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Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia

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Abstract

Advances in psychiatric neuroscience have transformed our understanding of impaired and spared brain functions in psychotic illnesses. Despite substantial progress, few if any laboratory tests have graduated to clinics to inform diagnoses, guide treatments, and monitor treatment response. Providers must rely on careful behavioral observation and interview techniques to make inferences about patients' inner experiences and then secondary deductions about impacted neural systems. Development of more effective treatments has also been hindered by a lack of translational quantitative biomarkers that can span the brain–behavior–treatment knowledge gap. Here, we describe an example of a simple, low-cost, and translatable electroencephalography (EEG) measure that offers promise for improving our understanding and treatment of psychotic illnesses: mismatch negativity (MMN). MMN is sensitive to and/or predicts response to some pharmacologic and non-pharmacologic interventions and accounts for substantial portions of variance in clinical, cognitive, and psychosocial functioning in schizophrenia. This measure has recently been validated for use in large-scale multisite clinical studies of schizophrenia. Lastly, MMN greatly improves our ability to forecast which individuals at high clinical risk actually develop a psychotic illness. These attributes suggest that MMN can contribute to personalized biomarker-guided treatment strategies aimed at ameliorating or even preventing the onset of psychosis.

Keywords

biomarker; cognitive remediation; mismatch negativity; neurocognition; schizophrenia

Introduction

Biomarkers are objective measures that can provide information on a variety of different clinical characteristics, such as an individual's normal biology, pathology including the trajectory of illness, or the response to a therapeutic intervention. While it is clear that

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Conflicts of interest

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symptom-based diagnostic schema can distinguish patients in a manner that predicts their trajectory and therapeutic sensitivity (e.g., in the parsing of a primary anxiety versus psychotic disorder), it is equally apparent that these schema have reached their limits of resolution with respect to pathophysiology and the development of novel and individualized therapeutics.

Biomarkers offer the hope that, despite great heterogeneity and multivariate interactions in the pathogenesis of brain disorders, objective measures will identify clusters of individuals that can then be reliably stratified on the basis of the cause, course, and/or treatment sensitivity of a given disorder. Of course, this hope is not new—the search for biomarkers for mental illness can be traced back decades and perhaps centuries—nor is it a hope fulfilled, as we presently lack biomarkers that contribute in a meaningful way to our treatment of any major psychiatric syndrome.

In this paper, we provide an overview of biomarkers and their potential utility for improving our understanding and treatment of psychotic disorders. Many neurophysiological biomarkers have already undergone extensive validation and may contribute to the development of next-generation therapeutics,[1] including mismatch negativity (MMN[2,3]), P300,[4] auditory brainstem event-related potentials,[5] and electroencephalography (EEG) measures of oscillatory dynamics,6–11,[a] as well as prepulse inhibition (PPI) of the acoustic startle response.[12,13] Here, we focus on MMN as an example of a simple, low-cost, translatable, and automatically elicited EEG biomarker. This measure has provided valuable insights into impaired and spared sensory processing in schizophrenia (SZ), with robust relationships to important domains of functioning. We also discuss a strategy for a rational coupling of biomarker performance with cognitive therapies for personalized assignment to treatments that alter the course or even prevent the development of psychosis in children at ultra-high clinical risk.

Biomarkers of pathology versus health

One assumption driving the search for psychiatric biomarkers is that their neural and genomic substrates will be simpler, more easily understood, and less heterogeneous than the biology of the clinical psychiatric syndrome. Since the pathogenic pathways leading to the syndrome are highly heterogeneous, we might expect that the biomarkers for these pathways will be similarly varied. For this reason, we have endorsed an approach in which biomarkers in psychiatric disorders are used not to identify pathological processes but rather intact healthy processes (e.g., brain circuitry). Although pathology biomarkers have been highly informative for understanding the neural and genomic heterogeneity of neuropsychiatric disorders and appear promising for the identification of individuals at ultra-high risk for developing psychosis (as described further below), biomarkers of spared functions offer some unique advantages for interpretation and application. For example, it is in many ways easier to interpret a biomarker of health than one of pathology. In a simple analogy, if you enter a room, flip on the light switch and no light turns on, there can be numerous

[a]See also Siegel *et al*., Javitt, and Digavalli in the current *Ann. N.Y. Acad. Sci.* volume entitled Translational Neuroscience in Psychiatry: Light at the End of the Tunnel.

explanations for this deficit. However, if you flip on the light switch and the light does go on, there can be only one parsimonious explanation: electrons are going to where they need to be.

It is not that biomarkers of health are simpler to understand but rather that they may be more actionable (i.e., biomarkers of healthy brain function in system X might provide more direct evidence that a patient with SZ is likely to benefit therapeutically from intervention Y). Several clinical models support this approach. For example, many interventions in stroke rehabilitation are designed not to re-grow brain circuitry that is lost or damaged, but rather to engage the normal physiological and anatomical properties of healthy brain circuits (e.g., in neighboring regions or parallel circuits) to restore or subsume the function of damaged ones.[14] In many forms of psychotherapy, the therapist's task is to identify an individual's psychological strengths (ego, intellectual, social, or otherwise) and then to engage them to overcome damaging thoughts or behaviors that are otherwise sustained by areas of psychological weakness. At a neural level, both stroke rehabilitation and psychotherapy engage viable and healthy systems to compensate for, or re-establish, functions lost to illness. Similarly, biomarkers of health can reveal a patient's neural assets, which can then be leveraged in the service of therapy. There are several hurdles to clear in this process, including that (1) it requires biomarkers that identify these assets with sufficient sensitivity, specificity, and other limits of resolution discussed below, and (2) it requires therapies that can engage these assets to improve function. There is growing evidence that both of these hurdles can be cleared.

For example, as discussed further below, robust, reliable, and repeatable measures can quantify working memory (WM) in SZ patients. Certain cognitive therapies place demands on SZ patients to engage WM to develop compensatory strategies for learning and applying information. In so doing, these therapies specifically activate prefrontal regions subserving WM and attention.[15] It is both parsimonious and testable that patients with the available neural asset of relatively intact WM, demonstrated laboratory measures, and hence frontal circuits that subserve WM, will benefit most from cognitive therapies that depend on WM.

Schizophrenia biomarker findings: Is the glass half-empty or half-full?

What is the likelihood of identifying healthy biomarkers in patients who are suffering from obvious brain dysfunction associated with profound functional impairment? We view this likelihood to be substantial: even with the most robust biomarkers suggesting pathology in the most severe cohorts of chronic SZ patients, many and sometimes most patients score in the normal range. This is true in markers using volumetric or functional neuroimaging, neurophysiology (reviewed in Ref. 16), or even neurocognition where up to 25% of patients exhibit normal performance across an extensive battery of cognitive tests.[17]

Biomarkers that identify differences with a Cohen's standardized effect size of d = 1.0 in SZ patients versus healthy comparison subjects are generally considered robust; in fact, most of the highly replicable SZ biomarkers fail to reach this level of group separation (Fig. 1). Notably, falling one standard deviation below normative samples (i.e., effect size of d = 1.0) is commonly used as a cutoff for impairment classification in neuropsychological

assessments. This means that even in the case of a d = 1.0 biomarker impairment, 50% of patients will by definition fall within the normal range (Fig. 2)—a largely overlooked or even misunderstood fact. Moreover, in this best-case example of a pathology biomarker, only 54.5% of the patient versus healthy group distributions are non-overlapping. Whether the metric is hippocampal volume,[18] PPI,[12,19,20] WM,[21,22] oscillatory dynamics,[a] or MMN, 1,3,23–30,[a] some or even most SZ patients exhibit evidence of intact function: the light switch works, and thus the neural assets can conceivably be applied toward a therapeutic response.

The search for biomarkers of health does not imply that we simply forego therapeutic options for patients whose biomarkers suggest a lack of health. Given the heterogeneity of performance across measures, it is often the case that patients exhibiting deficits in one biomarker or neural domain will perform normally in others. Indeed, many of the common neurophysiological biomarkers and endophenotypes of SZ are uncorrelated with one another even when measuring similar operational constructs (e.g., sensory versus sensorimotor gating,[19,31,32] sensory discrimination[29,30,33]). The key to using this strategy in a heterogeneous population is to be able identify areas of neural strengths using a battery of well-validated and dissociable tests, as shown in Figure 1. While cognitive therapies are generally benign and not prone to adverse events as traditionally measured in medicine, they are time consuming, resource intensive, and taxing. In addition to the logistical complexities involved in accessing treatment for a severely impaired individual, there may be negative psychological consequences if treatment is unsuccessful. Thus, a haphazard pairing of an individual with severe impairments in a biomarker of, for example, WM, with a time- and resource-intensive cognitive intervention that places heavy demands on WM, is likely to be unsuccessful. Unfortunately, such incidental couplings of individual patient characteristics with therapies represent the current state of the art. Treatment failures are far too common and have the potential to cost the patient, family, therapist, and larger social system. In contrast, biomarkers of health can guide patients towards viable therapies, and their absence can steer patients away from therapies that are not likely to be successful and whose failure carries significant real-life consequences.

Pharmacologic augmentation of cognitive training interventions

There may be ways to uncover biomarkers of potential function in SZ patients, even among neural systems that appear according to some biomarker evidence to be defective. The general principle behind this strategy is that a neural system at baseline may perform poorly but may still respond to the push of a pharmacologic challenge. In this case, evidence for the requisite spared neural circuitry, and hence a target for therapeutic intervention, might be provided by specific neurophysiological or neurocognitive changes in response to a drug challenge. This approach parallels the use of a test dose to predict clinical benefits from treatments ranging from hormones[34] to anti-Parkinsonian drugs[35] to bronchodilators.[36] If a patient generates a specific neurobehavioral signal in response to a drug challenge (e.g., increased neurocognitive or neurophysiological performance, or enhanced performance of a computerized cognitive training task (discussed below)), this suggests that neural circuits spared by their SZ remain viable targets under the right conditions. Creating such conditions is the goal of pharmacologically augmented cognitive therapy (PACT), as described

previously,[16,37] and departs significantly from what has been a 50-year-old largely failed strategy of trying to use drugs to undo the neuropathology of SZ.[38]

Criteria for biomarker selection

Regardless of whether the intended use of a biomarker is to identify health or pathology in SZ, its utility will depend on its ability to meet a number of important criteria. What are the optimal characteristics of biomarkers for informing the clinical neuroscience and future treatments of SZ? Over the past decade, several expert consensus panels were convened to attempt to overcome some of the obstacles of developing treatments to improve cognition and psychosocial functioning in SZ. The first initiative—the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)—brought together academia, the pharmaceutical industry, and the U.S. Food and Drug Administration (FDA) to identify cognitive targets in SZ and develop a brief, repeatable, and standardized battery of tasks for use in clinical outcome studies.[39] In this context, a RAND panel carefully evaluated the desired measurement characteristics of individual tests for inclusion in the final FDA-approved battery and concluded that measures should exhibit: (1) high test–retest reliability; (2) utility as a repeated measure; (3) a relationship to functional outcome; (4) potential response to pharmacologic agents; and (5) practicality/tolerability.

The benefits of neurophysiologic biomarkers were also recognized in the MATRICS initiative since such measures can probe the earliest stages of sensory-perceptual information processing and the subsequent transitions to higher-order cognitive operations with millisecond-level resolution. In many cases, responses can be automatically elicited in the absence of directed attention and do not require substantial effort or motivation on the part of the participant.[40] Neuroscience-derived biomarkers are also well-suited for linking cognitive deficits to specific neural systems using source imaging, pharmacology, and animal models.11,40–43,[a] Thus, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative was launched after MATRICS to identify the most promising brain-based tools for measuring cognition and testing new treatments in SZ patients.[44] This panel extended the five MATRICS criteria of cognitive tests described above by requiring that measures exhibit construct validity, clear links to neural circuits and cognitive mechanisms, and have an available animal model.[45] Out of this extensive process of evaluating the many promising measures in the existing literature, several tests were selected for further study and development. Critically, two neurophysiological measures were deemed already mature, fulfilling all of the MATRICS/CNTRICS criteria and suitable for immediate incorporation into multisite clinical studies:[46,47] MMN and PPI (reviewed in Refs. 13 and 48). Below, we provide a description of MMN and outline a rational and deliberate matching of patients with intact MMN biomarker functioning with appropriately targeted cognitive therapies that depend on the engagement of the neural substrates of MMN.

Mismatch negativity as a breakthrough biomarker in psychosis

MMN is a preattentive event-related potential (ERP) component with tremendous promise as a biomarker for predicting and tracking response to novel therapeutic

interventions.[1,12,49–52] Since the first description in 1978,[2] this measure has generated tremendous interest across disparate research areas, with nearly 80,000 “mismatch negativity” keyword citations in the Thomson Reuters Science Citation Index and more than 200 “mismatch negativity AND schizophrenia” MEDLINE-referenced articles. MMN is passively evoked when a sequence of repetitive standard stimuli are occasionally interrupted by infrequent oddball or deviant stimuli that differ in some physical dimension, such as duration or pitch (Fig. 3). The onset of MMN typically occurs within 50 ms of stimulus deviance and peaks after an additional 100–150 milliseconds. Since MMN requires no overt behavioral response and can be elicited even in the absence of directed attention,[53–56] it is presumed to reflect a predominantly automatic, preconscious process of detecting a mismatch between the deviant stimulus and a sensory-memory trace.[57]

MMN amplitude reduction in SZ was first reported over 20 years ago,[58] with subsequent studies consistently identifying deficits in chronic ($d \approx 1.00$[23,58–66]), recent onset[64–73] and even unmedicated SZ patients.[3,29,60,68,71,74] MMN is supported by a distributed network of frontotemporal sources, with deficits in SZ prominent in medial frontal brain,[30,41] and is sensitive to pharmacologic[75–89] and cognitive challenges.[56] The temporal window indexed by MMN may serve as a gateway to some higher-order cognitive operations necessary for psychosocial functioning.[40,56] Indeed, MMN accounts for substantial portions of variance in cognition,[41,90–93] psychosocial functioning,[27,41,94,95] and level of independence in community living,[26] and is a more potent predictor of functioning in SZ patients than neurocognition or social cognition.[96] We have recently demonstrated that MMN and related response measures, applied to cortical-source activities derived from independent component analysis (ICA) decomposition, can offer more detailed characterization of SZ group and individual deficits than single-channel measures, accounting for nearly half of the variance in multiple measures of clinical, cognitive, and psychosocial functioning.[41,43]

Important for clinical application, MMN exhibits substantial utility as a repeated measure with high test–retest stability over short and long (e.g., 12 month) retest intervals in both healthy subjects and SZ patients.[1,27] In fact, reliability coefficients are comparable to or even exceed those obtained from neuropsychological tests over 1 year (ICCs ≈ 0.90; Fig. 4[1,27]). This collection of attributes has contributed to the view of MMN as a “breakthrough biomarker”[50] that is “translatable”[51] and potentially, “the one we’ve been waiting for”[97] in neuropsychiatry.

Impaired MMN predicts development of psychosis

The vast majority of MMN studies in SZ have been cross-sectional characterizations of patient deficits. Recently, several independent longitudinal studies have shown that the prediction of conversion to psychosis in individuals at clinical high risk (CHR) for developing psychosis can be considerably improved by means of simple MMN recordings. Identifying biological markers in high-risk populations is a critical step toward understanding the pathology of the disorder, predicting psychosis onset, and potentially devising early interventions that alter the course of the illness.[43,48,50–52,97] A minority of individuals at CHR for psychosis (identified on the basis of clinical criteria alone) develop a psychotic disorder within a 2.5-year follow-up period (for review, see Ref. 51). Targeting

CHR individuals for preventive interventions could expose many to unnecessary treatments (with their accompanying side effects), underscoring the need to enhance predictive accuracy with nonclinical, objective, laboratory-based assays of brain function.

In the first of these studies, Bodatsch *et al.*[71] compared CHR participants who converted to psychosis versus those who did not convert to psychosis during a follow-up period of approximately 3 years. At baseline, converters had significantly reduced MMN, comparable in amplitude to early-illness psychosis patients. In contrast, MMN in non-converters was comparable to that of healthy age-matched controls. As an illustration of the importance of MMN as a pathology biomarker, greater severity of deficits contributed to higher estimates of individualized risk. Similarly, Perez and colleagues[98] showed that attenuated MMN amplitude can be used to forecast the time lag to psychosis onset in high-risk individuals—those with more severe MMN abnormalities developed psychosis more imminently. These and other related studies[72,73,99,100] demonstrate the feasibility of identifying biomarkers that are associated with disease vulnerability, predicting the development of psychosis, estimating the time interval to psychosis onset, and enhancing individualized risk-estimation/prevention strategies.[97]

Spared MMN predicts response to treatments

There is ample evidence that MMN is an informative biomarker index of early auditory processing in SZ. In fact, we have previously argued for pharmacologic and non-pharmacologic treatments that target early auditory perceptual processing with the hope that an amelioration of MMN deficits might accompany or even precede improvements in highly associated cognitive and psychosocial functioning.[40,48,50,52] We now consider a figure-ground reversal: in contrast to the predominant emphasis on the 50% of patients with deficient MMN, perhaps those with normal-range MMN will be most likely to benefit from therapies that are designed to target low-level auditory perceptual processes.

MMN may be particularly sensitive to one particular form of bottom-up cognitive training termed targeted cognitive training (TCT; Posit Science Brain Fitness auditory training[101]). TCT uses neuroplasticity-based computerized cognitive exercises that target the accuracy and fidelity of auditory sensory information processing and auditory/verbal WM. TCT relies on intensive, attentionally engaging, adaptive, and reinforcing exercises to capitalize on behavioral learning mechanisms[102] that are largely intact in SZ.[103] Conceptually, the goal of TCT is to induce plastic changes within the neural substrates of low-level auditory information processing, which then feed forward to improve higher-order cognitive operations, such as attention, WM, and the encoding and retrieval of verbal information. Fisher and colleagues[101,104] have shown that SZ patients exhibit large effect size ($d = 0.86–0.89$) gains in auditory-dependent cognitive domains (verbal learning and memory), global cognition, and quality of life after 50 h of this auditory training. Importantly, these gains persist for at least 6 months after the cessation of training.[105] Although TCT is efficacious at the group level, individual patient responses vary considerably; some patients exhibit little or no benefit even after 100 h of training.[106] Could MMN or other neurophysiological biomarkers of auditory sensory processing be used to predict whether an individual patient is likely to respond to this time- and resource-intensive intervention?

In addition to the emerging applications in neuropsychiatry, MMN is supported by a substantial cognitive neuroscience literature where this measure is already regarded as a dynamic index of central auditory system neuroplasticity that predicts cognitive enhancement in response to specific TCT-like auditory training interventions.[107,108] For example, Menning and colleagues[107] demonstrated that 3 weeks of intensive (approximately 1h/day) auditory frequency discrimination training produced significant increases in MMN amplitude that persisted for several weeks after the cessation of training in healthy volunteers. Other studies have shown that MMN both predicts and corresponds to changes in language acquisition, musical training, and other auditory-dependent cognitive tasks in nonpsychiatric individuals (for review, see Ref. 108). In the majority of studies, higher baseline MMN predicted better outcome. Likewise, MMN exhibits malleability after even a single session of auditory training in dyslexic children, which was associated with a significant amelioration of cognitive impairment in phonological processing, reading, and writing.[109] Thus, changes in MMN are detectable in the early stages of cognitive training, predict generalized improvements in non-trained higher-order cognitive domains, and correspond to measurable changes of cortical plasticity in intact and impaired neuropsychiatric populations. In all instances, larger baseline MMN (i.e., associated with healthy function) was associated with greater training gains.

Little is known about the neural mechanisms that underlie enhanced global cognition and interindividual variation in TCT response in SZ patients. Better characterization of biomarkers of TCT response will lead to more selective targeting of patients and neurobiological systems for preventive interventions. We have conducted a proof-of-concept validation study to begin to understand the potential relationship between MMN and immediate TCT effects (unpublished data, manuscript in preparation). MMN was assessed immediately before and after a 1-h TCT session (Posit Science, Frequency Sweeps) in chronic, medicated SZ patients. MMN amplitude exhibited a significant change at frontocentral electrodes ($P < 0.02$), confirming our prediction that MMN is sensitive to early target engagement after just 1 h of training. In addition, patients with larger pretraining MMN amplitude exhibited the greatest improvements across the single TCT session ($r = -0.5$, $P < 0.01$), confirming our hypothesis that baseline MMN predicted initial TCT performance gains. Thus, patients with larger (i.e., more normal) levels of MMN (i.e., those that are right) exhibited a greater initial response to training. While these results are encouraging, it is important to emphasize that the behavioral response to a single TCT session is not known to predict longer-term neurocognitive or functional gains in SZ patients undergoing a full course of training. Consistent with this model of larger MMN baseline predicting treatment response, Kawakubo and colleagues[49] showed that larger pretraining MMN predicted a greater response to an intensive, 3-month social skills training program.

MMN and other biomarkers[5] may therefore improve our ability to identify patients who are likely to be responders to TCT,[50,52] social skills training,[49] or perhaps other forms of cognitive remediation. In these seemingly disparate examples of bottom-up and more top-down interventions, evidence of intact functioning provided by a neurophysiological biomarker positively predicted the therapeutic response to a higher cognitive intervention. In each instance, patients who were capable of marshaling adequate cognitive resources to

meet the demands, and reap the benefits, of a particular therapeutic intervention were most likely to exhibit a benefit. Such predictive biomarkers may also facilitate screening drugs to augment cognitive and psychosocial training interventions.

As with our absence of predictive biomarkers in clinical practice, similarly few if any laboratory tests are available for monitoring response to treatments. In the example of MMN and TCT described above, studies have been conducted using various doses of TCT ranging from 20–100 hours. While group-level findings are robust, we are unable to reliably forecast whether an individual will exhibit a pro-cognitive response and are similarly incapable of determining when a given patient has reached the point of diminishing returns or has stopped responding to a treatment altogether. For example, perhaps 10 h of training is optimal for one person, whereas another patient might still be exhibiting significant evidence of improvements in biomarker/cognitive network functioning after even 100 hours. Such objective information would inform our ability to adapt training regimens.

Is MMN ready for use in clinical settings?

While it appears that EEG measures, including MMN, have tremendous promise for yielding actionable biomarkers of individual psychiatric status,[5] much work will be required to ensure their effective application in real-world settings. Given the low base rate of psychosis in the general population and the current movement toward implementing screening procedures in schools and clinics, obstacles to the potential use of neurophysiologic biomarkers (e.g,. false positives) are certain to arise. Beyond the substantial validation required for large-scale deployment, instrumentation will need to be simplified to allow administration by non-specialists in real-world community treatment centers. To this end, we have recently demonstrated in the Consortium on the Genetics of Schizophrenia (COGS) multisite study that MMN and P300 measures can be reliably obtained from settings without a requirement for EEG-specialized laboratories, extensive technician training, or on-site expertise in EEG assessment and analysis.[3] Despite relatively little dedicated face-to-face annual training, over 90% of data from 1,790 participants (Fig. 5, top panel) was usable, and this number could likely be greatly improved in future studies on the basis of lessons learned during the collection of this large multisite dataset. The COGS findings closely resembled those obtained from our more specialized EEG laboratory, including findings on response waveform morphology, the effect size of deficits in SZ (Fig. 5, bottom panel), and biomarker correlations with demographic characteristics, as well as measures of clinical, cognitive, and psychosocial functioning. Notably, site differences were not detected, encouraging efforts to take EEG measures from academic laboratories and into other settings that do not have specialty laboratories or on-site technical expertise. Such ready scalability remains a critical development goal for future studies and clinical applications.

Discussion

One of the challenges facing the use of biomarkers in SZ patient populations is that, for the most part, biomarkers are being applied after the fact. In other words, if we acknowledge that SZ is a neurodevelopmental disorder (or set of disorders), likely reflecting perturbations

of *in utero* neural development, then the events (genetic, environmental, or otherwise) that lead to the late-adolescent/early-adult manifestations of the disorder have come and gone, decades before biomarker data are measured. The number of variations in the expression of these early events—for example, variable neuronal migratory routes and the adjustments of the surrounding developing brain to them, the consequent alterations in premorbid behavior and the reflected impact of environmental responses onto brain development—from *in utero* causative events to adult manifestation is substantial if not limitless. Unlike disorders of adult onset in which an anatomically or neurochemically constrained lesion is superimposed on a normally developed brain, in SZ, the absent connections lost to cells that did not arrive, and the aberrant connections formed in their place, are infused throughout the matrix of a very complex forebrain circuitry. Making sense of right and wrong in this circuit context, as a basis for understanding the biology of SZ and its courses or treatments, may not be feasible or even productive in the foreseeable future. While awaiting this more comprehensive understanding of SZ, we propose further development of biomarkers for predicting treatment response in a manner that is consistent both with the therapeutic goals of personalized medicine and the scientific strategies of experimental medicine.[110] Individuals are characterized by measures of brain activity that are associated with neurocognition and function, and areas of healthy or normal-range performance are identified. In this process, drugs or other experimental manipulations and designs can be used as clinical probes to identify targets of residual neuroplasticity. Treatments are then identified that leverage the intact neural circuit or neurocognitive resources so that the individual patient can utilize their capacities to reap the gains of the therapeutic intervention. In truth, the basic principles of the biomarkers of health approach are simple ones, long espoused by disciplines ranging from childhood education to career counseling: a successful outcome is best achieved by matching residual strengths—areas of resiliency—with task demands. In the frenzied search for the genetic and molecular markers and mechanisms of that which is wrong in SZ patients, the field and its treatments may not have fully appreciated and leveraged all that is right.

One key to the successful use of biomarkers in this model is the ability to link a healthy biomarker with a positive response to a specific therapy. For example, as alluded to in the introduction, some forms of cognitive training put demands on processes requiring healthy WM and attention[15] and thus would be best pursued in patients with biomarker evidence of relatively intact WM and attentional capacity. Alternatively, evidence that WM and attentional performance could be enhanced in that patient by a psychostimulant challenge might predict benefits of psychostimulant augmentation of cognitive training. Different biomarkers of neurocognitive and neural circuit strengths might predict optimal responses of SZ patients to cognitive behavioral therapy (CBT), computerized cognitive training, social skills training, medications such as the pro-extinction drug D-cycloserine[111] or the pro-social drug oxytocin,[112,113] or even neurostimulation.[114] While there is substantial evidence that baseline cognitive deficits generally predict poor outcomes in cognitive interventions,[115–118] we are not yet at a point where we can apply specific algorithms other than clinical intuition to match biomarkers of intact neural function in a SZ patient with treatment response to different types of therapies (Fig. 6).[52] Developing such algorithms will be advanced by incorporating informative biomarkers, such as MMN, and detailed

neurocognitive assessments, into the designs of trials of cognitive interventions for SZ patients. Importantly, the fidelity and optimal methods for many potential biomarkers have already been established in multisite studies, where deficits in these measures have been used as endophenotypes to identify risk genes for SZ.[3,4,12] In the figure-ground reversal proposed here, these biomarkers are used not to predict a risk of illness, but rather, they are used to predict a likelihood of recovery.

Thus, we can envision a future in which biomarkers, used in conjunction with demographic, clinical, and genetic predictors, improve the identification of individuals at clinical risk for developing psychosis, inform individual assignment to beneficial interventions, and help quantify response to treatments.[3,5,52] Such an approach could contribute to the development of next-generation, precise, personalized, and even preemptive interventions.

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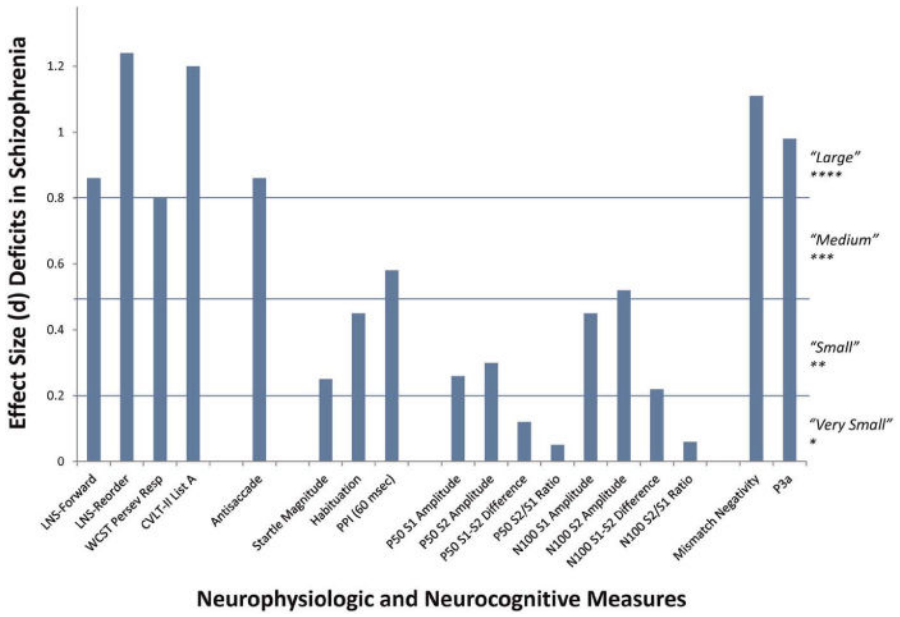

Figure 1.

Effect size (Cohen's d) of deficits in schizophrenia patients across leading candidate biomarkers. Data from Ref. 1. Abbreviations: LNS, letter number sequencing; WCST, Wisconsin Card Sorting Test; CVLT-II, California Verbal Learning Test—second edition; PPI, prepulse inhibition.

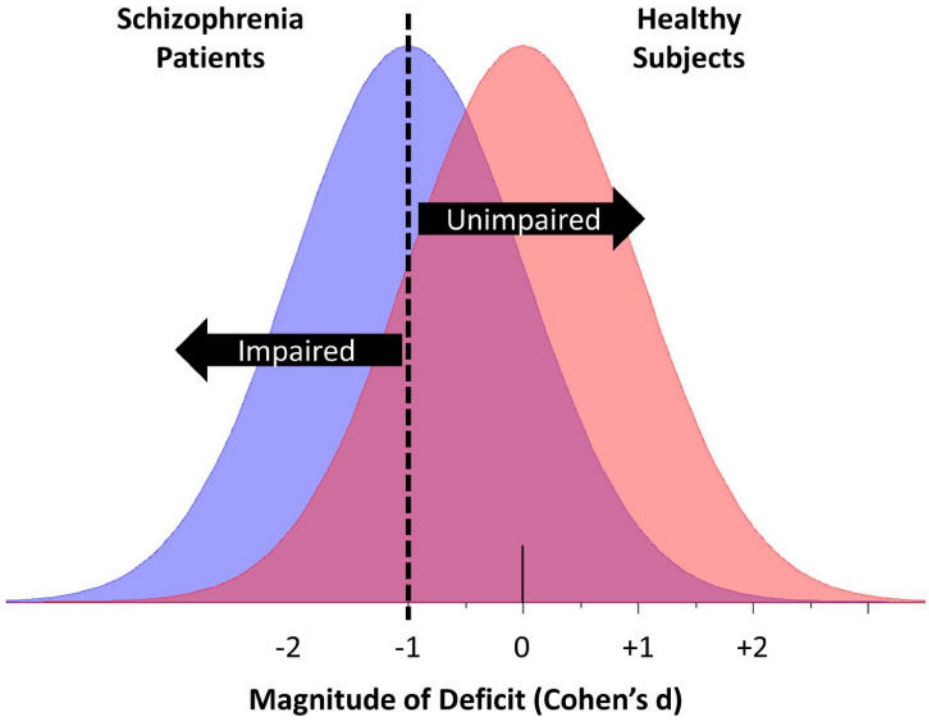

Figure 2.

Example of overlapping distributions in a robust (d = 1) effect size biomarker deficit in schizophrenia patients. In neuropsychological assessments, d = 1 standard deviations below the mean is commonly used for impairment classification. With an effect size d = 1 below the mean, 50% of patients exhibit unimpaired/normal-range biomarker values. Data from Ref. 48.

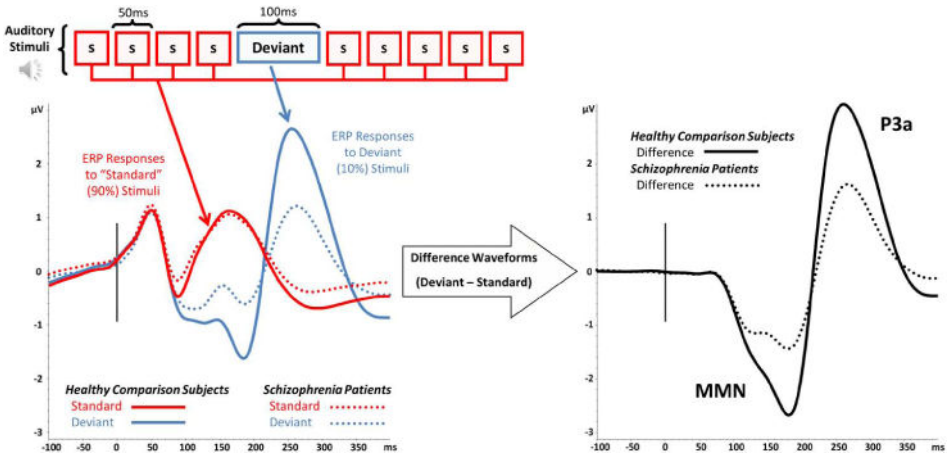

Figure 3.

MMN/P3a paradigm and group averages. Participants were presented with stimuli consisting of frequently presented standard stimuli (90% of trials, red box labeled “s”) interspersed with infrequent deviant stimuli (10% of trials, blue box labeled “deviant”). ERP waves to standard and deviant stimuli are calculated by averaging EEG responses to each stimulus type. Deviant–standard difference waves are generated by calculating MMN and P3a components (black lines). For all waveforms, solid lines represent healthy comparison subjects (n = 753) and dotted lines are used for schizophrenia patients (n = 877). From Ref. 3.

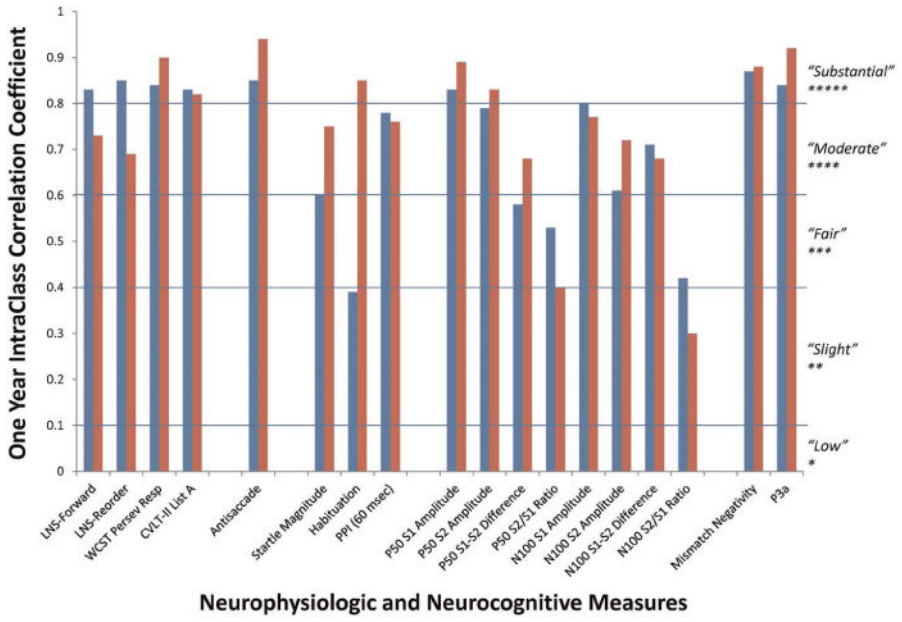

Figure 4.

1-year stability of neurophysiological and neurocognitive biomarkers. Intraclass correlation coefficients are shown for schizophrenia patients (blue; *n* = 163) and nonpsychiatric comparison subjects (red, *n* = 58). The mean retest interval was 364.57 (SD: 23.83) days. Data from Ref. 1. Abbreviations: LNS, letter number sequencing; WCST, Wisconsin Card Sorting Test; CVLT-II, California Verbal Learning Test—second edition; PPI, prepulse inhibition.

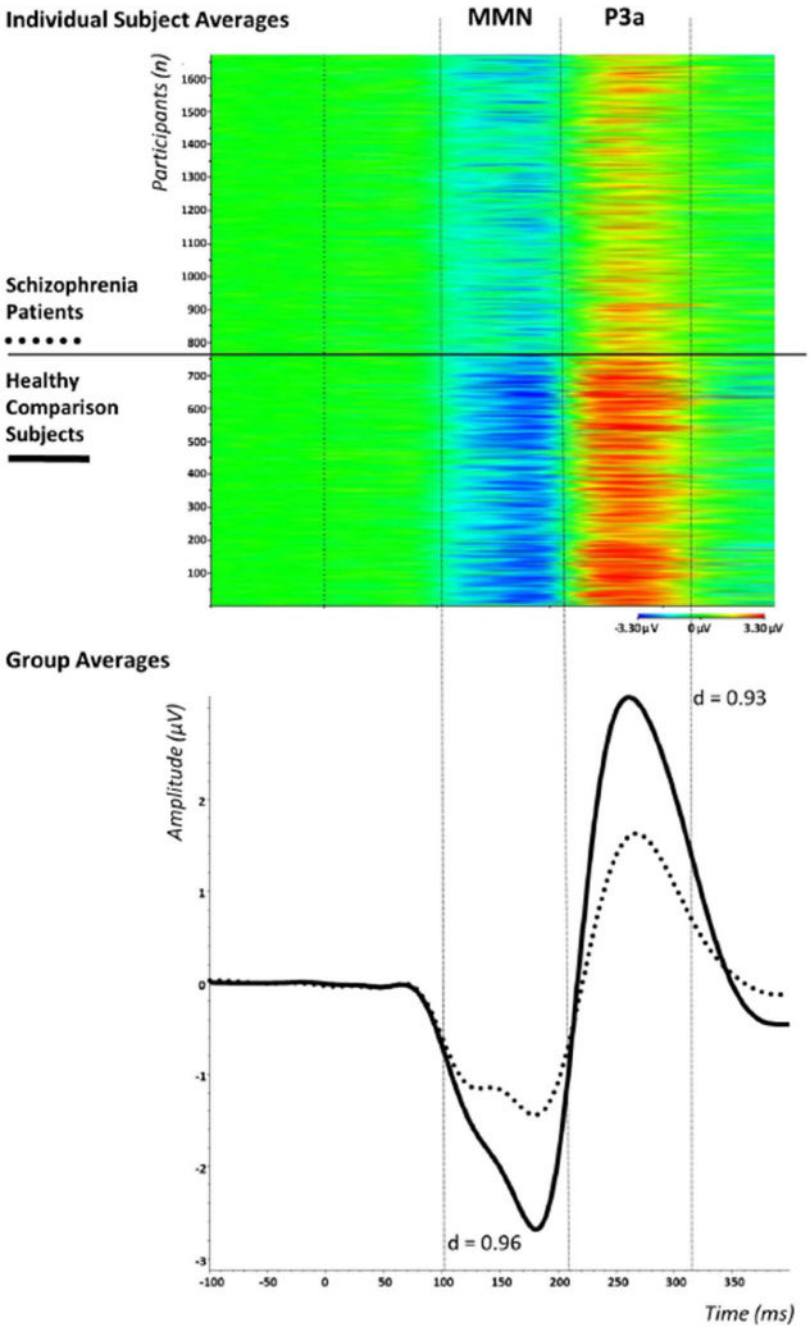

Figure 5.

Individual subject and group averaged waveforms. Individual subject deviant–standard difference wave averages (color coded by amplitude) are shown in the top panel for healthy comparison subjects (n = 753) and schizophrenia patients (n = 877). Group grand average wave forms are shown in the bottom panel. Data from Ref. 3.

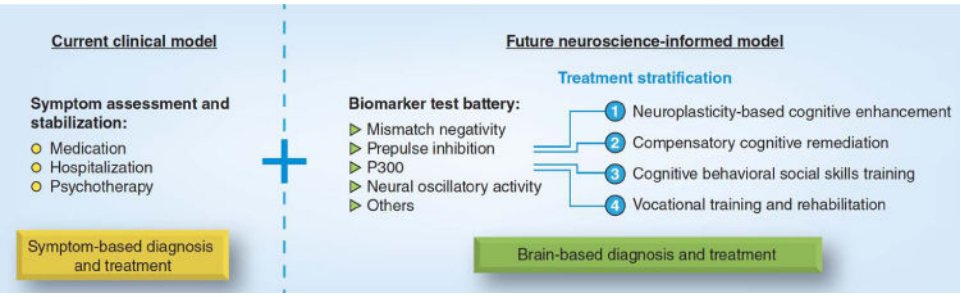

Figure 6.
Future clinical use of laboratory-based biomarkers to assign patients to treatments.[52]