Fig. 1 Incremental human plasma exposure of the P2X7 antagonist JNJ-54175446 caused a dose dependent attenuation of P2X7 dependent ex-vivo IL-1 β release (ex-vivo LPS primed, ex-vivo Bz-ATP as 2nd stimulus) from human subjects (left). The dose of 50 mg JNJ-54175446 produced central target engagement as assessed by displacing the P2X7 PET ligand, [¹⁸F]JNJ-64413739 (right)

and an absence of P2X7 upregulation should not be taken as proof of absence of P2X7 in the disease process. Patients with inflammatory burden and activated immune cells with enhanced IL-1 β and IL-18 signaling, ought to be tested in controlled clinical studies with doses of P2X7 antagonists that satisfy target engagement of brain P2X7 channels in humans.

We have recently disclosed two brain penetrant P2X7 antagonists in JNJ-54175446 [3] and JNJ-55308942 [4]. In a phase I single ascending dose study in human subjects, JNJ-54175446 demonstrated dose dependent increases in plasma exposure, CSF exposure and ex-vivo inhibition of IL-1 β from human blood (Fig. 1) [5]; more importantly, the P2X7 antagonist demonstrated robust occupancy at the human brain P2X7 as was assessed by a PET study (Fig. 1) [6]. Preliminary data from two Phase 1 human experimental medicine studies indicates a central effect of JNJ-54175446 in sleep deprived

and amphetamine challenged human subjects (ACNP 2018) setting the stage for proof of concept testing in treatment resistant depression (<http://www.isrctn.com/ISRCTN44411633>). We remain optimistic based on the preclinical body of evidence that P2X7 antagonism will bring in novel therapeutic options for patients and their physicians, either as mono/adjunctive therapies to address the unmet need in neuropsychiatry.

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ADDITIONAL INFORMATION

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Biological fingerprints for psychosis

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It is generally acknowledged that once the nosology of psychiatric disorders finds a basis in neurobiology, the field will be more successful at specifying, finding treatments, and predicting outcomes for psychiatric conditions.

THE NEED FOR BIOLOGY-BASED PARSING IN PSYCHOSIS

Leaders in psychiatry have called for biologic characteristics to be the basis for designating psychiatric diagnostic groups. Most

recent efforts have focused on genetics for biological classification, despite the weak genetic effects for the psychoses [1]. Geneticists themselves have concluded that their results “strongly suggest that our diagnostic categories do not define pathophysiological entities” [2]. Therefore, seeking clues to biology, we have turned to a comprehensive characterization of quantitative behavioral, cognitive, electro-physiologic, and imaging traits (each with some but not complete biological understanding) in a cross-diagnostic psychosis population.

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Fig. 1 Psychosis is a defining characteristic of schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, all mechanistically complex syndromes. These clinical syndromes were not distinguishable by the B-SNIP biomarker panel, with >70 individual biomarkers. Psychosis subjects, therefore, were combined into a single group, independent of conventional diagnosis. Then, biomarker variables were used to define subgroups with shared neurobiological variance. Two biomarker dimensions, “cognitive control” and “sensorimotor reactivity,” provided a means for creating biomarker-defined subgroups (called psychosis Biotypes). Biotype-1, -2, and -3 had distinctive neurobiological characteristics, including on variables *not* used in their definition (external validators). Within each Biotype, the level of cognition (see color intensity) can vary from low to high. Neural characteristics as they segregate in these groups could be the basis for distinct molecular and therapeutic targets

B-SNIP EXPERIENCE AND REPLICATION

The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) began by seeking quantitative markers for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition)-defined psychoses in 933 probands, and 1059 relatives with 459 healthy controls (HCs) [3]. Finding no markers strong enough for diagnostic distinctions [4], we proceeded to use computational approaches to develop biologically based clusters of psychosis probands from these deep phenotyping data. Using principal component analysis and *k*-means clustering, three distinct groups emerged, named Biotype-1, -2, and -3 (B-1; B-2; B-3). The groups show distinct biological characteristics: B-1 has *low* electroencephalography (EEG) power, profound cognitive dysfunction, gray matter reductions throughout neocortex, and reduced abstract thinking. B-2 has *high* EEG power, moderate cognitive dysfunction, a reduction in fronto-temporal gray matter volume, and increased thought disorder. B-3 is mostly normal on these features, with EEG power and cognition similar to the HCs and a distribution of gray matter reduction limited to limbic cortex, albeit with mild psychosis [5]. Four years later in an entirely new, well-phenotyped sample with 919 probands, remarkably high Biotype replication was found with the original sample with intraclass correlation coefficients of 0.85–0.90 [6].

PHENOMENOLOGICAL AND BIOLOGICAL GROUPS ARE ORTHOGONAL

Each psychosis Biotype includes individuals with representative DSM-5 psychosis diagnoses, with biomarker characteristics falling orthogonal to conventional diagnoses, with each of the Biotypes containing all conventional diagnoses. Biological variability is still not low within Biotypes and we predict more subgroups within each Biotype. We describe, as well, a common complex cognition measure that includes cognition determinants, cognition measures,

and biological correlates of cognition, potentially creating distinctive sub-classes within Biotypes (Fig. 1).

IT TAKES A BIOMARKER BATTERY FOR COMPREHENSIVE COVERAGE

To develop these large cross-cutting psychosis Biotypes took a *biomarker battery*, not just single biomarkers, a battery broad enough to capture neural complexity in the psychosis phenotype. Many different disorders likely reside within each Biotype, suggesting that these three organizing Biotypes are analogous to finding the overarching categories of *Dropsey*, with “cardiac,” “pulmonary,” and “renal” determinants.

MOVING FORWARD WITH BIOLOGICALLY BASED HYPOTHESES

The usefulness of these Biotypes for clinical care and disease understanding needs to be demonstrated, to establish that biomarker clusters predict treatments, correlate with disease, or define a genetic fingerprint. Moreover, we predict that these Biotypes will guide our search for pathophysiology, even though biomarker biology is not completely worked out. We see all of these applications as the goal of this work and anticipate breakthroughs based on biomarker-guided studies.

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Selection criteria for neurophysiologic biomarkers to accelerate the pace of CNS therapeutic development

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In recent years, the field of psychiatric neuroscience has generated numerous biological markers that have contributed to our understanding of central nervous system disorders. Despite the abundance of available “biomarkers” [1] and improved understanding of pathophysiology, drugs for the treatment of Alzheimer's Disease, schizophrenia, and other CNS disorders continue to fail at high rates and at substantial cost (e.g., aducanab and encenidine). In the preclinical stages of development, many assays, including those that purport to measure the same underlying cognitive constructs across species, have limited evidence for predicting responses in humans. Promising drugs graduate from preclinical to later clinical stages of development and are tested on broad diagnosis-based cohorts, without consideration of individual variations in the brain functions that govern treatment sensitivity. This “one-size-fits-all” approach limits the ability to differentiate treatment-sensitive individuals who may be hidden among non-responders in conventional group level analyses [2].

To address these and other limitations, NIH and/or FDA have established future research frameworks (e.g., Research Domain Criteria) and called for translational biomarkers that can rapidly detect treatment sensitivity and/or early response to interventions and thereby accelerate the development of novel therapeutics [1]. Based on prior review processes for selecting cognitive tests for clinical trials [3], we propose an expanded set of criteria (Table 1) for neurophysiologic measures that can be broadly used across multiple categories of biomarkers and surrogate endpoints including pharmacodynamic/response, predictive, prognostic, monitoring, and susceptibility/risk [1].

Proposed criteria for candidate translational neurophysiologic biomarkers have admittedly high standards for established psychometric properties and functional characteristics, applicable to both infra-human and human versions of the measures. Early “target engagement” identified in single-dose or limited-dose experimental medicine designs is both feasible [2, 4, 5] and particularly valuable but may not generalize across settings. Since the type and calibration of equipment, as well as data processing and analysis methods all can have a substantial impact on

psychometric properties, criteria established on one testing platform may not be applicable to another. For example, results obtained from high-density EEG recordings with advanced signal processing algorithms that leverage spatiotemporal relationships for sophisticated artifact reduction and analysis may not generalize to lower-fidelity recording systems with much more limited signal processing options.

While preclinical assays are often used in specialized laboratories, validation of human response homology tested in less controlled, real-world clinical trial environments is an important next-step for validation. Some translational neurophysiologic measures already fulfill all or many of the Table 1 criteria, including mismatch negativity (MMN), P3a, auditory steady state response (ASSR) and prepulse inhibition of startle (PPI), and have been used effectively in experimental medicine designs [2, 4, 5] and multi-site consortia [6]. Notably, even high-density EEG assessments can be feasibly scaled up for valid use in multi-center trials with proper training and centralized data processing and management.

We propose an initial set of criteria to guide development of neurophysiologic biomarkers for predicting psychotherapeutic sensitivity. These criteria offer the potential to advance treatments for major brain disorders beyond the “one-size-fits-all” approach based on fuzzy diagnostic categories, towards a more precise, personalized, and biologically informed strategy for matching CNS interventions with sensitive patient subgroups.

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