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Perez, Veronica B

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Using biomarkers to inform diagnosis, guide treatments and track response to interventions in psychotic illnesses

“As the clarification and development of neurophysiological biomarkers continues, shifts in our approach to diagnosis and treatment decisions should follow. After all, the success of precision medicine lies within these neuroscientific advances, and will likely be the roadmap to a next-generation brain-based Diagnostic and Statistical Manual.”

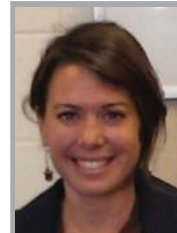
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Following the release of the recently updated fifth edition of the *Diagnostic and Statistical Manual* (DSM-V), psychiatry has fallen under fire from critics outside and even within the field [101,102]. Among the most frequently mentioned criticisms is that diagnosis and treatment decisions are based largely on patient reports, behavioral observation and our ability to make inferences about patients' true inner experiences (e.g., clinical judgment), rather than objective laboratory tests. Psychiatric researchers have long recognized that our current symptom-based diagnostic approach is inconsistent with our emerging understanding of the overlapping neural networks that subservise multiple psychiatric illnesses [1]. To address these and other shortcomings, the National Institutes of Mental Health (NIMH) has launched the Research Domain Criteria Project (RDoC) as a framework for the next generation of neuropsychiatric research. In this forthcoming RDoC era, researchers are encouraged to directly assay deficiencies in neural systems in order to guide diagnosis, develop and inform treatments, and predict and track outcomes. The RDoC aims to further expand our knowledge of brain-behavior relationships, and ultimately infuse this understanding of neural dysfunction into clinical practice and accelerate the development of more effective treatments. This paradigmatic shift toward “precision medicine” joins brain-based disruption with clinical observation, serving to align patient and provider treatment goals for more effective outcomes. Here, we provide an example of a translatable EEG biomarker, mismatch negativity (MMN), that offers great promise for improving our understanding, treatment, and perhaps even the prevention of a severely disabling and frequently intractable condition: psychosis.

Many candidate biomarkers have provided critical insights into the pathophysiology of schizophrenia and related psychotic disorders. Some of these biomarkers include: prepulse inhibition of the acoustic startle reflex [2,3], and EEG-based measures such as the P300 event-related potential amplitude [4] and cortical oscillatory dynamics [5]. In this paper, we focus on MMN [6]. In concert with efforts to further infuse neuroscience into psychiatric assessment and care, an expert consensus panel formed as part of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative highlighted MMN as one of the more “mature” biomarkers that is “promising” and ready for immediate incorporation into multisite clinical trials [7]. Recently, this measure has been described as a “breakthrough biomarker” [8] that is “translatable” [9] and potentially “the one we’ve been waiting for” [10] in neuropsychiatry.

Auditory MMN: critical findings in psychosis

Auditory MMN reflects an automatic change detection process that is elicited in response to unattended and infrequent sound stimuli embedded in a sequence of frequently presented standard stimuli. The MMN is elicited when a stimulus physically differs (e.g., in duration, pitch, intensity) from the context of the standard trials, and also during a sequential pattern violation [11]. Importantly, because MMN does not require sustained task engagement or even consciousness [12,13], it is thought to reflect an initial step from bottom-up sensory information processing leading to the conscious awareness of environmental change. MMN amplitude reduction in schizophrenia was first reported



Veronica B Perez

VISN-22 Mental Illness Research, Education & Clinical Center (MIRECC), VA San Diego Healthcare System, CA 92161, USA
and
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

Neal R Swerdlow

Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

David L Braff

Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

Risto Näätänen

Center of Functionally Integrative Neuroscience (CFIN), University of Aarhus, Aarhus, Denmark
and
Department of Psychology, University of Tartu, Tartu, Estonia
and
Institute of Behavioral Sciences, University of Helsinki, Helsinki, Finland



Gregory A Light

Author for correspondence:
VISN-22 Mental Illness Research, Education & Clinical Center (MIRECC), VA San Diego Healthcare System, CA 92161, USA
and
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
glight@ucsd.edu

over 20 years ago [14], and subsequent studies have consistently shown a reduction of MMN in chronic (effect size Cohen's $d = 1.00$ [14–23]), recent onset [21–30] and even unmedicated schizophrenia patients [16,25,28,31,32]. Over the past two decades, other studies have demonstrated robust relationships among MMN deficits and clinical and functional impairments (e.g., [33–35]). MMN amplitude exhibits 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 schizophrenia patients (retest correlation = 0.90 [36]), comparable to or exceeding reliability levels observed in common neuropsychological tasks [37]. Additionally, MMN testing is well-tolerated by a wide range of patients [32,38]. Based on this collection of attributes, MMN fulfills criteria for use as a biomarker in clinical outcome studies [37]. Moreover, MMN accounts for substantial portions of variance in cognition [6,39,40], psychosocial functioning [29,41–43] and level of independence in community living [35].

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The vast majority of MMN studies in psychosis, however, have been cross-sectional characterizations of deficits in patients who have already experienced a psychotic event. What is the time course of the emergence of MMN deficits? Are deficits present prior to the onset of psychosis? The answers to these critical questions are beginning to be addressed in longitudinal biomarker validation studies [28,44,45].

Using biomarkers to develop preemptive interventions for psychosis

There has been a recent surge of interest in improving the prediction of psychosis onset in individuals at high risk for developing schizophrenia (for review see [9], also [45,46]). In the past decade, several research groups have developed clinical criteria to identify individuals at clinical high-risk for psychosis. Under the Criteria of Prodromal Syndromes (COPS) [47] or the comparable At-Risk Mental States criteria (ARMS) [48], 18–36% of the individuals identified as clinical high-risk for psychosis subsequently developed a psychotic disorder within a 2–3-year follow-up period [49,50]. This means that approximately 65–80% of individuals identified as being at high risk do not convert to psychosis. This low hit rate is a major barrier for attempting prophylactic pharmacologic

interventions, particularly with antipsychotic medications, which cause metabolic or motor side effects. Ultimately, this lack of predictive power has raised doubts about the utility of the clinical high-risk syndrome [51].

Recently, longitudinal studies have shown that the prediction of the onset of psychosis in individuals at clinical high-risk can be considerably improved by MMN recordings [9,45]. In the first of these studies, Bodatsch *et al.* compared high-risk participants who converted to psychosis relative to nonconverters during a follow-up period of approximately 3 years [28]. At baseline, converters had significantly smaller MMN amplitude comparable to that in early-illness psychosis patients; MMN in nonconverters was comparable to that of healthy age-matched controls. As an illustration of MMN as a biomarker, greater severity of MMN deficits contributed to higher estimates of individualized risk. Furthermore, Perez and colleagues [45] 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 more imminently developed psychosis. These and related studies [30,44,45,52] demonstrate the feasibility of identifying biomarkers that are associated with disease vulnerability, predicting the development of psychosis, estimating the interval to psychosis onset, and enhancing individualized risk-estimation/prevention strategies [10].

Predicting therapeutic response: towards biomarker-informed treatment stratification

While it is now widely recognized that neurocognitive impairments present in most psychosis patients contribute to the severity of psychosocial disability, we can now be optimistic in our ability to ameliorate these impairments. Emerging findings indicate that the impaired neural systems of psychiatric illnesses are not fixed, but may be modified by carefully designed training interventions that harness neuroplasticity-based learning mechanisms [53–55]. One promising intervention, targeted cognitive training (TCT), is designed to sharpen the accuracy and fidelity of auditory information processing in psychosis via daily computer-based cognitive exercises [53,56]. Plastic changes within the neural systems that subserve early perceptual processing are thought to feed forward to enhance higher order cognition [56]. Studies in psychosis patients who completed 50 h (1 h/day, 5 days/week) of TCT demonstrated large effect size

gains that generalized to auditory-dependent cognitive domains (verbal learning and memory; effect size Cohen's $d = 0.86-0.89$), as well as global cognition (effect size Cohen's $d = 0.86$) and quality of life [53]. Although TCT is efficacious at the group level, individual participant responses vary considerably; some patients show little or no benefit after even a full course of training [53]. As such, there is a need to identify predictive biomarkers of response to this daily, resource-intensive intervention. Since MMN is regarded as a robust, reliable and sensitive index of central auditory system plasticity [57] with important relationships to cognition and psychosocial functioning [33,35,36,58], could it also serve as a biomarker that predicts or corresponds to changes following TCT? Studies are underway to investigate this application, with notable precedents showing that MMN predicts response to intensive computerized cognitive training [59] and psychosocial skills training [41] in clinical populations.

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 “...*biomarker-informed treatment stratification could delineate subgroups of individuals for better responses to even currently available treatments and contribute to future diagnostic classifications.*”

Since MMN improves the prediction of psychosis in clinically high-risk individuals and it reflects the neural systems targeted by TCT, it may prove useful in future treatment stratification algorithms (FIGURE 1). Current symptom-based models of diagnosis and treatment employ clinical assessment for symptom stabilization using medication, hospitalization and psychotherapy as treatment methods. As illustrated in the figure, the addition of biomarker profiles could indicate neural circuitry patterns

subserving/predicting: 1) disruption of auditory processing centers calling for neuroplasticity-based cognitive enhancing treatment such as TCT; 2) neuropsychological impairment to be addressed with compensatory cognitive remediation strategies [60]; 3) maladaptive thoughts and social skills targeted by cognitive behavioral and social skills treatment for psychosis [61]; or 4) impaired role development requiring vocational training and rehabilitation services [62,63]. If successful, biomarker-informed treatment stratification could delineate subgroups of individuals for better responses to even currently available treatments and contribute to future diagnostic classifications.

Future directions & unresolved issues

While it is easy to argue that MMN and related neurophysiological biomarkers have tremendous promise, much work is still required for their safe and effective application in clinical settings. For example, with a low base rate of psychosis in the general population and a movement towards implementing more widespread screening procedures in schools and clinics, false positives, the potential for misuse and other problems are a certainty. Aside from the substantial validation that will be necessary to develop protocols for considering false positives, biomarker instrumentation also needs to be greatly simplified for administration by nonspecialists. Studies are underway using low-cost, portable systems reliable for multisite studies, similar to electrocardiography, with even fewer, smaller and easier-to-use electrodes. Biomarker tools could also capitalize on telemetry monitoring, where testing could take place in clinics, with data being uploaded to the cloud for sophisticated offline analyses and expert consultation, if required. Aside from improving

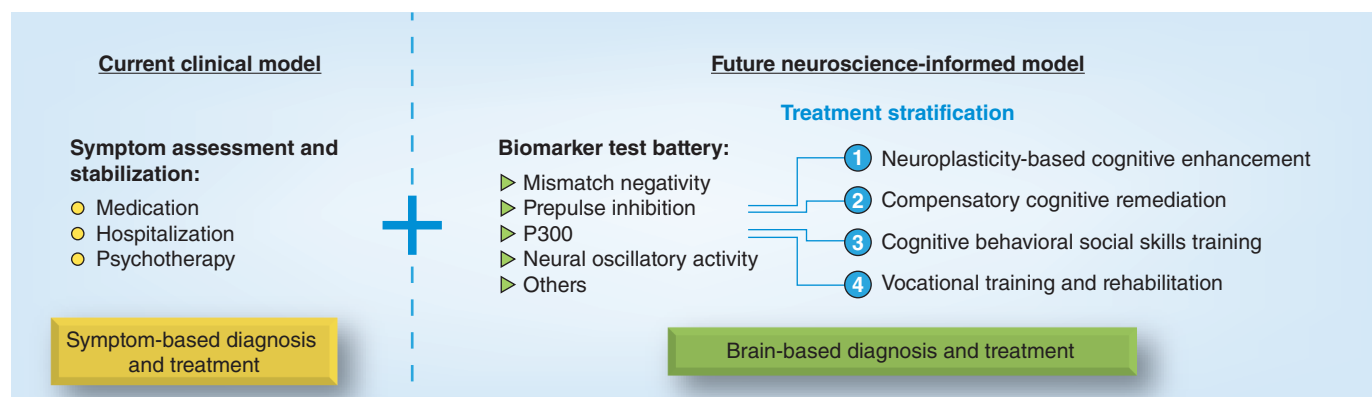


Figure 1. Clinical and neuroscience-based models combine to improve diagnosis and develop treatment algorithms for psychiatric illness.

the hardware, software and analytic capacity, we still do not know which (if any) parameters are maximally predictive of therapeutic response. If these barriers can be overcome, lengthy government and other regulatory oversight will be required.

Conclusion

The field of neuropsychiatry has made transformative advances in our understanding of the neural dynamics of normal and aberrant brain processes. In addition, many patients benefit from current mental health treatments that reduce seriously impairing symptoms and improve quality of life and daily functioning – facts that are often overlooked by critics of our field. Still, patients and their loved ones have grown impatient with our failure to take some of the promising advances out of the laboratories and into the clinics. Care providers have similarly called for upgrading our therapeutic arsenals to better combat the complex disabling conditions they face at the front lines of their clinics. Given the paradigmatic shift of the NIMH to apply a more dimensional RDoCs template to fuel ongoing research, we can continue to be optimistic about the future utility of biomarkers derived from clinical neuroscience. With many barriers to widespread implementation, a most promising example, MMN, can be used in conjunction with careful clinical assessment to identify individuals at highest imminent risk for developing serious mental illnesses to inform

early intervention decisions. To avoid undesirable medication side effects, cognitive training and/or psychosocial interventions may be course-altering early treatment options.

The time is ripe for advancing the use of biomarkers to redefine illness criteria and evaluate treatment efficacy. Qualitative symptom descriptions no longer need to be used as a stopgap for diagnostic clarity. As the clarification and development of neurophysiological biomarkers continues, shifts in our approach to diagnosis and treatment decisions should follow. After all, the success of precision medicine lies within these neuroscientific advances [64], and will likely be the roadmap to a next-generation brain-based *Diagnostic and Statistical Manual*.

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