REVISTA CEFAC
SPEECH, LANGUAGE, HEARING SCIENCES AND EDUCATION JOURNAL
Rev. CEFAC. 2016 Jul-Ago; 18(4):952-959 doi: 10.1590/1982-0216201618423415

Original articles

Applicability of Mismatch Negativity in children and teenagers: a descriptive review

Aplicabilidade do Mismatch Negativity em crianças e adolescentes: uma revisão descritiva

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Conflict of interest: non-existent

Received on: December 30, 2015
Accepted on: April 15, 2016

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ABSTRACT

The Mismatch Negativity (MMN) is a cortical potential that occurs in response to an acoustic stimulus modification amid a repeated stimuli sequence, which reflects the brain capacity of discriminate the sound passively, in other words, without necessity the individual attention to the sound stimulus. The purpose of this study is to perform a descriptive revision about MMN, in order to identify its applicability in child and youth, in the last five years. The search was realized in the database Lilacs, SciELO, Medline and Pubmed using the following key words: Auditory Cortex, Electrophysiology and Auditory Evoked Potentials. Besides that, the words Mismatch and Negativity were used. In this revision, it were found 14 studies which evaluated child and/or youth presenting difficulties in speech articulation, specific language impairment, auditory processing disorder, Attention Deficit and Hyperactivity Disorder, dyslexia, autism, schizophrenia, psychosis, amusia, phenylketonuria and selective attention. It was possible to perform the descriptive revision about the application of MMN in child and youth, concluding that in the last five years there were a reasonable article production about the theme, however, in Brazil, there are a few studies. There is a variety of applications to MMN, though; in the national population, there is a need for scientific evidences to use this potential in the different age groups. It was found, as well, that the search for MMN studies in the databases could be done only using the word Mismatch and Negativity.

Keywords: Auditory Cortex; Electrophysiology; Auditory Evoked Potentials

RESUMO

O *Mismatch Negativity* (MMN) é um potencial cortical que ocorre em resposta a uma mudança de um estímulo acústico em meio a uma sequência de repetidos estímulos, o que reflete a capacidade do cérebro em discriminar o som de modo passivo, ou seja, sem a necessidade de atenção do indivíduo ao estímulo sonoro. Diante disso, o objetivo deste estudo foi realizar uma revisão descritiva sobre o MMN, a fim de identificar a sua aplicabilidade em crianças e adolescentes nos últimos cinco anos. Para isso, realizou-se uma busca nas bases de dados *Lilacs*, *SciELO*, *Medline* e *Pubmed* utilizando os seguintes descritores: córtex auditivo, eletrofisiologia, potenciais evocados auditivos e as palavras *Mismacth* e *Negativity*. Nesta revisão, foram encontrados 14 estudos que avaliaram crianças e/ou adolescentes com dificuldade de articulação na fala, distúrbio específico de linguagem, transtorno do processamento auditivo, Transtorno do Déficit de Atenção e Hiperatividade (TDAH), dislexia, autismo, risco para esquizofrenia, psicose, amusia, fenilcetonúria e atenção seletiva. Foi possível, assim, realizar a revisão descritiva sobre a aplicação do MMN em crianças e adolescentes, concluindo-se que, nos últimos cinco anos, houve uma produção considerável de artigos sobre o tema, embora no Brasil a presença de estudos a esse respeito ainda seja escassa. Nesse sentido, apesar de existir uma variedade de aplicações para o MMN, no que diz respeito à população brasileira, necessita-se ainda de evidências científicas que assegurem o efeito deste potencial nas diferentes faixas etárias. Verificou-se, também, que a busca por estudos sobre MMN nas bases de dados citadas pode ser realizada apenas utilizando as palavras *Mismacth* e *Negativity*.

Descritores: Córtex Auditivo; Eletrofisiologia; Potenciais Evocados Auditivos

INTRODUCTION

Negativity Mismatch (MMN), first described in 1978[1], is a cortical potential that occurs in response to a modification of an acoustic stimulus (rare stimulus), from a sequence of repeated stimuli (frequent stimulus), reflecting the ability of the brain to discriminate the sound due to the fact that the stimuli are stored in memory[2]. MMN is considered an endogenous potential that occurs passively and automatically. In other words, it occurs without the need of attention of the subject to the sound stimulus[3,4].

This potential is generated at the moment the subject discriminate a sound change automatically. This occurs because the auditory system is based on memory traces of the regularity of a stimulus, detecting a change, independent of the attention of the subject[5,6]. Such potential is represented by a negative deflection or a valley that happens after the identification response of the different stimulus, which may occur approximately between 150 and 250 milliseconds (ms) after the stimulus presentation, depending on the used stimulus, which can be, in general, a pure tone or a speech stimulus[5].

MMN can be used to carry out an objective evaluation in patients with difficulty or impairment in communication or whose hearing is under investigation[7]. It can also be used in populations with difficulty in responding consistently to stimulation, or to subjects who do not cooperate, in order to evaluate the discrimination of different acoustic stimuli[2].

Then, the aim of this study was to perform a descriptive review of MMN to identify its applicability in children and teenagers, according to scientific studies that were published in the last five years. The justification for performing this study consists on the importance of understanding the research that are being carried out with MMN in national and international context. This seems to be an objective evaluation that is not yet part of routine clinical practice in Brazil, but that might be helpful to complement the basic audiological and differential evaluation, as well as to motivate Brazilian researchers to carry out research on the topic. It is believed, therefore, that in this context a descriptive review of the studies being carried out with MMN can be very useful to interpret the results associated to their use.

METHODS

This research presents a descriptive and retrospective approach. Data collection on MMN was performed from September to October 2015, by searching the following electronic databases: Lilacs, SciELO, Medline and Pubmed, which are databases used for searching articles in science health area, with free access.

The inclusion criteria for the selection of articles were: full text articles available in the aforementioned databases, written in Portuguese, Spanish and/or English and published between 2011 and 2015. Exclusion criteria were: literature review articles, abstracts published in annals of congress, case reports, studies which did not mention the use of MMN in their methodology, research which involved animals, articles whose study population consisted of adults or elderly people, as well as articles that used the visual stimulus for carrying out the MMN.

The following descriptors in Portuguese and their corresponding in English were used to find the articles: *córtex auditivo* (auditory cortex), *eletrofisiologia* (electrophysiology) and *potenciais evocados auditivos* (auditory evoked potentials). The terms were chosen according to the Descriptors in Health Sciences (DeCS). In addition to these descriptors, the words Mismatch and Negativity were also used. The purpose of using other terms that are different from the words "Mismatch and Negativity" consisted of knowing if it was possible or not to find articles on MMN when performing a search with other descriptors. It is also important to highlight that the Boolean operator "and" was used.

As a didactic way to present search strategies with the descriptors and the selected words, Table 1 was generated.

Table 1. Search strategies used to search the databases Lilacs, Scielo, Medline and Pubmed: descriptors / words and boolenos operators

Strategies	Portuguese	English
First strategy with descriptors (S1)	*Córtex auditivo* ***and*** *Eletrofisiologia*	Auditory cortex **and** Electrophysiology
Second strategy with descriptors (S2)	*Eletrofisiologia* ***and*** *Potenciais Evocados Auditivos*	Electrophysiology **and** Evoked Potentials Auditory
Third strategy with descriptors (S3)	*Córtex auditivo* ***and*** *Potenciais Evocados Auditivos*	Auditory cortex **and** Evoked Potentials Auditory
First strategy with words (S4)	Mismatch **and** Negativity	Mismatch **and** Negativity

The initial selection resulted from the previous reading of the titles and abstracts of articles in order to verify if they were about the proposed theme. After this first analysis, only those items related to the theme were selected for complete reading.

In the preliminary search for articles, it aimed to describe the applicability of MMN in different age groups, being selected a total of 359 articles for analysis, following the strategies mentioned above, as shown in Figure 1.

	LILACS	SCIELO	MEDLINE	PUBMED	TOTAL
Articles found in S1	1	1	511	988	1501
Articles of the last five years in S1	0	1	34	114	149
Articles adequate to the theme in S1	0	0	0	0	0
Articles found in S2	17	17	500	1374	1908
Articles of the last five years in S2	2	12	24	132	170
Articles adequate to the theme in S2	0	2	0	1	3
Articles found in S3	7	4	1953	6482	8446
Articles of the last five years in S3	1	2	397	1126	1526
Articles adequate to the theme in S3	0	0	11	29	40
Articles found in S4	11	7	2083	2175	4276
Articles of the last five years in S4	4	3	684	785	1476
Articles adequate to the theme in S4	2	1	142	171	316

Figure 1. Distribution of the number of scientific articles obtained and selected for all age groups, according to each database

After analyzing the selected articles, 161 articles were excluded because they were duplicated and 32 did not meet the eligibility criteria, remaining 166 articles. After checking the impracticality of a review with a large number of articles, it was decided, in a second moment, to write about the applicability of MMN only in adults, which generated a new search filter. During this process, 137 articles were selected. Again, the review would be impractical. Then, it was decided to verify the applicability of MMN in children and teenagers, which led to the selection of 14 articles according to the eligibility criteria. In this last stage, 15 articles were excluded by comparing children or teenagers to adults.

In the 14 articles selected for analysis, MMN was applied in children and teenagers with the following features: difficulty in speech articulation, specific language impairment, auditory processing disorder, Attention Deficit and Hyperactivity Disorder (ADHD), dyslexia, autism, risk for schizophrenia, psychosis, amusia, phenylketonuria and selective attention. It is also important to mention that when the search with different descriptors was performed, it was noticed that all the articles found on MMN, with the use of the descriptors - auditory cortex, electrophysiology and auditory evoked potentials, were always associated to the words Mismatch and Negativity, showing that for performing a search for studies of MMN in the databases that were cited, it is sufficient to use the words Mismatch and Negativity in a combined way.

LITERATURE REVIEW

With the descriptors used for the search in the selected databases, it was found 14 studies that used the MMN to evaluate children and teenagers in the last five years. From these ones, only five had children as the study population. The other nine studies were performed with teenagers.

One of these studies evaluated 12 children (six boys and six girls), Spanish speakers, aged from five years and two months to six years and three months. The children were then separated into two groups - with difficulty in articulation (five children) and without difficulty (seven children) – with the aim of verifying the features of MMN. For this purpose, they used word pairs in Spanish as stimulus. It was found that 83% of children had MMN as expected. Comparing the two groups, there was a reduction of latency and increase of MMN amplitude in the group with difficulty in articulation[8].

Other researchers, after comparing the application of MMN through speech stimulus (syllables), evaluated 75 children in the age group of six to 12 years. These children were distributed into three equal groups: children with specific language impairment (SLI), children with auditory processing disorder (APD) and children with typical development (TD). The authors showed that all members of TD group showed response to MMN. In APD group and SLI group, the response rate was respectively 84% and 76%. It is also noteworthy that, for both APD group and for SLI group, there was an increase of latency and a decrease of amplitude in MMN in relation to TD group, which demonstrates the difficulty of children with APD and SLI in discriminating acoustic signals[9].

Against the aforementioned study, researchers, with the aim of comparing the results obtained in MMN among 32 subjects with typical development and 32 individuals with SLI showed no significant difference in MMN in both groups, the group of children (seven to 11 years) and the group of teenagers (12 to 16). However, after submitting the groups to verbal and non-verbal stimuli (tone burst), differences in the tracing of waves among the age groups were identified[10].

In order to understand the functioning of the central auditory pathway in children from eight to 12 years with ADHD, researchers compared 15 children with ADHD and 15 children with good school performance for reading and writing, by using the tone burst stimulation with different frequencies and lengths. However, they did not find significant difference among groups for MMN. The authors believe that the lack of difference among the groups is due to the fact that MMN does not depend on the response of the subjects, thus not requiring their attention, which contributed to the normal results of MMN[4]. Corroborating this study, other researchers, by using stimuli that differed in frequency and also in verbal stimuli, did not identify differences in MMN when comparing a group of 15 children with ADHD and a control group with 16 children aged from six to 15 years[11].

Disorders related to oral and written language development have been associated with deficits in processing of auditory information. With this in mind, a study was carried out by comparing 20 children with dyslexia and 20 children in the control group, with ages ranging from six to 14 years through MMN. For this purpose, they used frequent stimuli (1000 Hz), interspersed with rare stimuli (1200 Hz – stimulus of large deviation in the frequency - and 1030 Hz - stimulus of small deviation in the frequency). No significant differences were observed in MMN among the groups to stimuli for both large and small deviation in frequency. Therefore, the detection and the discrimination of change of auditory frequency were evidenced as regular in children with dyslexia[12].

Another study, after evaluating 225 children, from the age group from 10 and 15 years, divided into three groups (comparing dyslexic children, their unaffected siblings, but with genetic risk for dyslexia and children from a control group), by using MMN with verbal stimuli (syllables), pointed out the potential presence in all groups. Furthermore, there was no significant difference between groups in relation to the first two components or peaks of MMN. However, it was identified significant differences between the groups for the late component, verifying an increase of the latency in the control group[13].

When investigating the potential MMN in 31 children with autism, aged between six and 15 years (mean age of 11.3 years) and 30 children of the control group, aged between six and 17 years (mean age of 11.2 years), by using different auditory stimuli on the frequency (tone burst), researchers found significant differences between the groups, noting a decrease in amplitude and an increase in latency in the group of autistic subjects when compared to the control group. Therefore, the authors suggest that people with autism have hearing loss in pre-attentional level[14].

In another study, MMN was used for the purpose of evaluating 22 children at risk for schizophrenia, compared to 24 children with normal development

- both groups with ages ranging from nine to 12 years. The authors of this study identified some differences in the responses of MMN, which was evaluated with stimulus of tone bursts of different lengths. There was a significant increase in the amplitude of MMN in the group at risk for schizophrenia in relation to the group with normal development. In contrast, with regard to latency, there was no significant difference between groups[15].

MMN was also applied to 14 teenagers with psychotic symptoms, without the use of medication, and to 22 teenagers of the control group, aged from 11 to 13 years in order to observe the difference in tone burst stimuli regarding length. As in schizophrenic subjects of the above study, no significant difference in the psychotic group was observed when compared to the control group regarding MMN latency. In contrast, it was noted a decrease in amplitude in the risk group, with significant difference[16].

In other research, through MMN, 24 children from eight to 10 years old with no experience with music, native speakers of French, with verbal stimuli (syllables) were evaluated and with tone burst characterized by stimuli that differed in frequency and for length. These children were divided into two groups: those who received musical training (12 children) and those who received training for painting (12 children). MMN was performed at three different times: before training, six months after training and 12 months after training to evaluate brain plasticity. Before the training, there was no significant difference between the groups regarding the amplitude of MMN. After training, the authors verified a significant increase in the amplitude of MMN for the three types of stimuli (difference between frequency, difference between length and difference between syllables) which increased gradually from six months to 12 months after training. This significant difference happened only for the group that performed musical training. It is also noteworthy that the authors of this study support programs based on musical training for education, besides new treatment strategies for children with language and/or learning difficulty[17].

Amusia is the inability of melodic perception or rhythm. However, it is not accompanied by peripheral hearing loss. Researchers, after evaluating six children with congenital amusia and eight children of the control group, aged between 10 and 13.2 years, through MMN, in a first moment, did not find significant difference for MMN using distinct tone burst regarding frequency stimuli. In a second moment, in order to verify whether the musical stimulation would benefit these children in relation to the cortical responses, participants were instructed to listen to 30 minutes of music every day during four weeks and, afterwards, they repeated MMN. The authors also did not find significant difference for both groups before and after stimulation, inferring that musical deprivation in childhood does not cause congenital amusia[18].

Another study aimed to verify the applicability of MMN in 64 children who underwent treatment for phenylketonuria (PKU), with ages ranging from seven to 14 years, diagnosed with PKU in the first two weeks after birth and in continued treatment with food restriction. There was a decrease in the amplitude of MMN in children with PKU in the control group, but this difference was not significant. The authors relate this to the diet restriction. In relation to the latency, there was no significant difference[19].

In order to verify the conditions of selective attention in 10 teenagers, aged from 13 to 17 years, using MMN with presentation of three stimulus of tone burst that range in relation to the frequency (a frequent stimulus; a rare stimulus with sequence every five frequent stimuli; and another rare stimulus that occurred in fewer moments) during the performance of three different tasks while receiving the same set of sounds, researchers observed that, in teenage years, selective attention changes the neural activity according to the goals of performance, thus indicating a specific neural adaptation modulated according to the behavior of the subject[20].

As it was possible to observe, there are several possibilities of application of MMN, with the aim of studying the central auditory pathway, the attention and the discrimination for sound. Furthermore, it was possible to verify the relationship between changes in MMN and other difficulties faced by children, especially regarding language, which shows the importance of this test for this population. Then, it is possible to affirm that it can be used as a biomarker for the therapeutic processes and follow-up of cases of psychoses.

From this review, it was found that, in Brazil, there are few studies that are carried out with this approach. For the age group of adults, for example, there are no studies published in the period from 2011 to 2015 in Brazil. On the other hand, for the age group of children and teenagers, two Brazilian articles were found in the same period, which reinforces the importance of further research that use this potential in different age groups for understanding this topic, so that MMN can be part

of routine clinic in Brazil. The distribution of the bibliographical references presented in the literature review on MMN in children and teenagers can be seen in Figure 2, exposed below.

Title	Author	Age Group	Theme	Journal	Year
Mismatch Negativity (MMN) y lenguaje en niños preescolares hablantes del idioma español.	Dora Elizabeth Granados-Ramos, Patricia Torres-Morales, Héctor de Jesús Cervantes-Méndez, Norma Castañeda-Villa, Gabriela Romero-Esquiliano	From 5 years and 2 months to 6 years and 3 months	Difficulty in articulation	Rev. Chil. Neuropsicol.	2013
Mismatch negativity in children with specific language impairment and auditory processing disorder.	Caroline Nunes Rocha-Muniz, Débora Maria Befi Lopes, Eliane Schochat	From 6 to 12 years	SLI and APD	Braz J Otorhinolaryngol.	2015
Lower-frequency event-related desynchronization: a signature of late mismatch responses to sounds, which is reduced or absent in children with specific language impairment.	D V M Bishop, Mervyn J. Hardiman, Johanna G. Barry	From 7 to 11 years and from 12 to 16 years	SLI	J Neurosci.	2011
Cognitive potential of children with attention deficit and hyperactivity disorder.	Ana Carla Leite Romero, Simone Aparecida Capellini, Ana Claúdia Figueiredo Frizzo	From 8 to 12 years	ADHD	Braz J Otorhinolaryngol.	2013
Attention deficits revealed by passive auditory change detection for pure tones and lexical tones in ADHD children.	Ming-Tao Yang, Chun-Hsien Hsu, Pei-Wen Yeh, Wang-Tso Lee, Jao-Shwann Liang, Wen-Mei Fu, Chia-Ying Lee	From 6 to 15 years	ADHD	Frontiers in Human Neuroscience	2015
Late, not early mismatch responses to changes in frequency are reduced or deviant in children with dyslexia: an event-related potential study.	Lorna F Halliday, Johanna G Barry, Mervyn J Hardiman, Dorothy VM Bishop	From 6 to 14 years	Dyslexia	Journal of Neurodevelopmental Disorders	2014
Evidence for the Late MMN as a Neurophysiological Endophenotype for Dyslexia.	Nina Neuhoff, Jennifer Bruder, Jurgen Bartling, Andreas Warnke, Helmut Remschmidt, Bertram Muller-Myhsok, Gerd Schulte-Korne	From 10 to 15 years	Dyslexia	PLoS ONE	2012
Automatic Pre-Attentive Auditory Responses: MMN to Tone Burst Frequency Changes in Autistic School-Age Children.	Mohamed Moustafa Abdeltawwab, Hemmat Baz	From 6 to 15 years	Autism	Int Adv Otol	2015
Mismatch negativity (MMN) and sensory auditory processing in children aged 9–12 years presenting with putative antecedents of schizophrenia.	Jason M. Bruggemann, Helen V. Stockill, Rhoshel K. Lenroot, Kristin R. Laurens	From 9 to 12 years	Schizophrenia	International Journal of Psychophysiology	2013
Reduced duration mismatch negativity in adolescents with psychotic symptoms: further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis.	Jennifer R Murphy, Caroline Rawdon, Ian Kelleher, Deirdre Twomey, Patrick S Markey, Mary Cannon, Richard AP Roche	From 11 to 13 years	Psychosis	BMC Psychiatry	2013
Twelve Months of Active Musical Training in 8- to 10-Year-Old Children Enhances the Preattentive Processing of Syllabic Duration and Voice Onset Time.	Julie Chobert, Clément François, Jean-Luc Velay, Mireille Besson	From 8 to 10 years	Effect of musical training	Cerebral Cortex	2014
Congenital Amusia Persists in the Developing Brain after Daily Music Listening.	Genevieve Mignault Goulet, Patricia Moreau, Nicolas Robitaille, Isabelle Peretz	From 10 years to 13 years and 2 months	Amusia	PLoS ONE	2012
Pre-attentive processing in children with early and continuously-treated PKU. Effects of concurrent Phe level and lifetime dietary control.	Leo M. J. de Sonneville, Stephan C. J. Huijbregts, Robert Licht, Joseph A. Sergeant, Francjan J. van Spronsen	From 7 to 14 years	Phenylketonuria	J Inherit Metab Dis	2011
Attention matters: pitch vs. pattern processing in adolescence.	Elyse S. Sussman	From 13 to 17 anos	Selective attention	Frontiers in Psychology	2013

Figure 2. Distribution of the bibliographic references discussed in the literature review on Mismatch Negativity (MMN) in children and teenagers (n -14)

Furthermore, this review may place researchers on further analysis with MMN in different populations, as well as bringing new knowledge about the forms of application of the exam. There is a variety of applications for MMN, however, in relation to the national population, scientific evidence is still necessary for the use of this potential in different age groups.

CONCLUSION

After performing this descriptive review on the application of MMN in children and teenagers, it is concluded that, in the past five years, there was a considerable production of articles on the theme. Nevertheless, in Brazil, there are few studies on this topic. It was also verified that the use of the words Mismacth and Negativity is sufficient for making a search for studies of MMN in the databases Lilacs, SciELO, Medline and Pubmed.

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