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Bipolar and Schizophrenia Network for Intermediate Phenotypes: Outcomes Across the Psychosis Continuum

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Bipolar and schizophrenia network for intermediate phenotypes is a network of investigator-driven laboratories focused on developing phenotypes, genotypes, and biomarkers for psychosis. Over the last 5 years, the consortium has accomplished a dense phenotyping protocol using probands with a lifetime history of psychosis, their relatives, and healthy controls. This has established a library of biomarker information on individuals with schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. The founding goal of establishing disease biomarkers for current psychotic diagnoses has been poorly met, because the cognitive, electrophysiologic, eye movement, and brain imaging biomarkers did not regularly discriminate individuals with different DSM psychosis diagnoses. In future, we will use this biomarker information to establish a pathway to biomarker-based classification in psychoses.

Key words: psychosis/phenotypes/biomarkers/diagnoses

Introduction

The science of ordering human psychopathology has always been difficult, resting as it does on an insufficient neuroscience knowledge base. Nonetheless, it has been attempted over the centuries.[1,2] Psychiatric diagnosticians have used clinical information—symptom phenomenology—to achieve disease organization, albeit with sophisticated and detailed information. But, the use of a phenomenological-based approach to psychiatric classification has become increasingly untenable because of its lack of validity. The categories that we regularly apply to serious mental illness are neither incisive in revealing genetic bases for psychotic illnesses nor in leading to replicable molecular disease mechanisms. Psychiatric diseases of the brain are described by complex genetics and expressed in poorly understood cerebral systems that influence both cognitive function and affect modulation. It has been hypothesized that those processes mediating activity-dependent neuronal signaling are particularly involved in functional disorders of cognition and affect.[3] The molecular targets described by the families of risk genes now being identified for psychosis include enzymes, transcription factors and ion channels as well as traditional neurotransmitter receptors, that function in signal transduction, neuronal development and cellular activity, and processes like receptor trafficking.[4–6] Extraordinary advances in basic neuroscience have been realized over the past several decades,[4] even in their translation to functional brain disorders.[7] The task of translating biological characteristics of the normal and abnormal human brain to an understanding of disease definition and mechanism is not an unreasonable expectation today, and is already being used strategically[8] and in several high profile phenotype/genotype experiments[9,10] and genetic studies.[5]

It has been the strategy of the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) consortium to adopt a broad and meaningful clinical phenotype, specifically psychosis within the schizophrenia-bipolar continuum,[11] to leverage our ability to test the distinctiveness of common DSM psychosis diagnoses and/or to identify biologically similar individuals with history of psychosis as their biomarker characteristics might cluster either within DSM diagnoses or in novel biologically defined groups.[12] Other significant questions were to what extent individual biomarkers were associated with one another and whether abnormalities seen in probands were apparent in first-degree relatives, constituting endophenotypes. The BSNIP consortium includes six collaborating sites in the United States with its lead clinical scientists (CT, GP, MK, JS, GT, BC) having a broad range of phenotyping expertise. This

includes experience in not only detailed clinical ascertainment, but also in cognition measurement, electrophysiology, eye movement, magnetic resonance imaging analysis, and genetic analyses with the goal of applying human brain disease biomarkers densely to the characterization of psychotic illness. The BSNIP network focuses on the recruitment and phenotyping of individuals with psychosis using a battery of evaluations previously found to distinguish psychosis from normal function—a battery that was standardized and matched across sites. It is clear that seeking a clinical phenotype of "psychosis" recruited a more heterogeneous population of serious mental illness than any single DSM diagnosis and that individual probands might not fit either schizophrenia (SZ) or bipolar disorder criteria precisely. The outcome of recruiting and testing this large number of individuals with psychotic illness, all diagnosed and intensively phenotyped, has been the creation of a well-characterized population in which to test the usefulness of psychosis biomarkers for genetic association, disease definition, and treatment prediction. It is a population in which the goals of the Research Domain Criteria (RDoC) can be examined around the clinical phenotype of psychosis.

Methodology

Participants and Phenotypes: The BSNIP population is a research sample, collected through regional advertising for research in Baltimore MD, Boston MA, Chicago IL, Dallas TX, and Hartford CT. Within the analytical data sample, the network included 933 probands along with 1059 of their first-degree relatives and 459 healthy volunteers without psychotic illness in their immediate family. Volunteers participated in the full clinical characterization and dense phenotyping, including[13] cognitive, electrophysiological, eye movement and brain imaging assessments, as previously described.[13–21] All test materials and procedures were standardized and identical across sites.[13] For cognition assessment, the Brief Assessment of Cognition in Schizophrenia (BACS)[14] was administered to all participants. Electrophysiological assessments included evoked potential with auditory probes (paired stimuli and oddball tasks), and resting EEG.[15,17] Eye movement assessments collected performance in both smooth pursuit and antisaccade paradigms.[16] Brain magnetic resonance imaging (MRI) at 3T included MPRAGE for structural analysis,[21] resting functional MRI (fMRI)[18–20] and, on part of the sample, diffusion tensor imaging.[19,22] All clinical and biomarker assessments were standardized across sites and maintained over the study duration. Volunteers participated in a SCID interview and relatives participated in additional interviews. Diagnosis was made in a consensus conference with multiple study-trained clinicians. Family history data were collected at a minimum from the most informed family member; more detailed information was gathered whenever possible. Positive and Negative Symptom Scale (PANSS), Montgomery Asberg Depression Rating Scale, and Young Mania Rating Scale were collected in all individuals with an Axis 1 clinical psychosis diagnosis. The Birchwood Psychosocial Function Scale was used to capture function in all groups.[13] All phenotype data were collected locally at each site, then scored centrally by the expert-PI in his/her laboratory. The resulting analytical data base is a full composite of the clinical, family, and biomarker data.

Results: Phenotypes of Psychosis

Overall illustrative results from BSNIP are presented in figure 1, illustrating data described in a summary fashion below.

Distinctiveness of Psychosis Diagnostic Groups

Three DSM psychosis diagnoses were included in this study, schizophrenia, schizoaffective disorder (SAD), and psychotic bipolar disorder (BDP). Each proband was rated on a Schizo-Bipolar Scale, developed by the BSNIP collaboration, which graded their component of the DSM's criteria for each of the three psychosis disorders.[11] The Schizo-Bipolar scale is graded from 1 (bipolar-like) to 10 (schizophrenia-like) with SAD in the middle. When the individuals with the three diagnoses were plotted by frequency across the Schizo-Bipolar scores, there was an almost complete admixture of diagnoses without any "point of rarity" between the actual diagnoses (figure 1b), suggesting a substantial overlap even in phenomenology across SZ, SAD, and BDP psychosis diagnoses.

Clinical Characteristics of Psychosis

Each of the 933 probands (397 SZ, 224 SAD, 312 BDP) was recruited along with at least one first-degree relative, forming a group of 1059 relatives (41.8% parents, 39.7% siblings, 18.5% children), matched with 459 healthy controls from the same catchment areas.[13] PANSS scores were higher in the SZ and SAD group than in the BDP, but the average differences were small and the variances were high, making their distributions highly overlapping. The SAD group was more often similar to the SZ than to the BDP volunteers (figure 1a). Among relatives, only approximately one-third in all groups lacked any Axis I or II disorder, with Axis I major depressive disorder and drug abuse and Axis II psychosis spectrum disorders being the most frequent diagnoses in relatives. Family histories of the probands show that these psychosis diagnoses do not breed true; both single-diagnosis families as well as mixed-diagnoses families are represented in each proband group. In SZ probands, 27% have only-SZ relatives and 17.3% have mixed-relative families; in BDP probands, 39.5% have BD-only relatives and 25.4% have mixed-relative families. Medication use included antipsychotic drugs (SZ 91.6%, SAD 86.7%, BDP 70.1%) mood

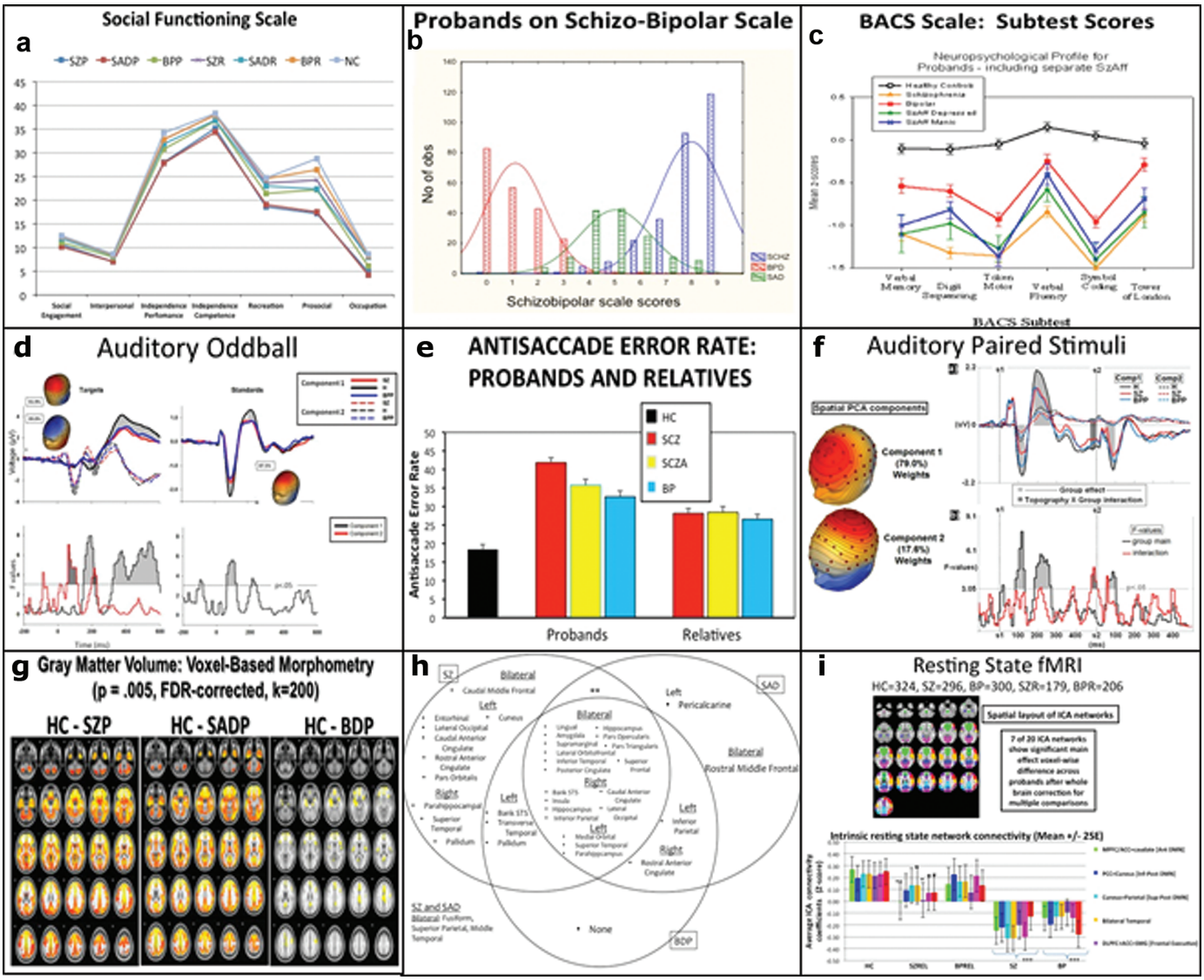

Fig. 1. Multiple illustrative data from bipolar and schizophrenia network for intermediate phenotyping (BSNIP) study. (a) Social function quantified with the Birchwood Social Function Scale in the BSNIP sample. Details in reference [13]. Schizophrenia (SZ) and schizoaffective disorder (SAD) groups were almost identical, while bipolar disorder (BDP) showed slightly higher scores. Relatives of all groups were modestly impaired. The patterns of impairment were similar across diagnostic groups. (b) The Schizo-Bipolar scale was developed from the SCID diagnostic criteria for these psychotic diagnoses.[12] There was almost continuous overlap between these diagnoses with no point of rarity over this spectrum, lacking support for distinct illness groups based on phenomenology. (c) Cognition was measured with the BACS.[14] Group scores are depicted for the diagnostic subgroups, showing the greatest impairment in the SZ group and the least in the BDP group with SAD in between, separated by severity; however groups did not show distinctive qualitative cognitive alterations from each other, except for the severity. (d) In the evoked potential auditory oddball paradigm, the patient groups (SZ and BDP) resembled each other rather broadly, with minimal, distinctive differences, discussed in reference [15]. (e) The antisaccade error rates were increased in all patient groups, highest in SZ and lower in BDP, without any differences across relatives.[16] Again, while severity differences were present, no other distinctions existed across diagnostic groups. (f) Differences between SZ and BPP groups are present after a pair auditory stimulus, including differences in both patient groups in baseline levels, especially before S2.[17] (g) Using VBM analysis to determine grey matter volume,[21] a distinctive difference between SZ/SAD, on the one hand and BDP on the other, emerged; specifically, SA and SAD groups demonstrated significant and widespread grey matter volume reduction, while the BDP showed very little grey matter reduction in any area. This would represent a difference between diagnostic groups of a qualitative as well as quantitative nature. (h) FreeSurfer showed a similar outcome, with grey matter reductions widespread in all cortical regions in SZ and SAD, while no distinctive reductions in BDP. (i). Resting state fMRI analysis shows a number of distinctive cerebral networks based on ICA, that were distinctive in some or all of the diagnostic groups.[18] In general, these networks were different between all probands and all healthy controls.

stabilizers (SZ 21.2%, SAD 49.5%, BDP 69.8%), and antidepressants (SZ 38.9%, SAD 56.9%, BDP 44.0%) at high and surprisingly similar rates across all proband groups. Overall, the clinical and demographic profile of the probands was remarkably similar across this psychosis spectrum.

Cognition in Psychosis

Cognition was assessed using the BACS[14] For this measure, the BACS summary score best represented the variance in cognition ratings for the groups. In the BACS summary scores, cognitive dysfunction was progressively more prominent from BDP (z = –0.77) to SAD (z = 1.08–1.25), to SZ (z = 1.42) (figure 1c). Familiality was noted with respect to the cognitive deficits, especially within the psychosis spectrum relatives. Unaffected SZ relatives, including those without any psychosis spectrum characteristics, showed modest cognitive deficits, whereas, nonspectrum BDP relatives did not evidence cognitive deficits. BACS performance was reduced across the psychosis groups, albeit with distinctive mean performance. Nonetheless, there was a high degree of overlapping distribution, without a clear way to classify individuals into DSM diagnostic groups.

Antisaccadic Eye Movements

Increased antisaccade error rate has been considered an intermediate phenotype for SZ. The BSNIP population was used to consider whether this marks a liability across psychotic disorders, as well.[16] Volunteers in the BSNIP study performed antisaccade and prosaccade tasks, and completed a neuropsychological battery. All probands showed an increased antisaccade error rate, unrelated to symptoms or to treatment, greatest in the SZ group albeit similar in character in all psychosis groups (figure 1e). The increased error rate was observed in relatives, even in those without psychosis spectrum personality disorder. Error rate was familial and remained abnormal even after accounting for generalized cognitive impairment. Therefore, elevated antisaccade error rate could be an intermediate phenotype of psychosis across these diagnositic groups. The severity of the antisaccade impairment and its independence from attentional shifting problems, suggest significantly impaired prefrontal inhibitory control deficits in psychosis, especially in SZ. The antisaccade deficit was present in all psychoses, even if most severe in SZ, and independent of attentional measures and present ubiquitously in relatives.

Evoked Potentials in Psychosis

Evoked potential data were gathered with 64-sensor EEG. The paired-stimuli (S1, S2) data showed that prior to S1 both SZ and BDP displayed augmented gamma band power that covaried with diminished N100 and evoked low frequency oscillations[15](figure 1f). Increased intrinsic high frequency activity is a common finding in psychosis theorized to indicate reduced NMDA receptor modulation of inhibitory interneuron activity and low signal to noise ratio. ERP peaks (N1,P2) and low frequency oscillations to S1 constituted broad, shared neuropathology between SZ and BDP, while late, slow developing neural activities showed both disease specificity as well as the strongest differentiation of biological relative subgroups. Responses to S1 were lower in amplitude among psychosis groups but were normal in relatives. Alternatively, S2-related responses showed SZ and BDP specificity, including among biological relatives. Familiality estimates were strong ($h^2_r > 0.5$; $P < 1E\text{-}8$) for many of the evoked response components as well.

During oddball processing early stimulus registration both N1 and P2 responses to standards significantly discriminated SZ and BDP from healthy persons [17](figure 1d). Both variables of these variables were also significantly familial. When examining biological relatives, however, only SZ relatives had N1 deficits and only BDP relatives had P2 deficits. The P3b to targets showed moderate familiality and discriminated both SZ and BDP (lower in amplitude) from healthy persons. Only the biological relatives of SZ showed significantly reduced amplitude on this component. When individuals with Cluster A and/or B personality disorders were removed from SZ relative groups, however, the difference was no longer significant, indicating an illness-related effect on P3b. These outcomes show considerable shared neurophysiological characteristics between SZ and BDP and some unique brain response patterns in each diagnostic group.

Brain Function in Psychosis

Differences Within Functional Brain Networks. Resting state fMRI in SZ and BDP, their respective first-degree relatives and healthy subjects, were interrogated using independent component analysis (ICA) to identify components representing various resting state networks, and spatial aspects of functional connectivity within all networks were similarly analyzed.[19] Seven networks revealed abnormalities: (1) fronto-occipital, (2) midbrain/cerebellum, (3) frontal/thalamic/basal ganglia, (4) meso/paralimbic, (5) posterior default mode network, (6) fronto-temporal/paralimbic, and (7) sensorimotor networks (figure 1i). Abnormalities in networks B and F were unique to SZ probands. Furthermore, abnormalities in networks D and E were common to both patient groups. Finally, networks A, C, and G showed abnormalities shared by probands and their relative groups. Negative correlation with PANSS negative and positive scores were found in regions within network C and F respectively, and positive correlation with PANSS negative scores was found in regions in network D among SZ probands only. Thus, SZ, BDP, and their relatives share both unique and overlapping within-network brain connectivity abnormalities, revealing potential psychosis endophenotypes.

Differences Across Functional Brain Networks. ICA was also used to detect differences across these circuits (ie, in

functional network connectivity).[18] First, we examined connectivity differences between probands and control subjects. Next, we probed these dysfunctional connections in relatives for potential endophenotypes. Network connectivity was correlated with PANSS scores to test clinical relationships. Five different network pairs were differentially connected in probands involving five individual resting-state networks: (1) fronto/occipital, (2) anterior default mode/prefrontal, (3) meso/paralimbic, (4) fronto-temporal/paralimbic, and (5) sensory-motor. One abnormal pair was unique to SZ, (3-5), one unique to BDP, (3-4), and one (1-2) was shared. Two of these three combinations (1-2, 3-5) were also abnormal in BDP relatives but none was normal in SZ relatives. The paralimbic circuit (3-4), which uniquely distinguished BDP, contained multiple mood-relevant regions. Network relationship (3-4) correlated significantly with PANSS negative scores in BDP probands, and (1-2) with PANSS positive and general scores in SZ. Overall, SZ and psychotic BDP probands share several abnormal resting state network connections, but there are also unique neural network underpinnings between disorders.

Brain Structure and Psychosis

VBM analyses using the MPRAGE scans showed equivalent and substantial reductions in grey matter volume in the SZ and SAD probands, but showed very little reduction from normal in the BDP group grey matter volume(figure 1g).[21] The small grey matter volume reduction in BDP was confined to prefrontal and limbic areas, whereas in SZ and SAD, the volume reduction included all neocortical regions. No relative group within the DSM diagnoses showed differences from each other or from the healthy controls. A dimensional analysis was also carried out with the VBM data, with psychosis as the dimension. Here the psychotic probands together showed remarkable grey matter reduction from normal, and the psychosis spectrum relatives (Cluster A) showed a reduction from normal as well, in the same distribution as the probands, but not as extensive. The nonpsychosis spectrum relatives were indistinguishable from normal. Convergent results have been observed across SZ, SAD, and BDP groups using the Freesurfer parcellation method as well (figure 1h).[23] Using the structural biomarker of volume, BDP were similar to controls and SZ and SAD showed similarly reduced neocortical volume; thus, BDP were distinctly different from the SZ and SAD.

Diffusion Tensor Imaging in Psychosis

Both SZ and BDP probands showed lower fractional anisotropy (FA) than the comparison subjects in multiple white matter regions; differences were more marked in SZ.[22] No significant differences existed between proband groups, but in some brain regions scores on a measure of the dimensional continuum between SZ and BDP, the Schizo-Bipolar Scale showed correlations with FA. Many regions affected in SZ probands showed similar but smaller effects in their relatives, with a continuous FA decrease from healthy subjects to relatives to cluster A/B relatives to probands. The pattern for BDP was similar but involved fewer brain regions. Effects in BDP relatives were limited to younger subjects. FA decreased with age in all groups; this decrease was exaggerated in SZ but not BDP. FA was highly heritable. In measures of FA, differences from the control group were evident and in the same direction in both SZ and BDP; clear distinctions were not apparent.

Discussion

In these initial biomarker analyses, there is an unexpectedly high overlap in the biological characteristics of psychotic diseases across the SZ-psychotic bipolar continuum. Even the phenomenology-based clinical characteristics of symptom manifestations overlap considerably. Although several of the biomarkers show significantly different average values across the proband groups, their individual distributions are nearly coincident, suggesting poor discriminability across these diagnoses.[13] VBM structural characteristics might be the most distinguishing biomarker among these brain measures, with SZ and SAD similar to each other and both showing considerable neocortical reductions from the normal group, but with BDP showing very few significant structural differences from normal. Here, however, an effect of lithium on enhancing cerebral volume has already been shown and lithium is a distinguishing medication with respect to its use in mania, hence this volume effect could be due to prior and differential medication treatment. Surprisingly, clinical symptomatology (ie, phenomenology) of individuals with psychosis distinguished by DSM criteria is highly overlapping and hence these disorders are poorly distinguishable also on phenomenology alone. Medication use is surprisingly similar across these DSM groups, even though there were recognizable differences. There are few categorical distinctions between the DSM groups, of the kind needed to estimate a distinctive biological difference. These data suggest that meaningful distinguishing biomarkers, useful in defining DSM groups of psychosis, are lacking even with a dense biomarker battery, as used in the BSNIP project. The phenomenological distinctions that are often invoked to support diagnostic distinction on a biological basis, when examined as a whole, do not appear to describe distinct diseases. These outcomes are consistent with our early observation that individuals with specific DSM psychosis diagnoses when rated on SCID criteria for both SZ and BD fall along a spectrum without distinct cut points.[11]

One of the stated goals of the BSNIP project has been to test whether the dense collection of phenotypes/

biomarkers will show stronger association to risk genes than to DSM disease constructs. We have begun these genetic analyses, initially using multivariate approaches,[24] and will be able to address this question with time. But, one would have to admit that this goal has already shown limited success as seen in the results of the COGS study,[10] where there were fewer than anticipated significant and clear associations between genes and phenotypes, suggesting that phenotypes at the level of biological detail provided by MRI, EEG, and cognitive testing may be little more straightforward to genotype than psychosis disease constructs. We will consider the possibility that associations between diseases, their biomarkers, and gene pathways, cluster around a brain function abnormality, as relatively more likely. If preliminary findings hold true, we might need to consider a radical overhaul of our nomenclature for psychosis in the future, if indeed, we pursue the naming of disease constructs according to their biological mechanism and associated risk genes.

The NIMH initiative called the RDoC project seeks to categorize cognitive and affective brain functions by neural circuits, as these circuits are used in normal cognitive and affective functions.[8] The RDoC framework will promote the development of neural systems knowledge, at the level of the region, gene, cellular systems and behavior, organized around those normal cerebral functions important to brain health. As a secondary step in examining these normal brain circuits, we will identify the circuits whose pathology could be associated with mental illness, when a gene, cell or circuit of a system is corrupted, the associated behavior altered, and the resultant behavior becomes dysfunctional.

It may take a "pull back" to a broader phenomenological pool, such as "psychosis" as was done in the BSNIP study, to create a heterogeneous enough proband group with a common clinical phenotype, to explore nascent homogeneous subgroups with respect to genetic, molecular, and pharmacological characteristics, that will explain and inform pathophysiological and treatment research to encourage new conceptual understandings.

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