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Authors

Light, Gregory A
Joshi, Yash B
Molina, Juan L
et al.

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Neurophysiological biomarkers for schizophrenia therapeutics

Gregory A. Light [a,b,*], Yash B. Joshi [a,b], Juan L. Molina [a], Savita G. Bhakta [a], John A. Nungaray [a], Lauren Cardoso [a], Juliana E. Kotz [a], Michael L. Thomas [c], Neal R. Swerdlow [a]

[a] Department of Psychiatry, 0804, University of California, San Diego, La Jolla, CA, 92093, United States
[b] VA Desert Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, United States
[c] Department of Psychology, Colorado State University, Fort Collins, CO, 80523, United States

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ABSTRACT

Chronic psychotic disorders, including schizophrenia (SZ), are highly heterogeneous at many levels of analysis, from genetics to clinical presentation and treatment sensitivity. This heterogeneity reflects both a divergence of shared biological pathways moving from over a hundred "risk genes" to many different clinical phenotypes, and the convergence of distinct biological pathways to a shared "phenocopies" of chronic psychosis. Successful strategies for developing "next generation" interventions in SZ – including "pro-cognitive" medications, cognitive remediation, neurostimulation and combinations thereof – will address these pathways to clinical heterogeneity by using biological signals, or "biomarkers" that characterize treatment-sensitive subpopulations. Identifying and detecting these meaningful signals in the complex biology of SZ is a vexing scientific challenge. We propose that rational starting points are neurophysiological measures of early auditory information processing (EAIP), based on their functional importance as strong mediators of both cognition and function in SZ, their plasticity in response to both pharmacologic and non-pharmacologic therapeutic "challenge", and their experimental characteristics as highly quantitative, robust and reliable measures of brain activity. Here we describe some of our current approaches to developing neurophysiological biomarkers for "next generation" therapeutic sensitivity in SZ, and some potentially novel experimental strategies that we envision on the near horizon.

Introduction

Despite the substantial resources devoted to understanding the biology and therapeutics of SZ, we still have a long way to go. There is both irony and tragedy in the fact that it took major advances in psychiatric genomics [1] to convince many in our field of the fact that "the schizophrenias" are a heterogeneous and complex group of syndromes, reflecting perhaps a small number of common endpoints for a much larger number of distinct causative biological pathways. Some of these common endpoints, such as subcortical dopamine (DA D2r) hyperfunction, and cortical DA (D1r) and perhaps N-methyl-D-aspartate hypofunction, have been targets for SZ therapeutics. Definitive multi-site studies including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) have demonstrated that drugs primarily targeting subcortical D2r activity have minimal impact on neurocognitive and functional deficits in SZ patients, and more limited trials with drugs targeting either cortical D1 or NMDA hypofunction have not yet yielded consistently promising results [2].

We should not be surprised by the challenges of clinical trials aimed at treating a complex clinical phenotype that has a highly heterogeneous biology. Indeed, the heterogeneity within any study cohort of psychotic patients reflects both a *divergence of shared biological pathways* moving from genotype to phenotype (producing, for example, shared genetic determinants of bipolar disorders and schizophrenias), and the *convergence of distinct biological pathways* to a shared phenotype (and hence the many distinct clinical pathways to psychosis – affective disorders, dementias, SZ, Parkinson's Disease, etc.). In order to detect biologically meaningful sub-populations within any SZ cohort that share by virtue of that biology a common therapeutic sensitivity, we will need measures that are sufficiently distal to these points of genetic divergence, yet proximal to the points of clinical convergence. We have proposed optimal characteristics for such measures (Table 1, modified from Light and Swerdlow [3]), and specifically suggested that neurophysiological measures of early auditory information processing (EAIP) – employed within experimental medicine or related study designs – might prove useful in detecting biologically and therapeutically meaningful subgroups of SZ patients [4,5].

All prevailing biological models for the genesis of mental illness incorporate, to some degree, dysfunction within neural circuitry; models

E-mail address: glight@ucsd.edu (G.A. Light).

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Table 1
Proposed Criteria for Neurophysiologic Biomarkers, adapted from Light & Swerdlow [73].

Psychometric Properties of Translational Biomarkers
• Substantial Test-Retest Reliability (intraclass correlations>0.8)
• Suitable for use as a repeated measure (i.e., no practice, maturation, instrumentation, testing or statistical regression effects)
Functional Characteristics
• Early sensitivity to single- or limited "doses" of pharmacologic agents, cognitive training or other CNS interventions
• Consistent relationships to important domains of clinical, cognitive and/or psychosocial functioning
Scalable for Use in Real-World Multi-Site Global Clinical Trial Settings
• Equipment uses identical interchangeable calibrated systems and components
• Measures are robust to variations in testers and testing environments
• Tests can be administered by non-specialists with appropriate training, certification, and oversight
• Does not require special testing environments, suitable for valid use in varied settings
• Objective automated analysis methods that are amenable to centralized blinded data processing

specifically focused on the genesis of SZ incorporate neural circuitry that regulates cognitive function and information processing that are known to be deficient in these disorders. Thus, neurophysiological measures of neural circuits regulating such "core" functions might be likely to yield signals that are informative regarding biological subgroups of SZ patients. The literature has described a number of neurophysiological and psychophysiological measures that detect deficits in SZ patients. The present review will focus more narrowly on a select group of these measures. Importantly, different measures and measurement characteristics best serve different experimental purposes, and the measures and their specific applications for therapeutic development for SZ would be expected to differ from those that might be optimally applied, for example, as endophenotypes for identifying SZ risk genes [6].

We previously noted that in the development of novel therapeutics for SZ it is important to consider the degree to which neural targets retain their plasticity (i.e. capacity for change). Intact plasticity might indicate capacity for positive change, given an appropriate intervention and based on the heterogeneous biology of SZ, it is very likely that the amount of meaningful plasticity retained will differ greatly across patients and across brain circuitries. Thus, a biomarker to identify retained plasticity among individual SZ patients, within cognition-relevant brain mechanisms, could be critically important for stratifying patients into groups that are more vs. less likely to show clinical, and specifically neurocognitive, gains in response to specific interventions.

Early auditory information processing: biomarker for drug sensitivity?

In our recent study of 1415 subjects who participated in the Consortium on the Genetics of Schizophrenia-2 (COGS-2), Thomas et al. [7] confirmed that neurophysiological measures of early auditory information processing (EAIP) had consistent bivariate relationships to important domains of cognition, symptoms, and functioning, consistent with many other studies [8–29]. The measures of EAIP in this study were amplitudes extracted from the passively evoked "auditory deviance response complex," a triphasic event-related potential (ERP) waveform consisting of MMN, P3a, and reorienting negativity (RON) components [28]. These 3 components are sequentially and automatically evoked in response to unattended, deviant sounds that are presented within the context of repetitive, identical sounds. Using structural equation modeling (SEM), we found that these preattentive EAIP measures had a direct causal effect on cognition, which in turn had a direct impact on negative symptoms; both cognition and negative symptoms demonstrated direct effects on functional outcome (Fig. 1). The cascading impact of EAIP on functional outcome was achieved via the engagement of general rather than modality (auditory)-specific cognition, indicating that measures of auditory information processing were not selectively more related to auditory-based measures of cognition. SEM predicts that a 1 μV change in this auditory deviance response complex should yield improvements of at least d = 0.78 in global cognition and an accompanying small-to-medium effect size improvement on psychosocial functioning. While the time-course and conditions necessary to support such cognitive and functional benefit in relation to increased EAIP is not known, these findings nonetheless suggest that interventions that can reliably enhance measures of EAIP in SZ patients are rational "targets" for therapeutic development.

Implicit in this line of thinking is that, at least in some subgroups of SZ patients, EAIP will retain enough plasticity to be "moved" by targeted therapeutics. One way to identify intact plasticity within EAIP or other cognition-relevant brain mechanisms is to "challenge" those mechanisms via a perturbation- pharmacologic or otherwise. The use of a drug challenge to identify enriched, sensitive subgroups of patients parallels the common use of a "test dose" to predict clinical benefit from interventions ranging from hormones [30] to anti-Parkinsonian therapies

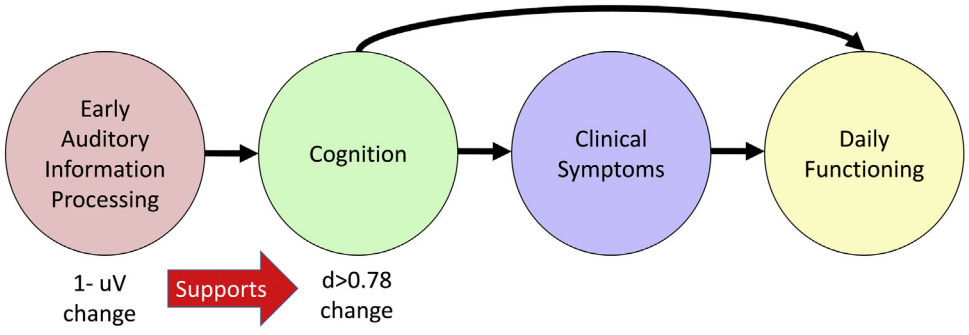

Fig. 1. Hierarchical information processing cascade: Pathways from Early Auditory Information Processing to Cognition, Symptoms, and Daily Functioning.
Simplified diagram of the path model presented by Thomas et al. [7] . Arrows suggest causal pathways between constructs (ovals). Cognition has both direct and indirect (mediated) effects on daily functioning. A 1-uV change in early auditory information processing is expected to produce large improvements in cognition, which in turn is expected to reduce clinical symptoms and improve daily functioning.

[31] to bronchodilators [32]; it is an established way to acutely probe for healthy biological mechanisms that might be leveraged in the service of therapeutics. Of course, the selection of the "probe" becomes a critical step in the success of this strategy. We can provide two examples in which targeting EAIP with a potential therapeutic intervention elicited a "signal" suggesting both plasticity and therapeutic sensitivity.

In one example, we examined changes in EAIP after an acute drug challenge in SZ patients and healthy subjects (HS). Memantine is an uncompetitive NMDA receptor antagonist with low-affinity but rapid blocking and unblocking ability. It has little impact on basal NMDA transmission; this distinguishes it mechanistically from other NMDA antagonists [33]. It has a number of neurophysiological effects in models relevant to SZ, including changes in excitation/inhibition (E/I) dynamics in frontal circuitry [34] which will be discussed below. In 2007, Korostenskaja et al. [35] reported that acute challenge with memantine increased MMN in HS by 0.91 μV – which, based on Thomas et al. [7] should be enough to produce clinically significant effect-size increases in cognition.

We studied the acute effects of memantine on measures of EAIP in chronic, antipsychotic (AP)-medicated SZ patients and HS. In addition to MMN, we measured two other promising measures of EAIP: prepulse inhibition of acoustic startle (PPI) and the auditory steady state response (ASSR). Details of the methods can be found in the original data reports [36,37]. For each of the EAIP measures, memantine "improved" performance levels, i.e. moved them in a direction associated with less pathology. Importantly, while in this group of patients there were significant deficits in MMN and ASSR, their PPI was quantitatively intact (consistent with the fact that all were AP-medicated, and almost all were taking 2nd-generation AP's, which are known to normalize PPI (cf [38].). Thus, memantine's effects were not dependent on deficits in EAIP measures, and were not impacted by AP medication, consistent with the possibility that - at least in the case of PPI - memantine was acting on intact mechanisms that were performing at "normal levels".

These findings demonstrate that EAIP is pharmacologically sensitive, and one inference from the Thomas et al. [7] findings is that under the right conditions, drug-enhanced EAIP might be expected to be associated with improved cognitive, clinical and functional outcome. However, this critical inference has not yet been tested. In fact, the most direct evidence to-date is that, despite gains in EAIP after one pill of memantine in SZ patients, measures 240 min post-pill detected a non-specific *reduction* in cognitive performance among HS and no significant gains among patients [39]. We previously offered several possible explanations for this apparent incongruence of acute memantine response on EAIP and cognitive performance. Most importantly, the strong mediating effect of EAIP on cognition and function observed in our COGS-2 study was detected at a single point in time [7], typically decades after the onset of illness. Thus, the relationships detected in these mediating effects evolved over decades, making it very unlikely that a transient change in EAIP after a single pill will lead to an instantaneous improvement in cognition, i.e. an "awakening".

Conceivably, gains at many intermediate steps between enhanced EAIP and neurocognition– such as gains in the fidelity of an auditory signal, or gains in the amount of information capacity of that auditory signal – might be detected long before the gains trickle up to impact more complex integrative neurocognitive functions. We recently had the opportunity to examine this prediction in a separate cohort of patients and HS, by assessing more "functional" effects of memantine in SZ patients, which might represent the "downstream" effects of enhanced EAIP. These studies remain in progress and are reported only in abstract form (Swerdlow et al., 2019), but in two cases – behavioral measures of auditory discrimination ("Words-in-Noise"), and measures of auditory perceptual learning within a frequency modulation "sound sweeps" paradigm – showed a memantine enhancement of these higher functions and associated with gains in EAIP. It is thus conceivable that these changes reflect processes intermediate between enhanced EAIP and gains in neurocognition and global function, and also reveal the available plasticity within auditory discrimination and learning processes in these patients. We have previously reported similar gains in auditory discrimination and learning in SZ patients after acute challenge with the psychostimulant amphetamine; these changes were moderated by baseline attention and vigilance (A/V) measures: patients with the lowest baseline A/V scores (MATRICS Comprehensive Cognitive Battery: MCCB) had the biggest amphetamine-induced gains in auditory discrimination and learning.

EAIP biomarker sensitivity to even non-pharmacologic interventions: cognitive training?

It is also possible to use a non-pharamacological "challenge test" to identify neurophysiological evidence of therapeutically-accessible plasticity. Perez et al. [40] demonstrated that baseline MMN significantly predicted auditory learning in this same frequency modulation "sound sweeps" paradigm, which is part of a larger suite of exercises within the targeted cognitive training (TCT) program, "Posit Science" [41,42]. While TCT is an efficacious treatment for cognitive functioning in SZ at the group level, individual gains from TCT vary considerably: up to 45% of SZ patients fail to benefit ($d \leq 0.2$ [43,44];), even after an extended 100 h course of TCT [45]. Given the high rate of TCT "non-response", and the modest overall effect sizes, the costs and logistical impediments associated with getting severely ill chronic psychosis patients to complete three 1 h sessions of TCT per week for 10–20 weeks can be prohibitive. In a recent study of treatment-refractory schizophrenia patients mandated to long-term locked care, Hochberger et al. [46] demonstrated that changes in EAIP after 1 h of sound sweeps strongly predicted both neurocognitive and clinical gains after a 30 h therapeutic trial of TCT administered over a 3 month period. In other words, EAIP plasticity after a "challenge dose" of auditory training was a powerful neurophysiological biomarker for sensitivity to therapeutic gains from TCT. These results suggest that performance during a sound sweeps "challenge" could be used to stratify patient subgroups that are much more vs. much less likely to be sensitive to the therapeutic gains from TCT.

Novel approaches to analyzing neurophysiologic EAIP signals: nonlinear dynamics and E/I balance?

New insights about the biological implications of brain electrical activity can occur via novel analytic approaches, and these in turn might produce new candidate biomarkers that are more, or at least differently, informative compared to existing measures. The majority of neurophysiologic studies in neuropsychiatry, including our own, have relied upon conventional, linear approaches to the analysis of EEG signals. These linear methods include standard assessments of peaks and latencies [14,20,47], frequency [48] or time-frequency oscillatory analyses [49,50], and even cross-frequency coupling [51]. While these approaches have been extremely informative, the prevailing focus on a priori determined peaks or frequency ranges may fail to capture rich information contained in whole EEG signals.

Since virtually all natural systems such as the weather, traffic, and brain dynamics have linear and non-linear properties, nonlinear analytic methods may serve as a "Rosetta stone" for decoding complex natural signals, including those of the brain in normal and impaired cohorts. To characterize the large-scale, neural system-level dynamics present in brain electrical activity in patients with SZ, Lainscsek et al. [52] recently applied methods derived from theoretical physics – chaos theory– to assess the nonlinear dynamics underlying EAIP in large groups of healthy subjects and patients with schizophrenia. These nonlinear analyses offer a number of important technical advantages over commonly used ERP measures: they are computationally fast, provide fine temporal resolution (10-ms data windows), and require only minimal preprocessing, so that even very large datasets, as in those from multi-site clinical studies such as the COGS-2 can be analyzed in a matter of minutes rather than days, weeks, or even months. We found significant nonlinear dynamics contribute to EAIP in both SZ patients and healthy subjects. Importantly,

nonlinear changes preceded sensory ERPs in response to frequently presented standard stimuli as well as MMN, P3a, and RON components. Marked abnormalities were detected in both linear and nonlinear features in SZ patients, highlighting the potential benefits of nonlinear analysis of brain signals.

Another promising and non-computationally intensive approach for biomarker development that also captures important features in EEG signals is the quantification of the relative contribution of excitatory and inhibitory functions. In this context, converging evidence from preclinical and translational studies have suggested that disruptions in the relative contributions of excitatory and inhibitory neuronal populations contribute to aberrancies in perception, cognition, and behavior [53,54]. Measuring this "E/I balance" in cortical circuits typically requires invasive electrophysiological recordings, such as electrocorticography in humans and non-human primates or voltage-clamp and local field potential recordings in rodents. The invasiveness of E/I measures has precluded its broader dissemination in studies of human cognition and behavior. Recent work suggests that the aperiodic component, or 1/f slope, of the EEG power spectra may index tonic E/I balance [55,56]. Interestingly, the 1/f slope has been shown to be differentially modulated by clinical states [57] and pharmacologic probes [58].

We recently assessed the effects of memantine on 1/f slopes estimated from measures of EAIP [59]. We found elevated 1/f slopes in SZ, suggestive of an altered E/I balance in the disorder. Similar to our findings in other measures of EAIP, acute administration of memantine had a 'normalizing' effect on 1/f slopes. Interestingly, the observed memantine effect was associated with baseline attention and vigilance. These findings confirmed deficient E/I balance in antipsychotic-medicated SZ patients and suggest that neurocognitive profiles might predict E/I sensitivity to memantine. Conceivably, 1/f slopes may help distinguish subgroups of patients who will most benefit from pharmacologic augmentation of cognitive therapy strategies based on individual variability in E/I tone.

Ways to *make* EAIP-based biomarkers better: ecologically and contextually relevant paradigms

In everyday life we are presented with complex sounds in the environment such as car honks, birds chirping, sound of laughter or baby cry or footsteps etc. We have previously shown that MMN elicited in response to tones is highly related to the ability to identify real-world environmental sounds [14]. Since these complex sound stimuli are processed in ecologically valid contexts, one could postulate that auditory oddball paradigms that evoke or mimic real-life environments might be better at eliciting EAIP-based biomarkers of procognitive treatment response and real-life function. In other words, an auditory oddball paradigm that utilizes contextually-relevant naturalistic sound stimuli might elicit MMN that has better predictive power of sensitivity to real-life clinical gains, compared to MMN generated using artificial and isolated sound fragments (tones). However, to elicit meaningful MMN, millisecond-level stimulus control within a structured test session is essential, which is difficult to obtain in a naturalistic setting. Nonetheless, newer technologies such as virtual reality (VR) offer both the naturalistic context and tight experimental control needed to generate meaningful MMN.

In an ongoing proof of concept study, MMN was successfully generated using contextually-relevant naturalistic sound stimuli in a VR-based oddball paradigm [60]. Likewise, Tromp et al. [61] assessed brain activity during language processing in a virtual restaurant environment that had both auditory and visual mismatch conditions. They reported that participants had greater N400 amplitude during mismatch condition compared to match condition. Collectively, these findings suggest that the rich, ecologically valid settings presented in the VR-based EEG paradigms might further enhance the predictive value of EAIP-based biomarkers for procognitive treatment response and/or real-life function.

Ways to optimize EAIP measurement

Neurophysiologic biomarkers are promising tools for deconstructing the heterogeneous biology of schizophrenia via the identification of therapeutically meaningful subgroups of SZ patients. For EAIP (and other) biomarkers to be more widely used in experimental medicine and innovative clinical trial designs, additional validation and adaptation to improve their performance in real world settings is required.

For validating biomarkers, evaluating their psychometric properties in their intended context of use is an important "next-step." For example, ensuring that the measures are both reliably measured and appropriate for use in a repeated design (i.e., no practice, maturation, or regression effects) is essential. Assuming that the measure is a convincing index of the process that is being assessed, test-retest reliability is another necessary precondition for valid use. Simply documenting "statistically significant" reliability is not sufficient. In this context, measures with higher test-retest reliability may also be more sensitive to detect small changes in brain function attributable to acute or prolonged exposure to an intervention. Reliability has a direct impact on statistical power – measures with higher reliability require fewer numbers of subjects and sites needed in clinical trial studies (Fig. 2). Given the substantial expense associated with clinical trials, even incremental improvements in reliability coefficients can ultimately save money, time, and the good will of difficult-to-recruit patient populations.

In light of the growing importance of the measures themselves and their psychometric properties, there are likely opportunities to improve their "performance" further. For example, even if an EAIP measure from a single electrode is defined as an outcome measure, higher EEG channel counts (~64 channels) allow for more precise separation of meaningful brain signals from sources of noise. This noise reduction yields both improved reliability as well as sensitivity to group deficits and clinical, cognitive, and functional correlates [28]. As a secondary benefit, the higher density EEG recordings also allow for improving the understanding of changes in neural substrates associated with the intervention. For example, source analysis can be used to demonstrate neural system target engagement and affected brain networks at the group level [65]. High density EEG recordings also permit the quantification of source-level ERPs at the individual subject level for future biomarker-guided

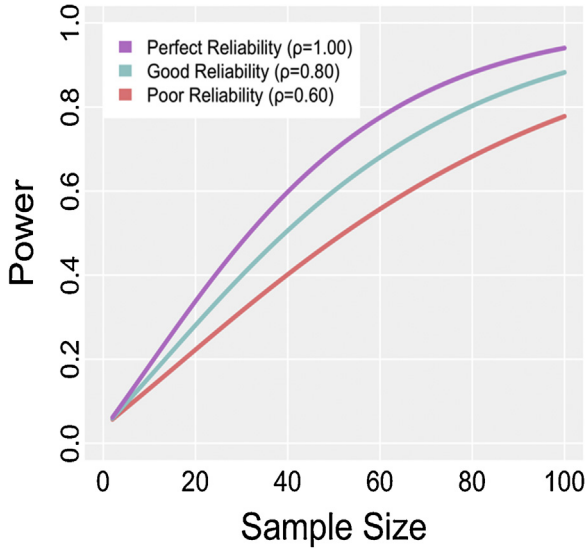

Fig. 2. Impact of Reliability on Statistical Power and Sample Size Requirements. **To generate this figure, a true effect size of Cohen's d = .50 (medium) was assumed. We then attenuated the effect size based on perfect (1.00), good (0.80), or poor (0.60) reliability [62,63], resulting in attenuated values of d = .50, d = .45, and d = .39 respectively. Finally, we calculated power using the R pwr package [64] for sample sizes ranging from 2 through 100 (α = .05).**

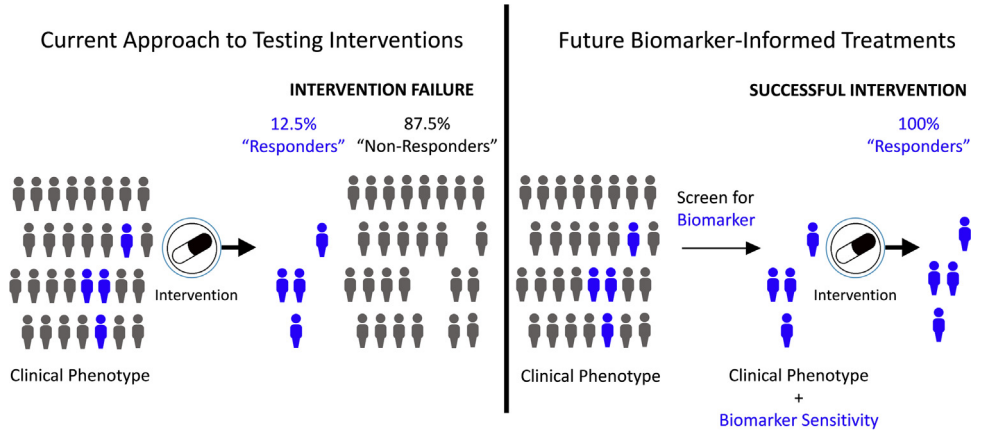

Fig. 3. Future Biomarker Informed Approach to Personalized Treatments.
Current treatments use a "one-size-fits-all" approach for assigning treatments to a heterogeneous group of patients, only a subgroup of whom will ultimately benefit (left panel). By contrast, using biomarkers to identify "sensitive" (and thereby also identifying "non-sensitive") individuals at the outset of treatment will allow the "right patient" to receive the "right treatment." Such a biomarker informed approach can also accelerate the pace of CNS therapeutic development.

assignments to treatments [66]. Lastly, multivariate composite measures may "outperform" single measures for predicting therapeutic gains.

In this context, we [50] recently found that a multivariate composite index of EEG variables improved the prediction of clinical and cognitive gains in SZ patients who underwent a 3-month cognitive remediation trial. This regression-weighted composite measure was derived from individual treatment outcome coefficients for MMN and P3a amplitudes and latencies as well as theta evoked power. Importantly, this single measure yielded a clinically applicable cutoff score with excellent sensitivity (91%) and specificity (80%). Such multivariate composite scores show tremendous promise for application in future biomarker-guided assignment to procognitive therapeutic interventions.

Despite enthusiasm for the more widespread use of neurophysiologic and other biomarkers in drug development, some caveats should be considered. First, given the absence of potential disease modifying agents, biomarker defined subgroups may not correspond to current diagnostic boundaries. On the other hand, MMN and other EAIP abnormalities are present across multiple neuropsychiatric patient populations [67], they may be readily amenable for application in transdiagnostic cohorts or subgroups defined based on sensitivity to an intervention rather than current DSM-defined disorders. Second, it is important to recognize that a mechanistic understanding of some novel metrics extracted from biomarkers (e.g., nonlinear dynamics, E/I balance measures, source level ERPs, multivariate composite index) is not yet available. Counterintuitive or even paradoxical effects (e.g. [40]) may occur in early-stage discovery science while awaiting mechanistic examinations [65]. Third, the desire to simplify the recording systems for the perceived benefit of improving scalability may ultimately be counterproductive to therapeutic development, since the resulting compromise in psychometrics and ability to understand mechanistic or neural substrates underlying therapeutic response could ultimately undermine efforts for continued development of the intervention.

Ways to *integrate* EAIP-based biomarkers better into clinical trials?

As noted above, the use of a biological signal (biomarker) together with a therapeutic challenge to identify sensitive clinical subgroups has been applied in multiple fields including endocrinology, neurology and pulmonary medicine. Once EAIP-based biomarkers are identified and suitably developed, they may be implemented in SZ clinical trials in similar ways. First, EAIP-based biomarkers might be used to select "enriched" SZ subgroups for trials testing novel pro-cognitive therapeutics. Patients demonstrating EAIP sensitivity in response to a pro-cognitive challenge would be included in such trials, while those who do not—whose neural substrates (as reflected by EAIP) are insensitive to the pro-cognitive intervention—would be directed toward other options. Using such an "EAIP-screen and stratification" model, where an EAIP threshold is used for selecting subjects, may help reduce heterogeneity and enhance the ability to detect therapeutic effects (see Fig. 3).

Aside from screening and stratifying subjects to test individual interventions, biomarkers can help enhance larger trials that aim to compare multiple different interventions, across multiple different subgroups of disease [68]. We can look to oncology where a variety of molecular biomarkers are used to identify and optimize novel anti-neoplastic strategies in study designs called "basket" and "umbrella" trials. Like schizophrenia, difficult-to-treat cancers are marked by convergence of distinct biochemical pathways that lead to an evolution of a phenomenologically common disease state. *Basket trials* assess the efficacy of a drug based on the molecular mechanism rather than origin. Thus, a neoplastic drug that targets a specific mutation would be given to cohorts, or "baskets," of patients with different cancers (i.e., lung, breast, prostate, etc.) that share the same underlying molecular pathology [69]. Similarly, in a basket trial for patients with psychotic disorders, EAIP biomarkers can help select individuals sensitive to pro-cognitive interventions regardless of diagnoses (i.e., across schizophrenia, schizoaffective disorder, and bipolar disorder). By contrast, *umbrella trials* take patients with the same type of cancer, and triage them to different treatments based on unique mutations— every treatment is a spoke of a larger "umbrella" of therapeutics being tested.

One such example is the National Cancer Institute's MATCH trial which recruits patients with advanced tumors, and after extensive genotyping, assigns participants to one of many different therapeutics [70]. In an umbrella trial for schizophrenia, EAIP biomarkers could be used to assign SZ patients to treatment arms that target cognitive impairment in different ways. In such a trial, EAIP-sensitive SZ patients would receive an EAIP-enhancing cognitive drug, EAIP-equivocal patients may receive cognitive remediation, and EAIP-insensitive individuals might receive intensive psychosocial services and support. Our current "one-size fits all" models for clinical trial design may not be optimal. New designs such as basket or umbrella trials discussed above, adaptive designs [71] may be more amenable for biomarker-guided development of novel treatments for schizophrenia and related disorders.

Conclusion

Despite substantial progress in our understanding of chronic psychotic disorders, we still lack pharmacologic treatments for the disabling cognitive impairments. Providers must still rely on careful behavioral

observation and interview techniques to make inferences about patients' inner experiences. Few (if any) objective measures (laboratory, imaging, cognitive) have graduated from our academic laboratories for valid use in real-world clinical settings to guide treatment decisions. Compared to clinical phenotypes, neurophysiological biomarkers of early auditory information processing may be more proximal to pathophysiologic mechanisms and demonstrate sensitivity to pharmacologic and non-pharmacologic interventions. Further, these neurophysiologic biomarkers index plasticity mechanisms in targeted neural systems that could be leveraged to stratify patients into appropriate interventions. Biomarkers will inevitably accelerate the development of novel CNS therapeutics and move us from the current "one-size-fits-all" approach to clinical trial designs into a new era of precision psychiatry [72].

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* Corresponding author at: UCSD Department of Psychiatry, 9500 Gilman Dr., La Jolla, CA, 92093-0804, United States.
E-mail address: glight@ucsd.edu (G.A. Light).