treatment pharmacopeia. Insights gained into the mechanism of its effects could also enhance medications development for AUD by identifying novel targets that, if exploited, could ultimately increase the use of FDA-approved medications to treat the disorder.

Despite these promising results, key challenges remain in evaluating the efficacy of hallucinogens for treating psychiatric disorders and in understanding their mechanisms of action. The lack of a suitable comparator limits the ability to mask treatment conditions, so that double-blind designs may be impossible. This is important because expectancies can strongly influence both the therapeutic and adverse effects of the medications, and an adequate control is needed to differentiate the expected effects from the pharmacologic ones.

An important question is the extent to which a hallucinogenic experience is required for psychedelic drugs to have a therapeutic effect, which has implications for both the appropriate dosage and frequency of administration in the large-scale trials that will be needed for FDA approval. This question is also key to developing novel agents to target the mechanisms of therapeutic effects specific to different psychiatric disorders. Although these factors complicate research on the mechanism of effects of hallucinogens, recent research on psilocybin's effects in treating major depression using functional magnetic resonance imaging suggests that its action depends on a global increase in brain network integration.[10] Similar research in AUD could help to characterize similarities across disorders that are responsive to psilocybin treatment.

Whereas the study by Bogenschutz et al[6] did not manipulate the psychotherapy provided in conjunction with the study medication, the optimal combination of medication and psychotherapy is unknown. This has implications for the feasibility of using hallucinogens in routine clinical practice, as intensive psychotherapy, such as was provided by Bogenschutz et al,[6] requires a significant investment in time and labor. Such concomitant therapy, if necessary to realize the therapeutic benefits of psilocybin for treating AUD, could limit its uptake by clinicians.


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# Ultrarare Coding Variants and Cognitive Function in Schizophrenia—Unraveling the Enduring Mysteries of Neuropsychiatric Genetics


David L. Braff, MD; Tim B. Bigdeli, PhD


**Building on a rapidly advancing literature** supporting a focal role of rare damaging variants in the etiology of neuropsychiatric illness, researchers from Cardiff University have examined the carrying of ultrarare constrained variants (URCVs) and the functioning of 802 patients with well-characterized schizophrenia.[1] This class of rare variation is analogous to de novo and private mutations but is further limited to protein-altering changes in regions of the genome that are mutationally intolerant (ie, with significantly fewer coding changes observed than expected among tens of thousands of genomes). They report that URCVs, especially in neurodevelopmentally relevant genes, affect the crucial outcome-related domain of cognition both before and after the onset of illness. Carrying such an event represents a neurodevelopmental insult and,

as the authors reasonably suggest, an enhanced vulnerability to secondary factors and worse outcomes. Prior research on intellectual disabilities, developmental delay, and syndromic presentations of copy number variants (CNVs) lend credence to this perspective. The authors emphasize this point by jointly modeling the current polygenic risk scores and schizophrenia-associated CNVs, finding that URCVs persist in their significance.

Mirroring the sample size-based trajectory of common variant discovery, the case for small rare coding variants is burgeoning. In 2014, a landmark pair of studies[2,3] demonstrated enrichments of rare (less than 1 in 10 000) or de novo variants in genes encoding glutamatergic postsynaptic proteins and Fragile X mental retardation protein targets, converging on prior biological insights from genome-wide association studies (GWAS) and CNV studies of schizophrenia. This demonstration parallels findings from autism and intellectual disability research. Genovese et al[4] later focused on ultrarare variants unique to individuals, finding strong enrichment of disruptive and putatively damaging variants in constrained genes, and noting that this enrichment surpassed the previously reported elevated rate of de novo events, indicating that rare variant effects on schizophrenia are largely inherited. More recently, the SCHEMA Consortium has aggregated whole-exome data for tens of thousands of patients and pinpointed 10 genes harboring rare variants that confer risk for schizophrenia.[5]

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The current report from Creeth et al[1] is thus quite timely: because their study participants were cognitively assessed, we are offered a glimpse of how this special class of rare variation affects patients' neurocognition with its association with real-world functioning (eg, household chores, interpersonal communication, finance, transportation, and planned recreational activities). Specifically, they used the MATRICS Consensus Cognitive Battery (MCCB) to assess current cognition and the National Adult Reading Test (NART), a convenient and available proxy measure, to estimate premorbid cognitive functioning. Carrying a URCV in a neurodevelopmentally critical gene corresponded to an approximately 5-point reduction in IQ, comparable to the effect size of current IQ polygenic scores. Future research would do well to use more extensive granular batteries assessing neurocognitive domains and real-world functioning. Compared with simple dichotomous case-vs-control outcomes, quantitative measures have 10 times the power to detect significant loci and are more closely linked to endophenotypic pathways and functional outcomes—the ultimate targets of our research.

## The Big Picture

In his seminal 1938 work *The Anatomy of Revolution*,[6] Crane Brinton noted that revolutions are characterized by an initial jacobean overenthusiasm, followed by a thermidorian period of reflection and moderation.[7] In this context, despite the initial enthusiasm following the results of the Human Genome Project 20 years ago, it is now clear that the human genome will not give up its secrets easily. The 2014 Psychiatric Genomics Consortium (PGC) study[8] of more than 36 000 patients that yielded 108 independent loci—each imparting a tiny effect but with tremendous statistical significance—was a milestone in this research, despite the daunting realization that these venerated loci combined accounted for only approximately 3.4% of the variance in risk. Today, this number stands at 270 loci, and our best indices of aggregated risk-codified as individual-level polygenic risk scores-account for approximately 7.7% of the variance in liability.[9] This amount of risk variance reflects an inconvenient truth: although through GWAS, we can identify many common risk factors for schizophrenia, the effect sizes we are dealing with are quite small (OR of approximately 1.1). In contrast, much rarer variants with much larger effect sizes, such as the newly reported loss of function variants in *GRIA3*, and canonical deletions of chromosomes 3q29 and 22q11.21, increase risk by 50-fold or more but are carried by fewer than 1 in 10 000 individuals.[5]

For neuropsychiatric genomics the big picture is that we are looking at a spectrum of common and rare (and ultrarare) variations to understand a whole-brain disorder that seems to involve a complex tapestry encompassing both cortical and subcortical dysfunctions. Synthesizing these findings into a coherent functional neurobiological model of schizophrenia will be our formative challenge. Notably, some convergent biological insights are starting to emerge. Both GWAS and exome-based studies[5,10] highlight that both common and rare variant signals are enriched in constrained mutationally intolerant genes. More pointedly, 4 of the SCHEMA loci (*GRIA3*, *GRIN2A*, *SP4*, and *TRIO*) implicate disrupted glutamatergic signaling. This finding resonates with crucial endophenotype-based research findings from the Consortium on the Genetics of Schizophrenia, which implicated *GRIN2A* and *SP4* in a 42-gene network related to neurocognitive dysfunction in schizophrenia.[11]

As discussed previously,[7] there are (at least) 3 pathways to incorporate the ultrarare and other findings into a comprehensive picture of schizophrenia genetic risk: (1) Incremental research: incrementalism is sometimes dismissed as nonimaginative but it is crucial as we advance our understanding step by step. (2) There is the role of serendipity as illustrated by the discovery of antipsychotic and antidepressant medications. This discovery process will take someone with careful observational skills to integrate novel findings. (3) There is the possibility of a transformative kuhnian insight by which someone generates a totally unique understanding of a scientific problem. Some nascent examples are so-called omnigenetics, in which 50 to 100 core genes are identified and they interact with essentially the entirety of the peripheral genome, watershed models of fluid IQ, and nonlinear models. Although they all have intuitive appeal, it is very hard to comprehend how they can be fully developed and falsified. Time will tell.

Schizophrenia is fundamentally composed of a number of quantitatively measurable deficits in or variants in neurophysiology, neurocognition, metabolism, inflammatory processes, and other domains. In weighing the pursuit of common vs rare variant findings, we are reminded that individual presentations of schizophrenia reflect combinations of shared or generalizable and unique or person-specific risk and resilience factors. At any given locus, incomplete penetrance is more rule than exception; modest effect sizes are a conse-

quence of averaging etiological relevance across many polygenic manifestations.

Noted researcher Samuel Barondes has been quoted as describing our most exciting GWAS findings as "just one step in a journey of a thousand miles."[12] In the big picture, we believe this metaphor reflects the reality that we are facing profoundly complex challenges in advancing our understanding of neuropsychiatric disorders. With all of these possible pathways for discovery and with so many variants contributing at least small portions of risk, we advance. A time will arrive when will we have a comprehensive understanding of schizophrenia genetics—not necessarily of the diagnosis but rather the quantitative measures related to outcome—and how it relates to patients real-world functioning.[13] As we glean additional biological insights, we are duty-bound to prioritize actionable findings, toward realizing some benefit sooner-rather-than-later (and equitably) to patients. The reality is that we do not know where discoveries will emerge, we do not know when they will happen, but we do know that this will not be easy. But that is not a reason for discontinuing our quest for understanding and treating schizophrenia, which is similar to challenges posed by diabetes, hypertension, and a plethora of other common and enigmatic heritable disorders. If you are looking for a quick answer, it is certainly not here yet.[12] The jacobean phase in schizophrenia genetics is over. We believe that answers will come but with a significant amount of time and effort.

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# What Makes a Useful "Predictor" of Risk for Suicide Attempt?

Deanna M. Barch, PhD; Laura Hennefield, PhD; Max P. Herzberg, PhD

**There is now robust evidence** that children as young as preschool-aged can express suicidal ideation, and even engage in behavior that can be understood as suicide attempts.[1,2] Young children who express suicidal ideation or exhibit suicidal behaviors have a more accurate understanding of death than their nonsuicidal peers,[3] and early suicidal ideation/behavior predicts ongoing suicidal ideation/behavior into school age and in some cases adolescence.[4] However, it is still not clear whether the risk factors and variables associated with suicidal ideation/behavior in early adolescence are the same as those later in adolescence or adulthood. To help address this question, Lee et al[5] used the large-scale Adolescent Brain and Cognitive Development study data to generate a very important and informative set of analyses examining whether polygenic risk scores (PRSs) for adult suicide are associated with childhood suicidal ideation and/or attempts, whether this relationship is independent from associations with PRSs for depression and attention-deficit/hyperactivity disorder (ADHD), and what mental health or behavioral factors might mediate the association between adult suicide PRSs and child suicide ideation or behaviors. There were several crucial findings from this study. First, PRSs for adult suicide were associated with child suicide attempts, but not ideation. Second, this association with adult suicide PRSs was over and above shared variance with PRSs for depression and ADHD. Third, this association was mediated in part through a variety of parent-reported behaviors, including increased aggression, attention problems, rule-breaking behavior, social problems, and somatic com-

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