Attenuated Mismatch Negativity in Attenuated Psychosis Syndrome Predicts Psychosis: Can Galantamine-Memantine Combination Prevent Psychosis?

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Abstract

Although first proposed in 1987, early diagnosis and intervention of psychotic disorders has only recently become a priority in the field. The interest in clinical high risk (CHR) for psychosis skyrocketed after attenuated psychosis syndrome (APS) was added to the DSM-5. There is evidence that in individuals with APS, attenuated mismatch negativity (MMN: functioning of the auditory sensory memory system) is a robust biomarker that can predict transition to psychosis. The underlying pathophysiological mechanism of MMN is via the interaction of N-methyl-D-aspartate (NMDA) and alpha-7 nicotinic acetylcholine (α-7nACh) receptors. Galantamine is an acetylcholinesterase inhibitor and a positive allosteric modulator of the α-7nACh receptors. Memantine is an NMDA receptor antagonist. Memantine has been shown to enhance MMN in people with schizophrenia. Although no studies with galantamine have measured MMN, encenicline, an α-7 nicotinic partial agonist, increased MMN in people with schizophrenia. MMN has been suggested as a potential biomarker with the galantamine-memantine combination for the treatment of neuropsychiatric disorders. Hence, the galantamine-memantine combination may enhance MMN, thereby preventing CHR to psychosis. With no treatments available, randomized controlled trials are warranted with the galantamine-memantine combination to delay or prevent conversion to psychosis in individuals with CHR.

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A focus on early intervention of psychotic disorders has emerged in the field. Clinical high risk (CHR) for psychosis [1] is diagnosed in individuals who meet at least one of the ultra-high risk inclusion criteria: brief limited intermittent psychotic symptoms, attenuated psychosis syndrome (APS), genetic risk and deterioration syndrome, and basic symptoms [2–4]. APS was added as a category in the DSM-5 as a condition for further study [5]. The DSM-5 APS criteria have similar prognostic accuracy as instruments used to assess CHR for psychosis such as the Comprehensive Assessment of at Risk Mental States [6].

Mismatch negativity (MMN) is a neurophysiological response elicited by a sequence of repetitive standard stimuli that is interrupted infrequently by a physically dif-

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ferent oddball stimulus. The nicotinic [7] and *N*-methyl-D-aspartate (NMDA) receptors [8] are critical for brain development. The underlying pathophysiological mechanism of MMN is via the interaction of NMDA [9–11] and alpha-7 nicotinic acetylcholine (α-7nACh) receptors [12–15]. Interneuron function is modulated by α-7nACh receptors that are activated by subcortical midbrain cholinergic pathways, which convey sensory gating responses from subcortical mechanisms, and NMDA receptors convey information about unusual or mismatched stimulus characteristics [16].

MMN, an index of a preattentive processing deficit, is reduced in schizophrenia [17]. Deficits in auditory MMN generation in schizophrenia have been replicated extensively since the 1990s. MMN deficits are tied to poor functional outcome [16, 18], as recently confirmed in a large cross-sectional study of 1,415 subjects with schizophrenia. In this study, early auditory processing event-related potential (MMN, P300, and reorienting negativity) predicted cognition ($\beta = 0.37$, $p < 0.001$), while cognition itself directly predicted negative symptoms ($\beta = -0.16$, $p < 0.001$) and indirectly predicted functional outcome [19]. Furthermore, MMN is highly predictive of response to auditory cognitive remediation [20]. MMN was found to be a sensitive and predictive biomarker of perceptual learning during auditory cognitive training in 28 individuals with schizophrenia [21].

In individuals with APS, attenuated MMN amplitude is a robust biomarker [22] that can predict (predictive value of 85%) a transition to psychotic disorder/schizophrenia [23]. However, a single time point of MMN to predict transition is unlikely to be the optimal approach [24]. MMN is a translatable brain marker toward early intervention for psychosis [25]. In 25 participants with schizophrenia, 21 first-degree relatives of participants with schizophrenia, and 29 healthy controls, MMN was a stronger predictor of functional outcome than cognition [26]. MMN was significantly reduced in the ultra-high risk group ($n = 42$, 27 completed the study) and in 6 participants who transitioned to psychosis compared to 29 healthy controls [27]. In a 6-year follow-up study comparing 47 healthy controls and 48 participants with CHR for psychosis, CHR nonremitters had reduced MMN at baseline compared to CHR remitters and healthy controls. The baseline MMN was the only significant predictor of remission [28].

Galantamine is not only an acetylcholinesterase inhibitor, but also a positive allosteric modulator of the $\alpha_4\beta_2$ and α-7nACh receptors. Memantine is a noncompetitive NMDA receptor antagonist. Galantamine and memantine are US Food and Drug Administration approved for the treatment of Alzheimer's disease (AD). In AD, galantamine 24 mg and memantine 28 mg daily are typically prescribed [29, 30]. The most common adverse reactions of galantamine (≥5%) are nausea, vomiting, diarrhea, dizziness, headache, decreased appetite, and decrease in weight [29]. The most common adverse reactions of memantine (≥5 compared to placebo) are headache, diarrhea, and dizziness [30]. However, these side effects are based on elderly people with dementia. Young adults with CHR may not have these side effects or may be able to tolerate galantamine and memantine better than the elderly. There are no specific contraindications with galantamine and memantine except known hypersensitivity to these medications [29, 30]. Galantamine and memantine are safe medications with no harmful short- or long-term side effects. Therefore, these individuals with CHR seeking help are more likely to remain adherent to "memory- and focus-enhancing medications." Finally, there is no compelling evidence to use antipsychotics to treat APS; in addition, antipsychotics are also associated with safety and ethical concerns.

MMN was enhanced in 13 healthy subjects with memantine 30 mg (Cohen $d = 0.87$) [31], in rodents with memantine 10 mg/kg [32], and in 41 people with schizophrenia with memantine 20 mg [33]. No studies with galantamine have measured MMN. However, a randomized controlled trial (RCT) of encenicline (an α-7 nicotinic partial agonist) in schizophrenia showed a dose-dependent increase in MMN [34]. Interactive effects of the α-7nACh and NMDA receptors on MMN are well documented [15, 35, 36]. MMN is a potential biomarker with the galantamine-memantine combination for treatment of neuropsychiatric disorders including, but not limited to, schizophrenia. Hence, the galantamine-memantine combination may enhance MMN, thereby preventing CHR to psychosis.

Cognitive and functional impairments are evident during the prodromal period [38]. In 3 meta-analyses comparing level of functioning ($n = 3,012$) and quality of life ($n = 945$), people with CHR had a significant impairment in functioning and worse quality of life than healthy controls [39]. Hence, the galantamine-memantine combination may not only enhance MMN, but also improve other cognitive symptoms and functioning as well. Negative symptoms are prevalent in CHR [40]; the galantamine-memantine combination may also improve these symptoms [37, 41]. In a meta-analysis of RCTs in people with schizophrenia ($n = 448$), memantine was found to have a trend ($p = 0.07$) antipsychotic effect compared to placebo [42]. This antipsychotic effect may be beneficial for transient and subthreshold attenuated psychosis.

The galantamine-memantine combination may be effective for cognitive impairments in schizophrenia [37, 41, 43–46]. Excess kynurenic acid (KYNA) may be associated with cognitive impairments in schizophrenia [47]. KYNA is an antagonist of the α-7nACh and NMDA receptors. The galantamine-memantine combination through the α-7nACh and NMDA receptors may counteract the effects of KYNA, thereby improving cognition [37, 41, 43–46]. Although the KYNA hypothesis is well established in schizophrenia [48, 49], there is no evidence of abnormal kynurenine pathway (KP) metabolites in CHR due to a lack of studies. Future studies are warranted to measure KP metabolites in CHR. KYNA and MMN are brain markers; the field has the opportunity to target both biomarkers concurrently with the galantamine-memantine combination [37] and "nip them in the bud" in people with CHR.

If RCTs are positive in CHR and full-blown schizophrenia, the galantamine-memantine combination may be utilized prodrome through syndrome. This is based on the assumption that not all CHR can be prevented from transitioning to first episode psychosis. Keep in mind that we may not detect all individuals with CHR, and several may have first episode psychosis even without having CHR. With no viable treatments available for individuals with CHR [50], RCTs are warranted with the galantamine-memantine combination to delay or prevent conversion to psychosis and schizophrenia. MMN may be utilized as target engagement to monitor progress with treatment.

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