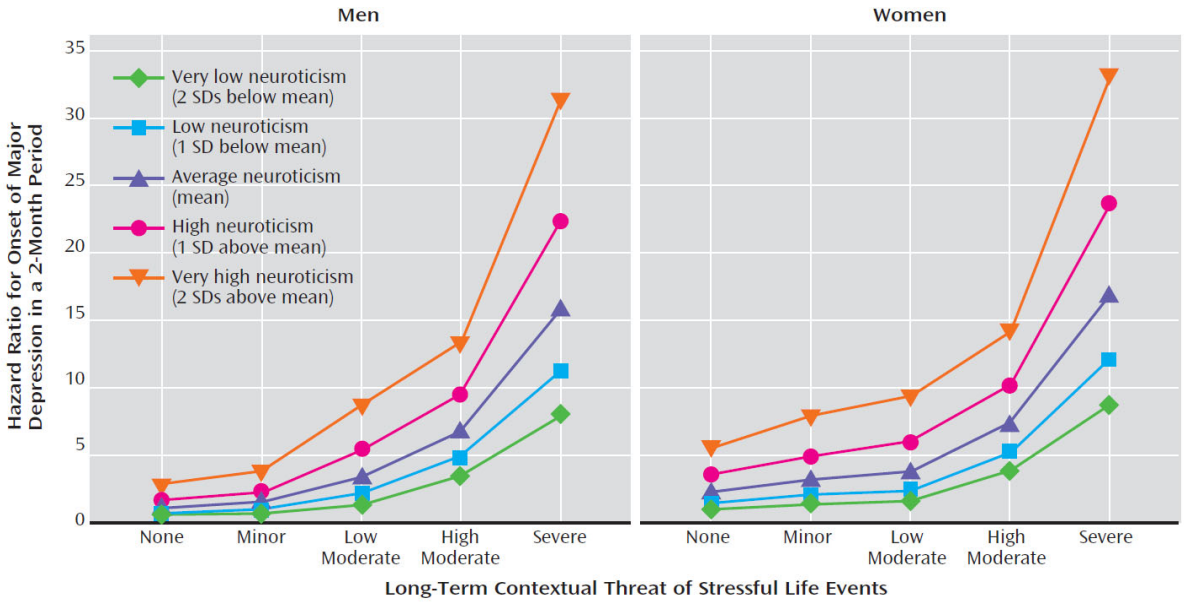


[a] Genetic liability is reflected by both the zygosity of the twin and the lifetime history of major depression in her co-twin. The results presented here are those predicted by the best-fitting logistic regression equation that contains the control variables outlined in the text and the main effects of the life event and genetic risk factors. A severe life event is defined as assault, serious marital problems, divorce/breakup, or death of a close relative.

From[5].

Figure 2

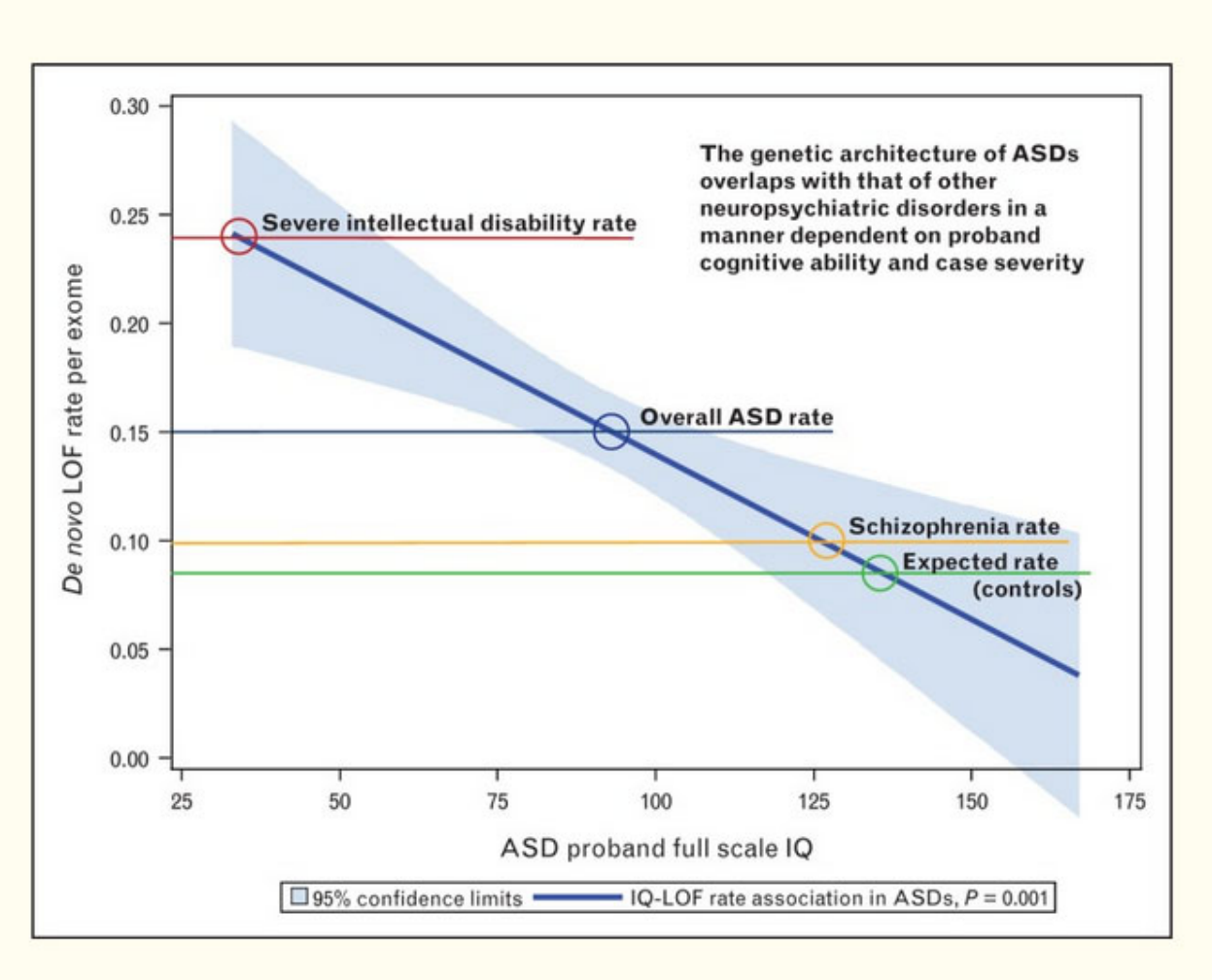
Hazard Ratios Indicating Risk of Onset of Major Depression for a Population-Based Sample (N=7,517) Classified by Sex, Neuroticism, and Stressful Life Events[6]



A hazard rate of unity was defined as the risk level for a man with a mean score on the 12-item neuroticism scale from the shortened Eysenck Personality Questionnaire (21) and no exposure to stressful life events. Descriptions of the types of stressful life events and the scoring of long-term contextual threat are given in text.

Figure 3

Loss of function (LoF) regression generated using data from the Simons Simplex Collection as described by Robinson et al[8]. ASD - autism spectrum disorder; IQ - intelligence quotient.



Addendum – Responses to Queries posted by Jim Woodward

Query # 1- In your essay, you emphasize the importance of pluralism, both in the sense of bringing different kinds of science to bear on scientific problems and in the sense that understanding some phenomenon of interest like addiction, delinquency, depression or schizophrenia may require recognizing causes at different levels or that are studied in different sciences—e.g. both genetic and social causes. What implications does this have for how we should think about an ontology for the behavioral sciences? Often ontologies are tied to particular sciences or levels (genetics has one ontology, social science another). Should we then be worried that ontologies get in the way of integration across different levels and sciences, that they encourage siloing? Is it a plausible response to this worry to suggest that in constructing ontologies we should also emphasize the importance of being explicit about how different ontologies relate to or might be integrated with one another?

Response – Scientific ontologies which would further re-enforce narrow disciplinary boundaries within the social and medical sciences would, in my view, be at risk for becoming counter-productive. Ideally, one would want to create a structure of knowledge that would support both careful deep inquiry within specific specialties (i.e. "levels") and be conducive to inter-disciplinary (I.e., pluralistic) science. In some cases, we might know enough to "pre-specify" cross-level relationships – for example the expanding science of mapping neuropsychological functions to cortical and subcortical circuitry via fMRI. In other areas, such as how the effect of individual risk snps (or PRS) might be modified by specific environmental exposures, we are too ignorant to be highly specific.

Query # 2- A related worry, also suggested by your essay: if behavioral science ontologies become too standardized, are we going to face a situation in which grant applications, journal submissions etc get rejected because they don't conform to this standardized ontology? How should this consideration be balanced against such frequently claimed beneficial features of standardized ontologies as that they facilitate communication, comparison of results etc.

Response – This is a hard problem as we have two contradictory impulses. On the one hand, heavily "top-down" science doesn't work very well, and many Western-trained scientists are likely to rebel against efforts to "tell them how to do their work." On the other hand, we want to avoid the "tower of babel" of multiple different operationalizations of key concepts. This is particularly problematic in behavioral sciences. For example, in psychiatry/clinical psychology, anyone trying to summarize a key literature in is often confounded by many different scale that measure key concepts such as social support, stressful life events, depressive symptoms or parenting. In 2016, Eiko Fried looked at leading scales measuring depressive symptoms, counting a total of 52 symptoms across scales with often only modest overlap across different instruments[10]. I might here point to one successful but unusual and oft-criticized reaction to the tower-of-babel problem – the American Psychiatric Association's Diagnostic and Statistical Manual. It has worked in reducing the variable of psychiatric diagnoses across both clinical and research domains. But its authority is partly a function of it being "official" and its codes needed for billing and reimbursement – so it might not stand as any general model.

Query # 3- People often think of ontologies as having to do with fundamental concepts and entities in some area of science. But your essay also emphasizes the point that researchers sometimes employ defective measures of these, perhaps especially when trying to do multi-level research since they may not be familiar with best measures outside their areas of expertise. Do you think it would be useful to the field for the report of our committee to emphasize the importance of identifying and agreeing on high

quality measures, (assuming that these are different from a focus on concepts and entities)?—E.g., If you want good measures of self-control this is how you should proceed. Your essay mentions stressful life events which I assume is not straightforward to measure. Presumably it would be very desirable to disseminate what you learned how to measure this as widely as possible. (Perhaps this has already been done—but there must be many other concepts of interest that non-experts don't know how to effectively measure).

Response – The NIH Toolbox had tried to fill this function with, in my impression, partial success. In my personal experience, the optimal approach is to find a collaborator expert in the measures you want to use. That is because it is not only finding a proper scale but how to administer it, how to analyze it, what training is needed etc. That is a bit more difficult to put on a web-site than references to particular measures.

Query # 4 - Perhaps you don't want to get into this but: in your examples of success stories, genetics (and particularly in the case of schizophrenia) neurobiology play a central role. Of course, this reflects your particular interests and areas of expertise. But do you have a view about the possibility of successful behavioral science research that is not informed by genetics and neurobiology? If the best research is likely to be informed by genetics and neurobiology would it be useful for the recommendations of this committee to reflect this? Would it be useful for the committee to suggest that the best ontologies for behavioral science will be those that make some contact with genetics, neurobiology, related fields? Will this be true for some areas of behavioral science but not others?

Response – I would not wish to suggest that all high quality work in the psychological sciences should strive to include neurobiological perspectives. That is too narrow a vision. Many legitimate questions even in psychiatry can be examined in great depth entirely in psychological space – e.g., what are the effective components of CBT for depression? But for some questions – the etiology of schizophrenia – connecting psychological and neurobiological levels is certainly a vital part of the story given the overwhelming evidence for the importance of genetic factors in schizophrenia. So, I would agree with your last comment – connecting to neurobiology would be important for some but far from all questions.

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