Mismatch negativity as a “translatable” brain marker toward early intervention for psychosis: a review

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INTRODUCTION

Recent reviews and meta-analyses suggest that patients with shorter duration of untreated psychosis (DUP) show better symptomatic and functional outcome (1–3). For example, early detection in first-episode psychosis (FEP) leads to a higher percentage of recovery over 10 years relative to usual-detection patients (4). Furthermore, early intervention in individuals with clinical high-risk (HR) for psychosis attenuates their symptoms and potentially delays or prevents their transition to psychosis (5–9). These findings suggest that early detection and intervention play a critical role in the improvement of functional outcome and even in the prevention of psychosis.

High-risk individuals can be identified using clinical criteria based on symptomatology (10); the rate of transition to psychosis is approximately 35% within 2–3 years of follow-up (11), which is substantially higher than the incidence rate of psychosis in the general population. Higher sensitivity and specificity are required from the viewpoint of targeted early intervention.

For this reason, identifying biological markers in the early stages of psychotic disorders is an important step not only toward elucidating the underlying pathophysiology but also toward improving prediction of the transition to psychosis and introducing targeted early intervention to help-seeking individuals aiming for better outcome (12–14).

Auditory mismatch negativity (MMN) is a component of the event-related potential (ERP) and a promising biomarker candidate for psychotic disorders such as schizophrenia. A meta-analysis and several reviews of MMN in chronic schizophrenia (CSZ) are currently available (15–21). In this article, we focus on MMN in the early stages of psychotic disorders.

Mismatch negativity may also be a “translatable” biomarker because MMN reflects N-methyl-d-aspartte (NMDA) receptor function which plays a fundamental role in schizophrenia pathophysiology. Furthermore, MMN-like responses can be recorded in animals such as mice and rats. This article reviews MMN studies conducted on individuals with HR for psychosis, first-episode psychosis, recent-onset psychosis, and on animals. Based on the findings, the authors discuss the potential of MMN as a clinical biomarker for early intervention for help-seeking individuals in the early stages of psychotic disorder, and as a translatable neurophysiological marker for the preclinical assessment of pharmaceutical agents used in animal models that mimic early stages of the disorder.

Keywords: mismatch negativity, early intervention, first-episode psychosis, high-risk for psychosis, schizophrenia, animal, translatable
characteristics in the early stages of psychosis. Based on the results of these studies, the authors discuss the potential of MMN as a clinical biomarker for early intervention in help-seeking individuals and also as a translatable neurophysiological marker for the preclinical assessment of pharmacological agents tested in animal models that mimic early stages of the disorder.

**GENERAL BACKGROUND OF MMN**

Mismatch negativity is an ERP component elicited when an infrequent deviant stimulus occurs in a sequence of repetitive auditory stimuli. In an oddball paradigm, deviant stimuli differ from repetitive standard stimuli in one or more perceptual characteristics, including frequency, duration, intensity, location, spectrotemporal pattern, and phonemes (16, 19). MMN is even elicited under passive conditions when subjects ignore the stimuli. Thus, it is considered an index of preattentive auditory discrimination as well as a preattentive form of sensory memory (24).

Mismatch negativity relates to the difference wave obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP (Figure 1) and usually peaks between 150 and 250 ms after presentation of the deviant stimulus (24). On electroencephalogram (EEG), maximal MMN responses are evident at frontocentral scalp recording sites, with phase reversal at mastoids.

**MMN IN CHRONIC SCHIZOPHRENIA**

Reduced MMN amplitude is one of the most robust findings in schizophrenia (25), and the mean effect size is approximately 0.99 (17). Given its high test-retest reliability (26), MMN has been proposed as a statistically reliable biomarker for schizophrenia. Although many studies have used duration and/or frequency as deviant stimuli in auditory oddball paradigms, MMN in response to duration deviants (dMMN) and in response to frequency deviants (fMMN) have different sensitivity. Michie et al. (15) examined both duration and frequency deviants in CSZ patients and demonstrated that amplitude reduction is larger in dMMN than in fMMN. Meta-analysis conducted on CSZ patients also revealed that the effect size of dMMN is larger than fMMN (17).

Mismatch negativity amplitude reduction reflects sensory network dysfunction in schizophrenia, as attention and motivation have little effect on MMN (15, 16, 19, 24). This provides an important advantage in clinical settings since patients are not required to perform an active task.

Previous studies have shown that antipsychotic medication has little effect on MMN (27–32); however, recently Zhou et al. (33) reported that antipsychotics such as aripiprazole improve MMN amplitude reduction in schizophrenia. Benzodiazepine has been reported to have no significant effect on MMN amplitude (34). Interestingly, it has been suggested that drugs acting at the NMDA receptor may have a significant effect on MMN in schizophrenia. Lavoie et al. (35) reported that N-acetyl-cysteine, a glutathione precursor that can potentiate the activity of NMDA receptors, increases fMMN amplitude in schizophrenia patients. However, further studies are needed to clarify whether other modulators of NMDA receptors, such as glycine transporter inhibitors and D-serine, can similarly enhance MMN amplitude in schizophrenia. Correlations between MMN amplitude and clinical variables have been described in the literature. For example, it has been reported that the amplitude of dMMN is associated with social

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**FIGURE 1 | MMN waveform.** MMN relates to the difference wave obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP.
function (36), social cognition (37), and executive function (38) in CSZ, while phonetic MMN amplitude has been reported to be associated with verbal memory (39) and social skills acquisition (40). These findings indicate that MMN is a biologically and clinically significant index of schizophrenia.

**MMN IN PATIENTS WITH FIRST-EPISODE OR RECENT-ONSET PSYCHOSIS**

In recent years, the number of MMN reports on FEP and on recent-onset psychosis (ROP) has grown (see Table 1). These studies suggest that dMMN and fMMN have different properties, as seen in CSZ.

All of these studies reported a significant attenuation of dMMN and fMMN amplitude in ROP, including recent-onset schizophrenia (RSZ), subjects compared to healthy controls (HC). Excluding the findings of Magno et al. (46), they also reported a significant attenuation of dMMN amplitude in FEP subjects compared to HC. In contrast, only Devrim-Ucok et al. (45) noted a significant reduction of fMMN amplitude in FEP subjects compared to HC (see Table 2). Salisbury et al. (54) reported that fMMN amplitude in first-episode schizophrenia (FES) patients became significantly smaller compared to HC approximately 1.5 years after onset of the illness, which correlated with a reduction in Heschl’s gyrus volume. Thus, fMMN may reflect progression of the disease pathology, and dMMN amplitude may be attenuated before the onset of psychosis.

Within dMMN, the duration increment deviants (long duration) and the duration decrement deviants (short duration) may have different sensitivity. One study has demonstrated that a duration increment condition can discriminate between patients with CSZ and HC better than a duration decrement condition (16). While it is unclear whether this superiority of duration increment over duration decrement is true of FEP, it is interesting to note that all of the studies reporting a significantly attenuated dMMN in FEP or ROP utilized duration increments, whereas only Magno et al. (46) chose duration decrement and failed to show significantly decreased dMMN in FES (see Table 2). Atkinson et al.

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**Table 1 | Demographic data of previous studies of FEP or ROP.**

| Publication | HC | Patients | Comments |
|-------------|---------------------|---------------------|----------|
| N M/F Age | N M/F Age DOI (y) | | |
| Javitt et al. (41) | 20 8/7 36.3 (9.5) 13 (RSZ) 10/3 27.4 (2.7) | Most patients took medication |
| Salisbury et al. (42) | 27 20/7 24.2 (4.3) 21 (FES) 18/3 24.9 (6.2) | Most patients took medication |
| Oades et al. (43) | 22 12/10 176 (0.4) 28 (FES) 21/7 175 (0.4) | |
| Umbricht et al. (44) | 39 26/13 30.5 (7.1) 26 (FES) 19/7 23.9 (5.5) 0.05 (0.1) | Most patients took SGA |
| Devrim-Ucok et al. (45) | 34 19/15 24.5 (6.4) 30 (FES acute) 15/15 22.1 (5.7) 3.4 (1.5) | Ten acute FES patients took medication |
| Magno et al. (46) | 27 13/14 38.0 (12.9) 12 (FES) 9/3 24.3 (6.2) | Drug-naive except for one patient taking chlorpromazine |
| Todd et al. (47) | 14 7/7 24.0 (11.7) 14 (SZ short) 8/6 25.0 (10.7) 2.6 (1.7) | Most patients took SGA |
| Hermens et al. (48) | 17 7/9 22.6 (2.8) 17 (FEP) 12/5 22.5 (3.2) | Patients; 1 SZ, 3 SZA, 5 SZP, 2 BP, 6 MDD; Medication; 15 SGA, 9 AD, 3 mood stabilizers |
| Bodatsch et al. (49) | 67 35/32 25.8 (4.0) 33 (FES) 26/7 26.0 (6.5) | |
| Jahshan et al. (50) | 28 18/10 19.2 (3.4) 31 (RSZ) 25/6 29.8 (3.6) 1.2 (0.8) | Twenty-five patients took SGA |
| Kaur et al. (51) | 18 11/7 23.1 (3.0) 17 (FEPA) 10/7 22.8 (4.6) 18 (FES) 13/5 22.2 (3.5) | Most patients took SGA |
| Atkinson et al. (12) | 61 20/41 19 (3.5) 11 (FEP) 5/6 21 (2.7) | Eight patients took antipsychotics |
| Higuchi et al. (52) | 20 14/6 25.4 (6.9) 20 (FES) 9/11 272 (7.3) 0.65 (0.5) | Seven patients had no medication |
| Mondragon-Maya et al. (53) | 24 14/10 22.6 (5.8) 20 (FEP) 13/7 26.1 (7.2) | | Antipsychotic naive |

All values are shown as mean (standard deviation).
AD, antidepressant; BP, bipolar disorder; DOI, duration of illness; FEP, first-episode psychosis; FEPA, FEP with affective-spectrum; FES, first-episode schizophrenia; HC, healthy controls; MDD, major depressive disorder; ROP, recent-onset psychosis; RSZ, recent-onset schizophrenia; SGA, second-generation antipsychotics; SZ, schizophrenia; SZA, schizoaffective disorder; SZP, schizophreniform disorder.

FES acute means patients with FES on acute phase.
FES post means patients with FES on post-acute phase when their symptoms improved.
SZ short means patients with schizophrenia who received their first diagnosis within 5 years.
Table 2 | Oddball paradigm and results of previous studies of FEP or ROP.

| Publication | Deviant | Stimulus characteristics | Probability (%) | ISI/SOA | Electrodes | Results of MMN amplitude |
|-------------|---------|--------------------------|----------------|---------|------------|-------------------------|
|             | Standard (Hz) | Deviant (Hz) |                |         | FC         |                         |
|             | Frequency | Duration | Frequency | Duration |            |                         |
| Javitt et al. (41) | Duration | 1000 | 100 | 1100 | 100 | 12.5 | 667–770 | Fz | dMMN; HC > RSZ |
|             | Frequency | 1000 | 250 | 12.5 | | | | Fz | tMMN; HC > RSZ |
| Salisbury et al. (42) | Frequency | 1000 | 100 | 1200 | 100 | 5 | 333 | All and midline | tMMN; HC = FES |
| Oades et al. (43) | Duration | 800 | 80 | 800 | 40 | 10 | 850–1050 | FC | |
|             | Frequency | 600 | 80 | 10 | 850–1050 | | | FC | |
| Umbricht et al. (44) | Duration | 1000 | 100 | 1500 | 100 | 10 | 300 | FC | |
|             | Frequency | 1000 | 250 | 10 | 300 | | | FC | |
| Devrim-Ucok et al. (45) | Frequency | 1000 | 50 | 1500 | 50 | 20 | 1500 | FCP | tMMN; HC = FESa, HC > FESp |
| Magno et al. (46) | Duration | 1000 | 50 | 1000 | 25 | 10 | 500 | FC | tMMN; HC = FES |
|             | Frequency | 1200 | 50 | 10 | 500 | | | FC | |
| Todd et al. (47) | Duration | 1000 | 80 | 1000 | 125 | 6 | 450 | FC | tMMN; HC > SZ short |
|             | Frequency | 1200 | 80 | 6 | 450 | | | FC | tMMN; HC = SZ short |
|             | Intensity | 1000 | 80 | 6 | 450 | | | FC | iMMN; HC > SZ short |
| Hermens et al. (48) | Duration | 1000 | 50 | 1000 | 100 | 8 | 500 | Fz, Cz | dMMN; HC > FEP |
| Bodatsch et al. (49) | Duration | 1000 | 80 | 1000 | 40 | 10 | 500 ± 150 | FC | dMMN; HC > FES |
|             | Frequency | 1200 | 80 | 10 | 500 ± 150 | | | FC | tMMN; HC = FES |
| Jahshan et al. (50) | Duration | 1000 | 50 | 1000 | 100 | 10 | 500 | FC | dMMN; HC > RSZ |
| Kaur et al. (51) | Duration | 1000 | 50 | 1000 | 100 | 8 | 500 | Fz, Cz | dMMN; HC > FEPs, HC > FES |
| Atkinson et al. (12) | Duration | 1000 | 50 | 1000 | 100 | 7.5 | 600 | Fz, Cz | dMMN (increment); HC > FEP |
|             | Duration | 1000 | 100 | 1000 | 100 | 7.5 | 600 | Fz, Cz | dMMN (decrement); HC > FEP |
| Higuchi et al. (52) | Duration | 1000 | 50 | 1000 | 100 | 10 | 500 | Fz | dMMN; HC > FES |
| Mondragon-Maya et al. (53) | Frequency | 1000 | 100 | 1500 | 100 | 10 | 300 | FC | tMMN; HC = FEP |

FC, frontocentral; FCP, frontocentral and parietal; HC, healthy controls; ISI, interstimulus interval; FEP, first-episode psychosis; FEPa, FEP with affective-spectrum; FES, first-episode schizophrenia; ROP, recent-onset psychosis; RSZ, recent-onset schizophrenia; SOA, stimulus onset asynchrony; SZ, schizophrenia.

FESa means patients with FES on acute phase.

FESp means patients with FES on post-acute phase when their symptoms improved.

SZ short means patients with schizophrenia who received their first diagnosis within 5 years.

“A > B” means that A is significantly larger than B. “A = B” means that A and B are not significantly different.
(12) examined both duration increment and duration decrement and found that MMN to both duration deviants was reduced in FEP compared to HC. Discrepancies in the results of Magni et al. (46) and Atkinson et al. (12) may be due to differences in sample characteristics and the methods used to measure MMN.

The effect of medication on MMN has not been sufficiently investigated in FEP and ROP, although the finding that medication has little effect on MMN in CSZ lends to the possibility that a similar effect may be observed in FEP and ROP. However, further studies are needed to clarify this point.

Todd et al. (47) reported a significant positive correlation between fMMN amplitude and total score of the Schedule for Assessment of Positive Symptoms (SAPS), Delusions, Positive Formal Thought Disorder, and between iMMN amplitude and Halucination, which indicates that higher symptom severities were associated with smaller MMN amplitude. In contrast, no correlation was found between dMMN amplitude and SAPS. Other studies have reported that no significant correlation exists between MMN amplitude and positive symptoms, as assessed by the Brief Psychiatric Rating Scale (BPRS) or the SAPS (12, 42, 43, 45).

As to negative symptoms, Oades et al. (43) reported that reduced mastoid dMMN is related to anergia and flat affect, as assessed by the Schedule for Assessment of Negative Symptoms (SANS). Umbricht et al. (44) demonstrated that a larger fMMN is associated with a higher SANS total score. However, other studies have described no significant correlation between MMN amplitude and negative symptoms, as assessed by BPRS or SANS (12, 42, 45, 47).

Besides positive and negative symptoms, MMN amplitude has also been significantly associated with anxiety depression factor (42), Clinical Global Impression (CGI) (43), and cognitive functions (48, 51). On the other hand, it has been reported that MMN amplitude does not correlate with DUP (45), duration of illness (DOI) (46), or the Global Assessment of Functioning (GAF) (50).

Although a number of studies have noted a correlation between MMN amplitude and various clinical ratings in FEP as well as in CSZ, the findings are relatively inconsistent. Further studies with a large sample size are needed to confirm these correlations. In addition, a cross-sectional design study may not be appropriate since fMMN shows a progressive decrease after the onset of psychosis. Longitudinal studies will be more useful for investigating the association between MMN and clinical variables.

**MMN IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS**

Since Brockhaus-Dumke et al. (55) first examined MMN in individuals at clinical HR for psychosis, several MMN studies targeted at HR individuals have been reported (see Table 3). Regarding the criteria for HR, all of the studies utilized either the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (56), Comprehensive Assessment of At-Risk Mental State (CAARMS) (57), or the Structured Interview for Prodromal Symptoms (SIPS) (58). CAARMS and SIPS include three subgroups for HR: attenuated psychotic symptoms (APS), brief limited intermittent psychotic episode (BLIP), and genetic risk and deterioration syndrome (GRD). BSABS describes basic symptoms (59).

The average observation period in these studies was approximately 7 months to 2 years, and the rate of conversion to psychosis was as follows: 13% [2/16; (60)], 40% [25/62; (49)], 8% [2/26; (50)], 20% [6/30; (12)], 24% [10/41; (14)], and 24% [4/17; (52)]. Most of these rates were consistent with a previous study that assessed nearly 300 HR help-seeking individuals whose conversion rate was approximately 35% within 2–3 years of follow-up (11).

Most of these HR-focused studies examined dMMN (see Table 4), which might be because dMMN amplitude attenuation has a higher sensitivity than fMMN in FEP and in CSZ. Three studies examined fMMN (49, 53, 55), and all of them failed to show reduced fMMN amplitude in HR compared to HC, which is consistent with the previous findings that fMMN reflects the progressive pathological process and that fMMN amplitude reduction is marked after the onset of psychosis (54). Significant reductions of dMMN amplitude were observed in most of the studies (12, 14, 50, 60). However, in two studies, dMMN amplitude in HR individuals was not significantly smaller than that observed in HC, and dMMN amplitude of converters to psychosis was significantly attenuated compared to HC (49, 52). Therefore, dMMN amplitude reduction seems evident as early as before the onset of full-blown psychosis.

Shin et al. (60) demonstrated that a smaller left dMMN magnetic counterpart dipole moment was associated with a larger positive symptom score, as measured by CAARMS. Other studies reporting on the association between MMN amplitude and clinical symptoms, as assessed by BPRS, SANS, or SANS, have not described any significant relations. Although an association between dMMN amplitude and GAF was reported in CSZ, two studies that examined GAF and MMN in HR failed to find a significant relation (50, 60). As to the relation between MMN and cognitive function, Higuchi et al. (52) showed that a larger dMMN amplitude was associated with a larger score of verbal fluency, as assessed by the Brief Assessment of Cognition in Schizophrenia (BACS). On the other hand, Brockhaus-Dumke et al. (55) reported no relation with multiple domains of cognitive function.

Finally, dMMN might have the ability to predict the conversion from HR to psychosis. Bodatsch et al. (49); Shaikh et al. (14), and Higuchi et al. (52) reported that converters to psychosis have significantly reduced dMMN amplitudes at presentation relative to non-converters. Furthermore, Bodatsch et al. (49) showed that dMMN amplitude could predict onset of psychosis; a prognostic score was calculated based on a Cox regression model and stratified into two risk classes, which revealed significantly different survival curves. Previous studies with a large cohort of individuals at clinical HR have demonstrated that clinical variables such as clinical symptoms and social dysfunction can predict the onset of psychosis in multivariate prediction algorithms (11, 61). Thus, dMMN may improve the predictive power for onset of psychosis in HR individuals.

**MMN IN ANIMALS**

MMN-like responses have also been reported in monkeys (62, 63), cats (64), guinea pigs (65), rats (66–75), and mice (76–78). Some studies have reported that evoked ERP responses are not necessarily MMN in rabbits (79), rats (80, 81), and mice (82).
Table 3 | Demographic data of previous studies of HR.

| Publication | N     | M/F  | Age     | N     | M/F  | Age     | Criteria | Medication          | Conversion to psychosis |
|-------------|-------|------|---------|-------|------|---------|----------|----------------------|------------------------|
| Brockhaus-Dumke et al. (55) | 33    | 28/15| 24.5 (3.3) | 43    | 29/14| 25.4 (5.8) | BSABS    |                      |                        |
| Shin et al. (60)    | 18    | 12/6 | 22.1 (2.0) | 16    | 10/6 | 21.3 (3.2) | CAARMS   | 3 SGA                | 2 Individuals          |
| Bodartsch et al. (49) | 67    | 35/32| 25.8 (4.0) | 62    | 41/21| 24.8 (6.0) | BSABS    | None                | 25 (23 SZ, 1 SZP, 1 DD)|
| Jahshan et al. (50) | 28    | 18/10| 19.2 (3.4) | 26    | 22/4 | 21.9 (3.7) | SIPS     | 7 SGA                | 2 (1 Manic, 1 SZ)      |
| Atkinson et al. (12) | 61    | 20/41| 19 (3.5)   | 30    | 10/20| 17 (3.6)   | CAARMS   | 7 RIS                | 6 (3 SZA, 1 SZPa, 1 SZUn, 1 P-NOS) |
| Shaikh et al. (14)  | 50    | 25/25| 24.6 (4.5) | 41    | 26/15| 24.7 (4.7) | CAARMS   | None                | 10 (9 SZ, 1 Bipolar)   |
| Higuchi et al. (52) | 20    | 14/6 | 25.4 (6.9) | 17    | 4/13 | 19.4 (4.4) | CAARMS   | 3 AP                 | 4 (4 SZ)               |
| Mondragon-Maya et al. (53) | 24    | 14/10| 22.6 (5.8) | 23    | 16/7 | 20.1 (5.4) | SIPS     | None                |                        |

All values are shown as mean (standard deviation).

Table 4 | Oddball paradigm and results of previous studies of HR.

| Publication | Deviant | Stimulus characteristics | Probability (%) | ISI/SOA | dB | Electrodes | Results of MMN amplitude |
|-------------|---------|--------------------------|-----------------|---------|----|------------|-------------------------|
|             | Standard | Deviant | Frequency | Duration | Frequency | Duration |                      |                         |
| Brockhaus-Dumke et al. (55) | Duration | 1000 | 80 | 1000 | 40 | 10 | 500 ± 150 | 75 | FC | dMMN; HC = HR |
| Shin et al. (60) | Duration | 1000 | 50 | 1000 | 100 | 18.2 | 300 | 80 | FC | dMMN Dipole moment; HC > HR |
| Bodartsch et al. (49) | Duration | 1000 | 80 | 1000 | 40 | 10 | 500 ± 150 | 75 | FC | dMMN; HC = HR |
| Jahshan et al. (50) | Frequency | 1200 | 80 | 1200 | 80 | 10 | 500 ± 150 | 75 | FC | dMMN; HC > HR-C |
| Atkinson et al. (12) | Duration | 1000 | 50 | 1000 | 100 | 10 | 500 | 85 | FC | dMMN; HC > HR |
| Shaikh et al. (14) | Duration | 1000 | 25 | 1000 | 50 | 15 | 300 | 80 | FC | dMMN; HC > HR |
| Higuchi et al. (52) | Duration | 1000 | 50 | 1000 | 100 | 10 | 500 | 60 | Fz | dMMN; HC > HR-C |
| Mondragon-Maya et al. (53) | Frequency | 1000 | 100 | 1500 | 100 | 10 | 300 | FC | FC | dMMN; HC = HR |

FC, frontocentral; HR, clinical high-risk for psychosis; HR-C, HR who converted to psychosis; ISI, interstimulus interval; SOA, stimulus onset asynchrony.

"A > B" means that A is significantly larger than B. "A = B" means that A and B are not significantly different.

Previous studies using animal models have shown that antagonists of NMDA receptors reduce MMN (22, 69, 77). Given that NMDA receptors play an important role in the pathophysiology of schizophrenia, MMN may be a biomarker of dysfunctional NMDA receptors in this disease. Ehrlichman et al. (78) reported that mutant mice heterozygous for neuregulin 1 showed reduced MMN. Since neuregulin 1 is one of the susceptibility genes for schizophrenia, MMN may be an intermediate phenotype that links genes to schizophrenia. These findings suggest that MMN may be...
useful for investigating molecular and cellular mechanisms of schizophrenia.

Recently, the neural adaptation hypothesis has been proposed as a general mechanism underlying MMN, which challenges the traditional sensory memory hypothesis (83). The former hypothesis argues that repeated presentation of standard stimuli results in an adapted and attenuated response of neurons in the auditory cortex, whereas rare deviant stimuli evoke a larger response of neurons that are less adapted. Thus, MMN might reflect a stimulus-specific adaptation (SSA) rather than genuine deviance detection. A number of studies have attributed MMN-like responses to SSA in monkeys (84), cats (85), rats (86–91), and mice (92).

In order to resolve the controversy between the two hypotheses, several studies have adopted a many standards control paradigm to differentiate between SSA and genuine deviance detection. Some studies support the deviance detection theory (73, 74, 88), while others do not (84). Although NMDA receptor antagonists have been shown to attenuate MMN amplitude (22, 69, 77), Farley et al. (88) reported that SSA is not affected by NMDA receptor antagonism and suggested that the NMDA sensitivity reported for the MMN might occur at a mechanistic locus outside of SSA. In other words, the SSA hypothesis cannot explain MMN.

Recent modeling studies have proposed that MMN reflects prediction rather than adaptation (93, 94). These studies found that the prediction error hypothesis based on Bayesian inference can explain the property of MMN measured in human subjects. To our knowledge, however, there is no animal study that has investigated MMN based on the prediction error hypothesis. Since it has been found that NMDA receptor antagonists alter the process associated with prediction error (95), this hypothesis may provide a neurobiological mechanism that links NMDA receptors to MMN.

Overall, compared to human studies, there are more inconsistencies in the MMN studies carried out on animals. Even if MMN-like responses are evoked, the polarity and latency window of responses vary in rats (74). These inconsistencies could result from species or line differences, anesthesia effect, stimuli or paradigm differences, and different cortical layers targeted.

Improved protocols and replication of studies might overcome these variables, after which utilization of MMN as a translatable brain marker for the preclinical assessment of pharmacological components designed to improve symptoms and cognitive and/or functional impairment in individuals in the early stages of psychosis.

CONCLUSION
Mismatch negativity amplitude reduction is one of the most robust neurophysiological findings in schizophrenia patients. The amplitude of dMMN and that of fMMN have different characteristics. The fMMN amplitude may reflect the progressive pathological process and is attenuated after the onset of first-episode psychosis along with the reduction of Heschl’s gyrus volume. The dMMN amplitude reduces before the onset of psychosis and may be a significant predictor of the conversion to psychosis. Since early interventions may delay or prevent the transition to psychosis, dMMN may be useful for identifying people who require early intervention. In contrast, fMMN may be a potential therapeutic target for preventing the disease progression. Although further longitudinal studies are needed, MMN may be an important step toward introducing targeted early intervention of help-seeking people aiming for a better outcome.

Animal studies have shed light on the underlying cellular mechanisms of MMN. If further studies could clarify these molecular and cellular mechanisms then MMN could potentially be used as a translatable brain marker for the preclinical assessment of pharmacological components designed to improve symptoms and cognitive and/or functional impairment in individuals in the early stages of psychosis.

AUTHOR CONTRIBUTIONS
Tatsuya Nagai wrote the first draft of the manuscript. Mariko Tada, Kenji Kirihara, Tsuyoshi Araki, and Kyoto Kasai discussed and revised the manuscript.

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