Review

Alejandra Mondragón-Maya[1, 2]
Jorge Bernal-Hernández[1]
Guillermina Yáñez-Téllez[1]
Yaneth Rodríguez-Agudelo[2]

Mismatch Negativity (MMN) and schizophrenia: A revision

[1]Facultad de Estudios Superiores Iztacala
Universidad Nacional Autónoma de México

[2]Departamento de Neuropsicología
Instituto Nacional de Neurología y Neurocirugía
"Manuel Velasco Suárez"

The Mismatch Negativity (MMN) is an auditory Event-Related Potential which is generated as an automatic cerebral response to any change in the auditory stimulation that exceeds a limit corresponding to the discrimination threshold. It has been widely and consistently reported that patients with recent and chronic schizophrenia display smaller MMN amplitudes, suggesting that this component may be related with alteration in sensory memory and stimuli integration capacities, which seem to increase with the disease progression. Recently, new research areas have emerged, and studies of MMN of relatives of patients with schizophrenia have been conducted in order to assess the MMN efficacy as an endophenotype. Likewise, there have been MMN studies in schizophrenia prodromes or clinical high risk subjects, aiming to know if there are cerebral processing disturbances prior to the onset of the disease. The results of these studies have been promising, suggesting the presence of auditory stimuli processing disturbances in this population. These disturbances are subtle and seem to increase as the disease appears. The MMN component may be a very effective electrophysiological tool that provides information about the automatic auditory processing in schizophrenia related to its chronicity. It may also be a relative reliable index of genetic vulnerability and clinical risk for developing schizophrenia. Nevertheless, it is necessary to continue performing studies to get comparable and replicable studies in the future that could confirm the information about MMN utility.

Key words:
Mismatch Negativity (MMN), Schizophrenia, Prodromes, High clinical risk, Endophenotype, Auditory sensory memory

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Correspondence:
Dra. Yaneth Rodríguez Agudelo
Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez"
Departamento de Neuropsicología
Insurgentes Sur 3877, Col. La Fama
C.P. 14269, México D.F.
Tel. (5255) 55287878
E-mail: yaneth_r@hotmail.com

Mismatch Negativity (MMN) y esquizofrenia: Una revisión

El componente Mismatch Negativity (MMN) es un Potencial Relacionado con Eventos (PRE) de tipo auditivo, que es generado por la respuesta cerebral automática a cualquier cambio en la estimulación auditiva que excede un límite correspondiente al umbral de discriminación. Se ha reportado amplia y consistentemente menor amplitud de MMN en pacientes con esquizofrenia reciente y crónica, por lo que se ha propuesto que este componente se relaciona con alteraciones en la memoria sensorial y en las capacidades de integración del estímulo, las cuales parecen progresar a lo largo de la enfermedad. Recientemente se han abierto nuevas líneas de investigación al respecto, y se han realizado estudios con familiares de pacientes con esquizofrenia para evaluar la eficacia de la MMN como endofenotipo. Asimismo, se han llevado a cabo estudios de MMN en pródromos o sujetos en riesgo clínico de desarrollar esquizofrenia, con la finalidad de conocer si existen alteraciones en el procesamiento cerebral previas al inicio de la enfermedad. Los resultados de estos trabajos han arrojado resultados prometedores, que sugieren la presencia de alteraciones sutiles en el procesamiento de estímulos auditivos en esta población, las cuales parecen aumentar con la aparición de la enfermedad. Es así como el componente MMN puede ser una herramienta electrofisiológica eficaz para proporcionar información sobre el procesamiento automático auditivo relacionado con la esquizofrenia y su cronicidad, así como para indicar la vulnerabilidad genética y riesgo clínico para desarrollarla. Sin embargo, es necesario realizar estudios futuros comparables y replicables que permitan confirmar tales hallazgos.

Palabras clave:
Mismatch Negativity (MMN), Esquizofrenia, Pródromos, Sujetos en riesgo clínico, Endofenotipo, Memoria sensorial auditiva

INTRODUCTION

Definition and characteristics of the MMN component

The MMN component is an Event-Related Potential (ERP), which is generated by the automatic cerebral response

to any change in the auditory stimulation that exceeds a limit corresponding to the discrimination threshold. Thus, when a stimulus with a different, duration, intensity or localization is presented in a series of stimuli with already established characteristics, the MMN appears. When there is an auditory stimulus, this is automatically compared with the previous stimuli. If the stimulus is different, MMN appears. This automatic cerebral response indicates that MMN has a pre-attentive nature, that is, its generation is related to processes that are independent from attention.[1]

The MMN component is a negative wave, whose appearance is typically found between 100-250 ms after the initiation of the different stimuli and reaches maximum voltages in the frontal and central zones.[2, 3] It should be stated that MMN is defined as a differential waveform, that is obtained through the subtraction of ERP obtained from the different stimulus minus the ERP obtained from the standard stimulus.[2, 4]

An important requirement to obtain the MMN is that the central auditory system has a representation of the characteristics of the repetitive auditory stimulus so that the MMN appears when any stimulus appears that violates said representation because of differences of one or several of its characteristics.[2]

The MMN has polarity and latency characteristics that are similar to other electrophysiological components such as the case of the N1 and N2b. However, the MMN shows specific attributes that make it possible to differentiate it from these. On the contrary to the N1, whose generators could be in the dorsal surface of the temporal lobes,[5] the MMN seems to have a supratemporal generator[6-8] and may be registered in the newborns.[9-12] In addition, it has been reported that when subjects are trained in complex discrimination tasks, the amplitude of the MMN increase, which does not occur with the N1.[13] On the other hand, the possibility of an overlapping of MMN on N2b has been proposed. However, the MMN shows an inversion of polarity in mastoids on being referenced to the nose while the N2B does not show such an inversion.[2]

Paradigms for obtaining MMN

The paradigm used most to obtain MMN is the classical condition called "*oddball,*" where frequent stimuli occur with established characteristics that are mixed with infrequent stimuli that differ in some of these characteristics (duration, frequency, intensity or localization).[2] Lang et al.[14] and more recently Duncan et al.,[15] have established some parameters for the standardized obtaining of the MMN, for which they suggest the maintenance of a proportion of probability of appearance of the frequent and infrequent stimuli of 0.85 and 0.15, respectively. In fact, it has been observed the lower the infrequent stimuli are maintained, the clear the appearance of the MMN.[2, 4] Furthermore, it has been suggested that the best way to obtain the MMN is under passive stimulation conditions, that is, it is not necessary for the subject to direct their attention towards the auditory stimulation applied. The subject can be performing another activity during the registry (reading, watching a video).[15, 16] It is recommended that the electrode used as reference should be placed on the tip of the nose. It is also suggested to place mastoid electrodes, to then re-reference the registry with these electrodes and more clearly observe the component, improving the signal-to-noise ratio.[14, 15, 17] Furthermore, during the registry originally referenced to the nose, an inversion of the MMN in the electrode placed on the mastoid is observed, confirming the presence of MMN and differentiating it from other potentials such as the N100 or N200.[2]

The duration of the paradigm "*oddball*" is variable, since it depends on the total number of stimuli presented. However, because the difference in the proportion between frequent and infrequent stimuli is very large, a significant total number of stimuli is necessary to have a sufficient amount of infrequent stimuli. This may require a considerable registry time, from 75 minutes up to 3 hours.[4] If there are several types of infrequent stimuli in this paradigm, each type of infrequent stimuli would usually occur in a separate block in order to avoid the contamination that may appear when several types of infrequent stimuli occur in the same stimulation block. (Figure 1.A)

In recent years, Näätänen et al.[18] have proposed new paradigms called "optimals" for the registry of MMN in order to overcome the disadvantage in regards to the long duration of the registry when an attempt is made to obtain a MMN to several types of infrequent stimuli that differ from the standard stimulus. In the paradigms proposed by Näätänen et al., 5 types of infrequent stimuli are incorporated in the same block (that differ in frequency, duration, intensity, localization and interruption of the tone presentation), under the logic that the other infrequent stimuli reinforce the memory trace of the standard stimulus in regards to those attributes of the stimuli that they could have in common. Because there are different stimuli in a same block, the registry duration is less than under the "oddball" condition, it being between 15 and 18 minutes approximately (Figure 1.B, 1.C).

MMN Generators

Several studies have reported that the MMN registries show greater amplitude in frontocentral areas, suggesting the sum of the activity of both supratemporal cortices.[6-8] These results

Figure 1A

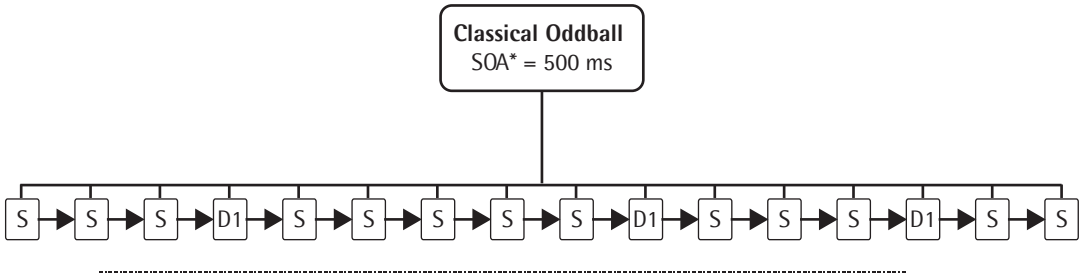


Figure 1B

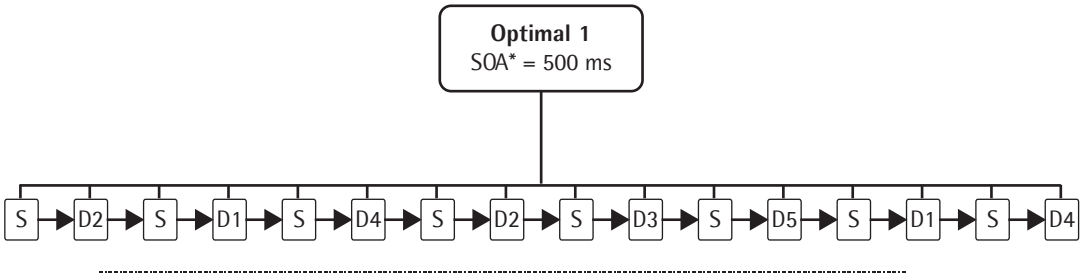
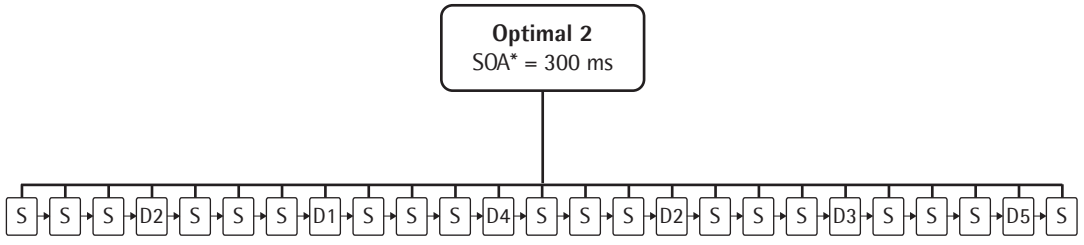


Figure 1C



S: Standard Stimulus; D: Different Stimulus; the number indicates the type of different stimulus that is presented (frequency, duration, intensity, localization, interruption of tone); *SOA: stimulus onset asynchrony: it refers to the interval between the onset of the stimulus and another one.

Figure 1 Paradigms used to obtain MMN

coincide with investigations where magnetoencephalographic registries have been made of the MMN, that show maximum signals in both supratemporal cortices.[19, 20]

In a review by Alho[7] on the possible MMN generators, it is suggested that the auditory cortex is related to the generation of MMN. However, the exact localization of this generation could depend on the type of characteristic in which the infrequent stimulus (frequency, duration, intensity or localization) is differentiated and on the complexity of the stimulus (simple tones vs. complex sounds). Thus it appears that the different characteristics of the stimuli are processed in different regions of the auditory cortex, where this potential seems to be generated.

In addition to the activation of the auditory cortex, activity has been observed in the frontal cortex related with the appearance of MMN.[21, 22] This activation is greater in the right hemisphere.[21] It has also been reported that the frontal activation seems to be slightly delayed in relation to the supratemporal activation, this suggesting functional differences of both generators.[23]. This is how the two components making up the MMN have been defined up to now: one temporal, followed shortly after by another frontal one. The functional differences proposed on both components will be explained further below.

Some animal studies have reported relations between the appearance of MMN and activity in the thalamus and

hippocampus.[24, 25] However, the role these structures play in its generation is still not clear.

Cognitive processes related to MMN

As previously mentioned, the MMN is a potential having a pre-attentive nature. When an auditory stimulus is presented, this is compared automatically with the previous stimuli. If the stimulus is different, the MMN appears. That is how the generation of the MMN is an indicator of the auditory sensory memory, reflecting the context-dependent information processing on the level of the auditory cortex.[26] If only one sound is presented, without the existence of previous ones, the MMN does not appear.[27, 28] These findings have reinforced the idea that the MMN is related to a sensory memory trace, which has an approximate duration of 6 to 10 seconds.[29] Thus, the MMN may be considered to be the result of a discrimination process, where the different stimulus is identified as incongruous with the representation of memory that contains the predecessor stimuli, even in absence of attention.[2] In this way, it has been suggested that the MMN represents the initial process of important biological cognitive events involved in the alerting and redirecting of the attention of the body towards a novel and potentially significant stimulus of the setting.[3]

It has been proposed that the supratemporal component of the MMN is principally associated with the pre-perceptual detection of the change of a characteristic of the stimulus, while the frontal component (which appears shortly after that of the supratemporal) seems to be associated to the involuntary change of attention caused by the difference between the context and the different stimulus.[22, 30, 31] In accordance with these findings, it has been suggested that the stimulus change detector signal generated in the auditory cortex precipitates the frontal mechanisms of change of attention.[32]

Näätänen and Winkler[33] have proposed that during the integration of the stimulus, the stimulus is processed in each one of its characteristics (tone, duration, intensity or localization) and then as a unit. According to these authors, the integration of the different characteristics of the stimuli is presumably carried out during a period of 150-200 ms after the stimulus is presented. This period is called Time Window of Integration (TWIG). After, the representation of the stimulus arises as a unit, which forms the memory trace.

On the other hand, Garrido et al.[34] have proposed that the MMN may represent an error detection marker caused by the change of any characteristic of the stimulus within a series of equal stimuli. This error detection is the result of the erroneous prediction of the system based on the previous stimulation. When the system receives information with the same characteristics, this "predicts" or expects that the following stimuli will be maintained the same. However, when there is a change, then the system detects the erroneous prediction that is translated into the MMN.

This is the way in which the MMN can be considered as an indirect indicator of different cognitive processes that involve the integration and discrimination of the incoming stimuli and of the most complex cognitive functions as the auditory sensory memory and involuntary attention.

MMN in research and the clinical practice

One of the principal characteristics of the MMN paradigms is that the subject is not asked to carry out any specific task related with the component. That is why its application in clinical and research settings is extensive. In this way, it has been suggested that the MMN is an objective tool that makes it possible to study the physiology of the upper brain functions, independently of motivation, general intellectual ability or performance of the individual.[17]

The MMN is the earliest ontogenetically cognitive ERP that has been recorded in the human being.[9, 10] Thus, the clinical use of the MMN has been proposed in the field of neuropediatrics to know and detect development problems related to alterations in the auditory cortex.[35] Furthermore, the component has been used in the evaluation of learning problems such as dyslexia. The supposition underling the use of MMN in this population suggests that MMN is a neurophysiological indicator of the brain capacity to perform auditory discriminations in the face of small physical differences between acoustic stimuli or language sounds, so that its use in patients with dyslexia could reflect alterations in the stimulus discrimination process.[17] In these studies, a lower amplitude of MMN has been found in subjects with dyslexia compared to healthy subjects.[36, 37]

Some studies have also been found in which the MMN has been recorded in patients with neurological alterations. This is the case of Alzheimer's Disease,[38] chronic alcoholism,[39, 40] Parkinson's Disease[41-43] and comatose states.[44, 45] Smaller amplitudes of the MMN component have been reported in both Alzheimer's Disease as well as in chronic alcoholism when the inter-stimulus interval (ISI) is greater. This suggests alterations in the duration of the auditory sensory memory. In both conditions, using the MMN is important because it is a neurophysiological indicator of the mnesic functions, especially those related with sensory memory.[17] Such functions are affected both in patients with Alzheimer's Disease and in those with chronic alcoholism. In regards to Parkinson's Disease, there are contradictory reports that have found normal MMN[42, 43] and MMN reduced in

amplitude.[41] In accordance with Pekkonen,[46] the great variability of results observed in the studies in this population mainly arise from methodological differences and the few reports described, so that it is difficult to make a conclusion about it. On the other hand, besides the studies of patients in comatose states, the use of MMN has been proposed as a prognostic tool for the recovery of consciousness. On the contrary to the clinical evaluation and use of short late evoked potentials, the cognitive components, such as MMN make it possible to evaluate the upper cognitive functions (perception, attention, memory), indicating the abilities of the subject to recover consciousness.[47] Thus, under this supposition, different studies have been performed in which it is reported that those patients in coma who are capable of generating cognitive ERP tend to recover consciousness in the following days, weeks or months[48] MMN has been widely used in this field, since, as previously mentioned, it does not require a behavior response from the subject. From the theoretical point of view, it has been suggested that the subjects who are in a comatose state and can recover consciousness have the capacity to discriminate between different types of sounds. This implies that they are capable of creating and using neuronal representations of the immediate auditory sensory setting.[49]

The MMN has also been used in the evaluation of psychiatric and personality disorders. This is the case of Post-traumatic Stress Disorder (PTSD) and impulsive personality. Morgan III and Grillon[50] recorded the MMN of sexual abuse victim women who fulfilled the PTS criteria. They reported an increase in the amplitude of the component compared to a control group. This increase correlated with a scale that evaluated the symptoms of this alteration. The authors concluded that patients with this type of disorder could have auditory sensory memory problems due to the increase in sensitivity to stimulation changes. Another studied recorded the MMN in individuals with impulsive personality[51] in order to know the involuntary pre-attentive process in this population. The authors found a negative correlation between MMN amplitude and impulsivity levels reported by the subjects. Based on these findings, they suggest that the automatic processing of incoming stimuli that seem to be developed in the temporal lobes is strongly related with the impulsive behavior.

The psychiatric disorder studied the most in this regards has been schizophrenia. Several investigations have reported significant deficiencies in the MMN amplitude of these patients.

MMN and schizophrenia

Schizophrenia is a chronic psychotic disorder whose prevalence in adults is 0.5 to 1.5%.[52-54] The characteristic symptoms of the disease involve a range of cognitive and emotional dysfunctions that include perception, inferential thinking, language, behavior, affect, fluency and productivity of thoughts and speech, volition, drive and attention.[53]

The symptoms of schizophrenia are classified into positive and negative symptoms. Positive symptoms refer to behaviors and thoughts that are not present in the general population (hallucinations, delusions, bizarre/extravagant behavior) while negative symptoms refer to behaviors and thoughts that are present in the general population and absent in patients with schizophrenia (affective flattening, poverty of speech, apathy). Furthermore, the presence of cognitive disorders, mainly in attention, language, memory and executive functions, has been extensively documented as part of the symptoms of schizophrenia.[55] Several studies have reported the presence of these alterations together with affective and social changes that appear years before the first episode of the disease.[56-60] This period is known as the prodromic or pre-psychotic phase of the disease. In addition, the presence of cognitive and psychiatric alterations in healthy family members of schizophrenic patients has been widely documented.[61-64] This supports the notion of the hereditary character of the disease. However, the genetic influence of the disease is not governed by the classical genetic laws, but rather is the product of the interaction between several genes that establish vulnerability, but not the presence of the disease. Great efforts have been made to identify objectively those inheritable traits that are reflected in the particular characteristics (for example, cognitive functions) related with the genes involved with schizophrenia (endophenotypes) in order to better understand the etiology of the disease.

Because the MMN has been associated with processes related to auditory sensory memory and with the ability to discriminate incoming stimuli, there is great interest about its evaluation in subjects with schizophrenia, in order to know if there are alterations during these first phases of information processing.

MMN in patients with schizophrenia

A frequently reported finding in schizophrenia is the decrease in the MMN amplitude. The first study that described this fact was that of Shelley et al.[65] These authors based their findings on previous studies that reported alterations in selective or controlled attention processes in schizophrenic patients. They proposed that these deficiencies could be the result of automatic, pre-attentive alterations represented by the MMN. In this study, MMN was recorded in 11 medicated schizophrenic patients and 11 control subjects paired by age and gender. Two types of infrequent stimuli classified by duration were used: one with increase

and another with decrease. All the tones were 633 Hz and 80 dB, with a 10% probability for the appearance of the infrequent stimuli. The subjects were asked to perform a simple visual discrimination task during the registry so that they would not be paying attention to the auditory stimulus. Shelley et al.[65] found a lower MMN amplitude in schizophrenic subjects compared to control subjects for the infrequent stimuli that had a longer or shorter duration. The difference was statistically significant in the control group only in the first case, while it was not in the second case. After this first report, there were several studies that focused on knowing the differences in MMN amplitude presented by the subjects with schizophrenia[66-71] as well as the effect of antipsychotics on this component,[72, 73] the specificity of MMN on schizophrenia compared to other psychotic disorders such as bipolar disorder,[74] and the relation of the component with clinical characteristics of the disease,[70] among others. In the studies that have evaluated the effect of antipsychotics on MMN, it has been reported that there are no differences between the subjects treated with typical and atypical antipsychotics.[72, 73] In regards to the specificity of MMN in schizophrenia, Umbricht et al.[74] compared the amplitude of MMN in 26 schizophrenic patients, 16 with bipolar disorder and 25 psychiatrically healthy controls. They found significantly decreased MMN amplitudes in schizophrenic patients compared to bipolar and control patients, suggesting the presence of alterations in the early processing of auditory stimuli that is specific to schizophrenic patients. Based on these data, the authors concluded that the alterations observed in the MMN seem to be specific to schizophrenia. On their part, Light and Braff[70] registered 25 patients with schizophrenia using the oddball paradigm of MMN and they applied a battery of tests that evaluated daily living skills. These authors found that the subjects who had lower MMN amplitudes also reported less skill and greater disability in activity of daily living, suggesting that the alterations in the MMN represent specific neurophysiological deficits, that may be associated with global alterations in activity of daily living.

Most of the studies on MMN and schizophrenia have used those stimuli that vary in duration or frequency as infrequent stimuli. Duration is the characteristic of the infrequent stimulus used most and that has demonstrated greater specificity in the face of schizophrenia.[66] In fact, a meta-analysis on MMN and schizophrenia, performed by Umbricht and Krljes,[73] found that duration is more sensitive than frequency in patients with schizophrenia. However, they also proposed that alterations in MMN observed in the face of stimuli that differed in frequency could be associated with the chronicity of the disease while MMN alterations in relation to stimuli differing in duration seem to be present from the early stages of the diseases.

There are several studies in patients with schizophrenia in which duration is the characteristic of the infrequent stimulus. In these studies significantly lower amplitudes of MMN were found compared to the control groups.[65, 70, 71, 74, 75] However, there are other studies that do not report significantly reduced MMN amplitudes in this population, using duration as the characteristic of the infrequent stimulus.[76, 77] It should be mentioned that on the contrary to the other studies reviewed in which the reference during the registry was the tip of the nose, in the Korostenskaja et al. study,[77] the ear lobe was used and in that of the Thönnessen et al. study,[76] the Cz electrode was used. Thus, there seems to be a tendency of the patients with schizophrenia to have a lower amplitude of the component, however, the differences in the registry technique and obtaining of the potential can hinder the complete affirmation of this fact.

In regards to frequency as a different characteristic of the infrequent stimuli, there are also discrepancies in the results reported. Salisbury et al.[78] performed a study in which they compared 21 subjects with a first episode of schizophrenia with 16 chronic subjects. Both groups were paired by age with healthy subjects. These authors used a MMN paradigm in which the infrequent stimulus differed in frequency (standard: 1000 Hz/100 ms; infrequent: 1200 Hz/100 ms). The chronic patients had significantly lower amplitudes of MMN compared to the control subjects. However, no differences were found in the group of patients with a first episode. Umbricht et al.,[74] in his study on specificity of MMN in schizophrenia, observed an MMN amplitude decrease in the face of stimuli with different frequency, although these data did not reach statistical significance. After, these same authors performed a study, comparing MMN in 3 groups of patients with schizophrenia: patients with a first episode, with a recent diagnosis (1.5 to 5 years) and chronic patients (more than 5 years)[71] in order to discover if the chronicity of the disease is related to alterations in MMN amplitude. They found that both patients with recent diagnosis as well as chronic patients had significantly lower MMN amplitudes than the patients with first episode, both in stimuli that differed in duration as well as in frequency. This suggests that the MMN can be an indicator of alterations in cognitive processes associated to the disease progression. More recently, Todd et al.[79] carried out a study in which the MMN was recorded, using different characteristics of the infrequent stimulus (duration, frequency and intensity) in subjects with recent diagnosis of the disease (x = 2.6 years) and chronic subjects (x = 18.9 years) compared to an age-matched control group. They found that the subjects who had been diagnosed for a short time showed a lower amplitude of MMN in the factor of stimuli that were different in duration and intensity while the chronic patients had a lower amplitude of MMN in the face of stimuli that differed in frequency and duration. These results suggest that there may be a different pattern of MMN during the course of the disease and that the infrequent stimuli may be complementary to know the neuropathological changes that occur during the disease.

The findings of these different studies suggest that duration and frequency as characteristics of the different stimulus represent different processes of integration of the stimulus and may even be indicators of cognitive deterioration as part of the disease progression.

In accordance with the functional significance of the MMN, it has been proposed that the lower amplitude in schizophrenia subjects is an indicator of an alteration in the auditory sensory memory.[79, 80] However, the fact that most of the studies report consistent reports regarding the use of duration as a characteristic of infrequent stimuli more than other characteristics has lead to the proposal that the alteration in the auditory sensory memory is not generalized but that it may be that specific processes involved with the perception and integration of the stimulus are those that are affected in schizophrenia.[81] More specifically, a deficit in processing the temporal properties of the stimuli has been proposed. In accordance with Mitchie,[66] reduction of MMN in the face of infrequent stimuli whose different characteristic is duration may be the result of an alteration in the early Temporal Integration Window (TIW). This author proposes that the infrequent stimuli occurring at intervals less than 300 ms are those that show more sensitivity in the decrease in MMN amplitude in schizophrenic patients, a time that coincides with the duration of the TIW, period during which the temporal integration process of the characteristics of the stimulus are performed.

MMN as endophenotype

An endophenotype represents those observable characteristics of the organism that are the product of the interaction of genetic and environmental influences. An endophenotype is not clinically observed but can be indirectly observed through performances or carrying out of specific tasks. It has been proposed that endophenotypes are closely linked to genes susceptible to the disorder, these being characterized by being highly inheritable, being associated with the disease, being independent of the clinical condition and occurring in several members of a same family.[82]

Some studies have been carried out to know if the first degree relatives of patients with schizophrenia, considered as subjects with genetic risk, also have MMN amplitude deficiencies) in order to evaluate the role of MMN as a probable endophenotype of schizophrenia. The results have been contradictory since the studies performed by Jessen et al.[83] and Mitchie et al.[84] show a clear reduction of MMN in first degree relatives of subjects with schizophrenia, principally using paradigms where the characteristics of the different stimulus were frequency[83] and duration.[84] On their part, Bramon et al.[85] and Magno et al.[86] did not find differences in MMN amplitude in relatives of schizophrenic patients. Both studies used frequency and duration as characteristics of the different stimulus. However, they used paradigms with different parameters in regards to number of stimuli, duration of registry, characteristics of standard and infrequent stimuli and stimulus onset asynchrony. (SOA). Thus, it is important to establish defined guidelines or parameters that make it possible to compare the results between studies that have been performed under similar conditions.

Thus, it is necessary to continuing investigating on the efficacy of MMN as probable endophenotype for schizophrenia in order to know the inheritable biological mechanisms underlying the disorder.

MMN in persons at clinical risk of developing schizophrenia

As previously mentioned, schizophrenia has a prodromic or pre-psychotic phases in which subclinical cognitive, affective and social alterations appear.

In recent years, the need to establish indexes for early detection of schizophrenia has been suggested in order to offer the pertinent diagnosis and intervention and thus contribute to improvement of the prognosis and quality of life of the patient.[87] Up to the present time, the methods to identify the at risk population or prodromes of schizophrenia have principally focused on clinical interviews and neuropsychological evaluations. Little has been investigated on the electrophysiological changes linked to the prodromic state of schizophrenia. The studies performed using the MMN in prodromes are scarce. However, new fields of research in this regards are being opened. Such is the case of the Brockhaus-Dumke, Tendolkar and Pukrop study[88] who reported a lower amplitude of MMN in prodrome subjects in the face of infrequent stimuli that differ in duration from the standard ones. However, these differences were not statistically significant when control subjects and schizophrenic patients were compared. Nonetheless, it was observed that the amplitudes of the MMN in prodromes were found in intermediate values between control and schizophrenic subjects.

Recently, Soon Shin et al.[89] performed a magnetoencephalographic study to register the MMNm in prodrome subjects in order to evaluate pre-attentive auditory processing in this population. Sixteen patients identified as prodrome and 18 control subjects matched by age, gender and educational level were evaluated. An oddball paradigm was used in which the infrequent stimuli differed in duration from the standard ones, the infrequent ones being 100 ms and the standard 50 ms. These authors reported a significant reduction of the right dipole of the MMNm and

increase of the latency of the MMNm in comparison with the control group and a negative correlation between the left dipole and clinical symptoms evaluated by clinical interview. In accordance with these results, the authors suggest the existence of alterations in the early auditory processing in the face of the appearance of the disease, reflecting a function decline during the prodromic phase.

More studies of MMN are needed in this population to know if the subjects who are at clinical risk of developing schizophrenia have alterations in said component. This could lead to the incorporation of the use of the MMN as part of the comprehensive evaluation of the prodrome that would make it possible to establish the pertinent diagnosis.

CONCLUSIONS

The MMN is the event related potential (ERP) used as an indicator of the pre-attentive processes in the face of auditory stimuli. Because it is not necessary for the subject to direct attention towards the stimuli presented, it has been widely used in the clinical and research setting to know the auditory processing in different clinical populations, going from newborns to patients with dementia.

One of the lines of research that have been opened in recent years is the registry of the MMN in psychiatric disorders, especially in schizophrenia. A lower MMN amplitude has been widely reported in schizophrenic subjects compared to control subjects, principally when duration and frequency are used as alterations different from the standard ones presented. Each one of these characteristics seems to represent different alterations in the processing of the stimuli, principally related with the disease evolution time since the duration as infrequent characteristic tends to be more sensitive in subjects with recent diagnosis of the disease and in subjects with genetic or clinical risk while frequency seems to be more sensitive in chronic subjects. This has led to the suggestion that the alteration in auditory stimuli processing is not generalized but specific to the characteristics of the stimulus to be processed and that these alterations should progress with the evolution of the disease. Thus, it is necessary to continue along this line of research to obtain better information on the electrophysiological changes underlying the disorder. However, it should be mentioned that it is important to standardize the procedure of registry and to obtain the potential in order to reduce the variability of the results between studies or at least to follow the parameters established by the authors specialized in the subject, as Lang et al. and Duncan et al.,[14, 15] so that they can be compared.

In addition to the extensive literature that reports alterations in the MMN amplitude in subjects diagnosed with schizophrenia, in recent years, new lines of investigations have been opened in which it has been proposed that the MMN may represent an endophenotype. This could indicate the genetic vulnerability to develop the disease in relatives of patients with schizophrenia. However, the studies performed up to the present have not provided consistent results.

On the other hand, the evaluation of MMN in subjects at clinical risk or prodromes of schizophrenia is a very novel line of investigation. Thus line has demonstrated promising results that may provide important data on the electrophysiological and neuropsychological changes presented by vulnerable subjects before the development of the disease. In these studies, subtle changes have been observed in the MMN amplitude, which could be indicators of the presence of alterations in the process of integration of the stimulus or in the sensory memory trace. These alterations seem to become clearer when there is a complete clinical picture. That is how the MMN seems to make up a reliable indicator of vulnerability to develop schizophrenia. However, it is suggested that more studies should be performed to confirm the results of these first investigations.

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