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COMMENTARY

Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders

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As neuropsychiatry continues the quest to improve the diagnosis and treatment of serious mental illnesses, important converging findings are beginning to take place in psychosis research with EEG-based biomarkers. Although patients with schizophrenia and related psychotic illnesses show many neurobiological abnormalities that distinguish them from healthy volunteers, the identification of these abnormalities has seldom led to tests with clinical utility, contributing to the critical need for a paradigm shift in our approach toward studying and treating these disorders (1, 2). It has been suggested that the development of next-generation therapeutics has been disappointing, due in part to a dearth of cognitive paradigms with cross-species translational validity (3) and biomarkers that can inform diagnosis or treatment. Here we propose that mismatch negativity (MMN)—a neurophysiological measure of central auditory system functioning—may be informative in developing the next generation of neuroscience-guided cognitive-enhancing treatments.

Translational Models of Schizophrenia-Related Cognitive Deficits

Over the past 20 y, glutamatergic dysfunction of schizophrenia has become increasingly accepted as an etiopathological model of this illness, based on clinical observations that phencyclidine induces a schizophrenia-like psychosis by blocking neurotransmission at NMDA-type glutamate receptors (4). In PNAS, Gil-da-Costa et al. (5) demonstrate cross-species homology of electrophysiological responses to subanesthetic doses of the NMDA receptor antagonist ketamine, further establishing MMN and the closely linked P3a component as translational biomarkers that can model some of the core cognitive impairments of schizophrenia and related psychotic disorders.

The work by Gil-da-Costa et al. (5) extends a substantial and rapidly evolving knowledge base of the neural substrates of MMN (6–10).

MMN Deficits in Schizophrenia

Since the first description in 1978 (11), there has been tremendous interest in this measure across disparate fields of research, with nearly 80,000 "mismatch negativity" keyword citations in the Thomson Reuters Science Citation Index including more than 200 "mismatch negativity AND schizophrenia" Medline-referenced articles. MMN is an event-related potential component that is passively evoked in response to unattended changes in background stimulation. MMN is considerably attenuated in amplitude (effect size d ~1.00) in schizophrenia (12–14), and can be easily and reliably assessed even in the absence of attention or behavioral tasks, a major advantage in patient assessments. In addition, MMN has well-established relationships to cognition (15, 16) and psychosocial functioning in both healthy volunteers and schizophrenia patients (17, 18). The substantial 1-y stability of MMN (interclass correlation coefficients ~0.90) also lends support for its use as an endophenotype in genomic investigations, as well as a reliable biomarker in clinical outcome studies (19).

Gil-da-Costa et al. demonstrate cross-species homology of electrophysiological responses to subanesthetic doses of the NMDA receptor antagonist ketamine.

Forecasting the Development of Psychosis in High-Risk Individuals

The vast majority of MMN studies in schizophrenia have been cross-sectional characterizations of patient deficits. Recently, longitudinal studies have shown that the prediction of psychosis in individuals at clinical high-risk (CHR) can be considerably improved by means of simple MMN recordings. Identifying biological markers in high-risk populations is a critical step toward informing the pathology of the disorder, predicting psychosis onset, and potentially devising early interventions to alter the course of the illness (20). As noted by Perez et al. (21), however, only about one third of patients at high risk for psychosis, based on clinical criteria alone, develop a psychotic disorder within a 2.5-y follow-up period. 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 measures. In the first of these studies, Bodatsch et al. (22) compared CHR participants who did vs. did not convert to psychosis during follow-up. At baseline, converters had significantly smaller MMN amplitude, one comparable to that in early-illness patients, whereas MMN in nonconverters was comparable to that of healthy age-matched controls. Perez et al. (21) extended these findings to show that MMN amplitude also "forecasts" the time lag to psychosis onset in CHR individuals; those with more severe MMN abnormalities had shorter times to psychosis. These CHR and related studies (21, 23–26) draw attention to the importance of identifying early biologic markers of disease vulnerability for predicting the development of psychosis and

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enhancing individualized risk-estimation/prevention strategies (20).

A fundamental question is whether there are measurable brain changes occurring just before or during the transition to psychosis. Since glutamate dysfunction is recognized as a key pathological feature of schizophrenia (5–7, 27), which accounts for some of the cognitive and functional decline that accompanies and even precedes psychosis onset (4), clarifying the genomic substrates underlying these abnormalities is a focus of intensive investigation (28). It has been suggested that a contributing reason for MMN decrement in schizophrenia may be loss of dendritic spines, the primary loci of the NMDA receptors, resulting in progressive volume reduction of auditory cortex (9), a key generator of MMN (8).

Because neurocognitive impairments are present in the majority of schizophrenia patients and contribute to the severity of psychosocial disability, novel procognitive interventions are critically needed (1). As noted by Young et al. (3), developing these therapies will be facilitated by: (*i*) an understanding of the neural alterations underlying the targeted cognitive processes; (*ii*) knowledge of the neuroanatomical changes that underlie deficits in patients; (*iii*) animal manipulations that can re-create these deficits; and (*iv*) cognitive paradigms with cross-species translational validity to assess response to such therapies, as shown by Gil-da-Costa et al. (5).

Using Biomarkers to Predict, Track, and/or Inform Treatments

There is cause for optimism in the development of interventions designed to ameliorate the disabling cognitive deficits of schizophrenia. 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 (29). One promising intervention, Targeted Cognitive Training (TCT), is designed to sharpen the accuracy and fidelity of auditory information processing in schizophrenia via daily, computer-based exercises (29). Plastic changes within the neural substrates that subserve early perceptual processing are thought to feed forward to enhance higher-order cognition (8). Studies in schizophrenia patients who completed 50 h (1 h/d, 5 d/wk) of TCT demonstrated large effect-size gains in auditory-dependent cognitive domains (verbal learning and memory, $d = 0.86$–0.89) as well as global cognition ($d = 0.86$) and quality of life (29). Although TCT is efficacious at the group level, individual participant responses vary, with some patients showing little or no benefit (29). There is therefore a need to identify predictive biomarkers of response to this daily, resource-intensive intervention. Considering that MMN is regarded as a robust, reliable, and sensitive index of central auditory system plasticity (30) with important relationships to cognition and psychosocial functioning (15–18), could it also serve as a biomarker that predicts or corresponds to changes following TCT? Studies are underway to investigate this application, with a notable precedent showing that MMN predicts response to an intensive psychosocial skills training intervention (31). If successful, MMN could be used for biomarker-guided treatment stratification to optimize responses to even currently available treatments.

The collection of findings indicate that MMN—a low-cost, fast, and well-tolerated EEG-based translational biomarker—offers great promise for contributing to the continued development of pharmacologic and nonpharmacologic therapeutics (32). Moreover, MMN biomarker-informed prediction and treatment algorithms have the potential to pave the way for a next generation of "precision medicine" and perhaps even preemptive treatment approaches (1, 2).

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