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# From Epidemiology to Mechanisms of Illness

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## Abstract

Schizophrenia research encompasses many different categories of observation: (a) genetic research, which examines variants in single base pairs, (b) cellular and applied neuroscience, including animal models, (c) clinical research representing a broad spectrum of patient-centered research, and (d) population-based epidemiology and health services research. Each field of research has a natural tendency to become more specialized and, as a consequence, more inward looking. Meta-research, the study of the process of research per se, shows that creativity tends to occur at the boundaries of disciplines and research areas. This chapter examines ways to facilitate this type of cross-disciplinary translational research. Examples are provided of collaborative scientific programs that have used clues from fields such as epidemiology and genetics, and these clues are explored via the prism of various neuroscience platforms (e.g., molecular, cellular, behavioral, animal models, brain imaging). Cross-disciplinary projects have the potential to catalyze new discoveries in neuroscience. Our field needs to build efficient shared discovery platforms to encourage greater cross-fertilization between schizophrenia research and the general neuroscience research community.


## How Can We Optimize Discovery? Research on Research

There is a natural order in the way scientific disciplines evolve: complex areas of enquiry require highly specialized and focused research skills. Within each disciplinary niche, different cultures emerge in a healthy and appropriate fashion. Local dialects develop within a group and world views are shared within the tribe. These cultures are handed down to the next generation of scientists. Although this process introduces efficiencies within a field, it can also lead to inward thinking and creative stagnation. There is a general awareness that the sociology of science can hinder as well as advance scientific process. For example, important discoveries in one arcane field may not be immediately

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appreciated by the general research field. As a consequence, new discoveries may not be efficiently translated into distant fields.

In recent years the sociology of science has itself been the focus of research, addressing the central question of how scientists can optimize discovery (Lehrer 2009). Leaving aside rate-limiting steps, such as adequate research funding and quarantined research time (versus administrative, teaching, and clinical duties), there are interesting lessons to be learned. For example, researchers need to understand the dangers of "failure-blindness" (i.e., we need to appreciate findings that contradict our assumptions). A key feature of productive research groups relates to intellectual biodiversity. The meta-research evidence shows that research creativity is optimized when we actively "seek out the ignorant." For example, when we are required to talk to those who are unfamiliar with our experiments (other disciplines, students, the general public), we sometimes reframe research findings in a fresh perspective. Similarly, talking to colleagues from other disciplines can spark the creative exchange of fresh metaphors or provide missing pieces of the intellectual jigsaw puzzle. These notions have been influential in the formation of new research clusters, such as the Howard Hughes Medical Institute Janaelia Farm site (Cech and Rubin 2004).

## Optimizing Discovery in Schizophrenia Research

People who enter schizophrenia research tend to be incurable optimists. In spite of the bewildering heterogeneity of our target phenotype, and in the face of limited knowledge of the neurobiological correlates of schizophrenia, we remain confident that the questions we ask are tractable and that progress is being made. Self-proclaimed "decades of the brain" come and go and still clinical outcomes for people with schizophrenia are suboptimal. There is, however, good cause for optimism in light of examples of excellent clinical research that is fuelling discoveries in basic neuroscience and vice versa.

We present examples where ideas from within one field of schizophrenia research have been efficiently translated into other fields. We acknowledge that there are many examples of such types of research. Our selection is intended to prompt further debate on this topic.

### From Scottish Pedigrees to Neuronal Hub Proteins: DISC1

In the early 1970s, observant clinicians linked a chromosomal translocation involving chromosome 1 with a range of neuropsychiatric outcomes in an extended Scottish pedigree (Blackwood et al. 2001). The translocation disrupted a protein coding gene, which was subsequently labeled "disrupted in schizophrenia 1" (DISC1). Mindful that this structural variant was associated with other clinical outcomes, the ability to explore the function of the protein in

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transgenic models quickly revealed that the large protein coded by this gene was involved in an unexpectedly wide range of functions in the developing and adult brain (Porteous et al. 2011). Based on research conducted over the last few years, this protein has now been linked to a very wide range of molecular and cellular functions (Hayashi-Takagi et al. 2010; Seshadri et al. 2010). The protein acts as a hub for a large number of protein interactions.

Regardless of how prevalent this particular structural variant is in the general population, and regardless of what proportion of all schizophrenia is linked to mutations in this particular gene (probably very little), there is no doubt that this discovery has triggered important advances in basic neuroscience.

## From Mental Health Registers to *De Novo* Mutations: Advanced Paternal Age

Epidemiologists use population-based studies (e.g., cohorts, mental health registers) to search for gradients within and between groups as well as across time. This category of research is good for generating clues (e.g., links between a particular disease and different candidate risk factors), but it is limited with respect to (a) exploring the underlying biological mechanisms and (b) proving causality. Indeed, in the absence of randomized controlled trials, clues from observational epidemiology (e.g., a cross-sectional study that links a candidate risk factor with a disease outcome) are notoriously prone to the influence of unmeasured confounding (Davey Smith and Ebrahim 2001). A good example of how epidemiology can drive neuroscience discovery relates to the work by Malaspina et al. (2001), who reported an association between advanced paternal age and an increased risk of schizophrenia in offspring. Importantly, this paper suggested that *de novo* mutations in the male germ cell may contribute to this finding. The epidemiology research community quickly replicated and extended the finding to a range of other health outcomes, including childhood and adolescent behavior, intelligence, bipolar disorder, and autism.

Resultant clues from epidemiology were then examined in rodent models (Garcia-Palomares et al. 2009; Smith et al. 2009; Foldi et al. 2010); these studies reported altered behavioral and brain structural outcomes in the offspring of older sires. The use of inbred rodent models allowed for prompt testing of the underlying hypothesis regarding *de novo* male germline mutations. Experimental studies based on the mouse confirmed that the offspring of older sires had significantly more *de novo* copy number variants (Flatscher-Bader et al. 2011). Remarkably, the study found that the mutations involved genes previously linked to autism and schizophrenia. There is now convergent evidence linking copy number variant (CNV) load with schizophrenia (O'Donovan et al. 2008). Thus, within schizophrenia research, there has been an unexpected convergence between risk factor epidemiology and genetic studies.

With the advent of affordable high throughput genetic sequencing as well as access to mother–father–offspring schizophrenia trios, the relationship

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between paternal age, *de novo* mutations, and risk of schizophrenia can now be explored. Recent deep sequencing studies have confirmed the association between paternal age and *de novo* mutations (Kong et al. 2012). This type of research may help define subgroups within the heterogeneity of schizophrenia.

## From Place of Birth to Functional Magnetic Resonance Imaging

Prior epidemiology data suggests a two- to threefold increase in schizophrenia risk in individuals brought up in urban environments (Krabbendam and van Os 2005). The relationship follows a dose-risk response function: the longer individuals are exposed to highly urban environments during childhood and adolescence, the greater the risk of developing schizophrenia in adulthood (Pedersen and Mortensen 2001). Not surprisingly, adverse effects of urban upbringing are moderated by risk genes (Krabbendam and van Os 2005; van Os et al. 2008) with excessive rates of incidence in genetically vulnerable individuals brought up in the city. Similarly, first- and second-generation immigrants have a twofold increase in risk for schizophrenia independent of the specific characteristics of a given ethnicity or host country (Bourque et al. 2011). Both urbanization and migration processes challenge the capacity of an individual to cope with complex social stressors, such as disintegration of family networks, tightened competition, and discrimination. Epidemiological data suggest that the incongruence of subject-specific and environment-specific features is particularly crucial: the more an individual stands out from the social milieu in terms of minority status, social fragmentation, and socioeconomic status, the higher the risk is to develop schizophrenia (Zammit et al. 2010b). It has been proposed that social stress plays a key role in mediating these effects, possibly via dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and sensitization of the mesolimbic dopamine system (Pruessner et al. 2004; van Os et al. 2008). On the epigenetic level, an important mechanism for the effects of adverse environmental exposure during development involves hypermethylation of the promoter region of the glucocorticoid receptor gene (*NR3C1*), which reduces the expression of *NR3C1* in brain and promotes the manifestation of increased sensitivity to stress and HPA dysregulation in adulthood (McGowan et al. 2009). The neural system correlates in humans, however, are largely unexplored.

Lately, a new line of neuropsychiatric research aims to delineate these social-environmental risk effects in brain. Recent functional neuroimaging work, for example, examined the effects of urban upbringing on social evaluative stress processing in human social-emotional circuits (Lederbogen et al. 2011). In this study, the functional integrity of the neural stress response system was challenged using cognitive tasks presented in the context of disapproving video feedback from investigators. This work provided evidence for a link between early-life urbanization and anterior cingulate cortex (ACC) function during social stress processing, a key region involved in the regulation of limbic activity

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and negative emotion. Robustness and specificity of the effects of urbanization were confirmed in supplementary studies examining ACC function in the context of a different social stress paradigm and during cognitive processing without stress, respectively (Lederbogen et al. 2011).

## From Genetic Clues to Brain Functioning: "Genetic Imaging"

Twin, family, and adoption studies clearly indicate that genetic factors contribute substantially to the risk for psychiatric disorders. Heritability estimates, such as 81% in schizophrenia (Sullivan et al. 2003) and 37% in major depression disorder (MDD) (Sullivan et al. 2000), reflect the varying ratio of genetic and environmental factors which jointly determine risk or resilience (Caspi and Moffitt 2006). There is an obvious interest in identifying the gene variants underlying this hereditary component, since they promise valuable insights into pathophysiology, diagnosis, and treatment of the associated disorders (Hyman 2007). However, attempts to reveal the "culprit" genes by linkage analysis turned out to be of little value, although they had been applied to Mendelian disorders very successfully (Gottesman and Gould 2003). Apparently, the effects of psychiatric risk variants were too modest to be detectable by linkage. As a promising solution to study such subtle effects, association studies were introduced (Risch and Merikangas 1996). These studies apply a candidate gene approach requiring a priori defined genes. Accordingly, these studies are intrinsically prone to a bias in the selection of candidates, which usually focus on genes that are known to code for key player proteins involved in neurotransmission and suspected to be linked to mental illness, such as the monoaminergic system in mood and anxiety disorders (Levinson 2006) and the dopaminergic or glutamatergic system in schizophrenia (Owen et al. 2004).

This approach resulted in a plethora of studies reporting associations between single candidate genes and clinical or treatment-related phenotypes of mental illness, such as MDD (Levinson 2006; Kato and Serretti 2010) or schizophrenia (Owen et al. 2004; Arranz and de Leon 2007). However, the initial gold rush in the search for candidate genes has been followed by a disillusioning decade of failed replications and considerable disagreements among scientists (Abbott 2008). In fact, many genetic associations were likely overestimated by initial studies (Trikalinos et al. 2004) or may have even been chance findings given the common practice of selective reporting (Sullivan 2007).

With the advent of genome-wide association (GWA) approaches, it is now possible to test associations of more than one million DNA variants simultaneously. This technique holds the promise of hypothesis-free gene discovery for common disorders by mapping the whole genome with common markers. However, there are several limitations to this technique, such as statistical compromises which have to be made, given the incredibly high number of investigated genes (Psychiatric GWAS Consortium Steering Committee 2009; Cichon et al. 2009). This notion is reflected in the weak support of GWA studies

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with regard to traditional candidate genes and the limited agreement among the increasing number of GWA studies (Pezawas and Meyer-Lindenberg 2010; Bosker et al. 2011).

After the first report of an association between genetic variation and a neuroimaging measure in 2000 (Heinz et al. 2000), imaging genetics has developed into a leading research strategy in neuroscience. Countless studies have demonstrated the influence of risk alleles on neural intermediate phenotypes which, in turn, relate to different psychopathological manifestations and diagnostic entities (Bigos and Weinberger 2010; Domschke and Dannlowski 2010; Meyer-Lindenberg 2010b; Scharinger et al. 2010). In contrast to several candidate endophenotypes, which turned out to be equally complex as behavioral phenotypes, recent meta-analyses indicate that neural intermediate phenotypes satisfy the premise of increased penetrance (Gottesman and Gould 2003; Munafo et al. 2008; Mier et al. 2010). For instance, a polymorphism in the promotor region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) has been shown to account for up to 10% variance of amygdala activation, whereas its role in predicting behavioral phenotypes such as neuroticism, MDD, or antidepressant treatment response is at least one order of magnitude lower (Serretti et al. 2007; Munafo et al. 2008, 2009; Clarke et al. 2010; Taylor et al. 2010). Accordingly, imaging genetics may eventually provide one of the tools needed to decipher the polygenic heritability of psychiatric disorders as anticipated by Gottesman and Shields more than four decades ago (Gottesman and Shields 1967).

These genome-wide significant variants are opening up new avenues to risk pathways of executive function in imaging genetics. In the first such study, a sample of healthy individuals was used to verify a variant (rs1344706) in the zinc finger protein 804A gene (*ZNF804A*) that has been implicated in schizophrenia by GWA (Esslinger et al. 2009). Remarkably, healthy carriers of the risk variant exhibited unfavorable prefrontal-hippocampal functional connectivity in a pattern characteristic for schizophrenia (Meyer-Lindenberg et al. 2005; Esslinger et al. 2009). Following this approach, several new results emerging from GWA studies using clinical or neurocognitive phenotypes have been confirmed by imaging genetics methods, such as variants in *HOMER1, CACNA1C*, or *SCN1A* (Bigos et al. 2010; Rietschel et al. 2010; Papassotiropoulos et al. 2011).

## From Influenza Epidemics to the Impact of Maternal Immune Activation on Brain Development

Soon after the renaissance of the neurodevelopmental hypothesis of schizophrenia (Murray and Lewis 1987; Weinberger 1987), various researchers proposed that the offspring of mothers exposed to influenza may have an increased risk of schizophrenia (McGrath and Castle 1995). While the evidence linking exposure to this particular infectious agent has been mixed, there is now a

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large body of research which suggests that prenatal infection to a wide range of early life infections is associated with increased risk for schizophrenia in the offspring (Brown and Derkits 2010).

Using rodent models and noninfectious agents designed to trigger immune responses (e.g., agents that mimic the bacterial cell wall or RNA polymers that resemble viral RNA), experimental studies have uncovered previously unexpected reciprocal interactions between immune pathways and brain development (Meyer et al. 2009; Patterson 2009). This research converges with evidence from (a) genetics to link regions of the genome critical for immune response to schizophrenia (Ripke et al. 2011), and (b) developmental neurobiology to implicate mechanisms initially thought to be restricted to immune pathways with brain development and function (Boulanger 2009). These discoveries are now able to feed back into more focused and hypothesis-driven analytical epidemiology.

## General Reflections and Recommendations

The need to support translational research that facilitates discoveries in basic science into clinical settings is now widely recognized by funding agencies. With respect to the care of people with schizophrenia, there is a need for this type of research, just as there is a need to ensure that known effective treatments are delivered to those in need. However, in poorly understood fields of research, we first need to do the basic science in order to fuel the subsequent translational pipeline. We argue that complex brain disorders such as schizophrenia require continued investment in research which takes clues from various fields of schizophrenia research and feeds them back into high-quality neuroscience. Put bluntly, if we want to fix broken brains, we first need to understand how healthy brains are built and how they work.

The need to facilitate the fertile intersection between schizophrenia epidemiology and developmental neurobiology has been detailed elsewhere (McGrath and Richards 2009). Because neuroscience is such an intensely productive and fast-moving field of research, trying to engage with the field as an outsider is akin to "sipping from a fire hose." Despite this, we argue that it is critical for schizophrenia research to be firmly anchored to a neurobiologically informed framework. Schizophrenia researchers have the skills to generate candidate exposures and to identify neuroanatomical, neurochemical, or behavioral phenotypes of interest to clinical research. Rodent models (Arguello and Gogos 2006), zebrafish, or invertebrates such as *Drosophila* and *Caenorhabditis elegans* (Burne et al. 2011) can provide powerful and efficient research platforms to explore key research questions for both genetic and nongenetic risk factors and to help identify the function of genetic candidates.

From our current perspective, one of the more exciting developments in this field has been a renewed focus on the social world and its evolutionarily

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honed counterpart, the social brain. In a recent review (Meyer-Lindenberg and Tost 2012), we concluded that the existing evidence, while preliminary in nature, supports a causal role for the social environment in risk, resilience, and manifest illness, suggesting that everyday social interactions are both actor and stage for mental illness. Novel translational research strategies are needed to delineate the neural outcomes of the complex underlying gene–environment interactions. An in-depth understanding of these mechanisms holds the prospects of novel strategies for pharmacology, psychotherapy, and social policy that target and converge on the identified neural circuits. In the "decade of psychiatric disorders" (Bassett et al. 2010), a renewed focus on social neuroscience has therefore much to offer for scientists, patients, and therapists alike.

The challenge is to optimize links between researchers from (a) the diverse fields of schizophrenia research and (b) the even more diverse fields of neuroscience. How can we engineer future research between these groups to "set traps for discovery"? Building shared research platforms between groups with different skills is clearly an important step. As Cech and Rubin (2004:1167) note:

> The spark of transdisciplinary approaches and insights requires "productive collisions" between people in different disciplines, just as atoms and molecules must undergo productive collisions to react. If engineers, biologists, and computer scientists live apart, they need to make an appointment in order "to collide."

Shared research platforms need to be engineered to encourage "collisions" between diverse scientists. We argue that schizophrenia research needs to take a more assertive stance in driving neuroscience research. Too often we have been passive recipients of "leftover" neuroscience. Neuroscience needs us, just as much as we need neuroscience (McGrath and Richards 2009).

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Second column: Michael O'Donovan, Kristin Cadenhead, Steve Silverstein, John McGrath, Michael O'Donovan, Kristin Cadenhead, and Steve Silverstein
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