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Cortical responses to tone and phoneme mismatch as a predictor of dyslexia? A systematic review

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ABSTRACT

Evidence from event-related-potential (ERP) studies has repeatedly shown differences in the perception and processing of auditory stimuli in children with dyslexia compared to control children. The mismatch negativity (MMN) – an ERP component reflecting passive auditory change detection ability – has been found to be reduced, not only in children with a diagnosis of dyslexia, but also in infants and preschool children at risk of developing dyslexia. However, the results are controversial due to the different methods, age of the children and stimuli used. The aim of the present review is to summarize and evaluate the MMN research about at-risk children in order to identify risk factors that discriminate between children with and without dyslexia risk and to analyze if the MMR (the abbreviation refers to positive and negative mismatch responses) correlates with later reading and spelling ability.

A literature search yielded 17 studies reporting MMR to speech or non-speech stimuli in children at risk of dyslexia. The results of the studies were inconsistent. Studies measuring speech MMR often found attenuated amplitudes in the at-risk group, but mainly in very young children. The results for older children (6–7 years) and for non-speech stimuli are more heterogeneous. A moderate positive correlation of MMR amplitude size with later reading and spelling abilities was consistently found. Overall, the findings of this review indicate that the MMR can be a valuable part of early dyslexia identification, which can enable efficient support and intervention for a child before the first problems appear.

1. Introduction

Dyslexia is one of the most frequent learning disorders, affecting approximately 4–8% of children (Fortes et al., 2016; Landerl and Moll, 2010; Lewis et al., 1994). Specific learning disorders are defined by difficulties in the development of academic skills which are not the result of inadequate schooling, neurological, visual, or auditory impairment. The affected abilities lie significantly below the level that is to be expected due to chronological age. Usually, the difficulties begin to show in the early school years. They interfere with academic achievement, occupational performance, or activities of daily living. Reading and spelling abilities can be affected separately or together; the term dyslexia normally refers to both difficulties in reading (exact and fluent word recognition, reading speed, reading comprehension) and spelling (American Psychiatric Association, 2013).

Comorbidity rates of emotional and behavioral disorders are high, i.e. of attention deficit hyperactivity disorder, conduct disorder, anxiety disorders and depressive symptoms (McGee et al., 1986; Ruland et al., 2012). Children with dyslexia have more difficulties in school (e.g. poor grades, conflicts with teachers or other students), reach lower academic qualifications than children without reading problems (Esser et al., 2002; McGee et al., 2002) and as a result have a limited career choice. To mitigate, or in the best case prevent this negative development, effective intervention is very important. However, the success of reading and spelling interventions is limited (Ehri et al., 2001; McArthur et al., 2012). Furthermore, interventions are more effective for younger children at risk of or with mild dyslexia than for older children with more severe deficits (Galuschka et al., 2014). Thus, early intervention is necessary to alleviate the negative consequences of dyslexia on the lives of affected children and adults. This raises the challenge of identifying reading problems before they become severe. The easiest and most reliable way of identifying reading problems is by measuring reading ability. However, this is only possible at school age. Precursors of reading, such as rapid automatized naming (the ability to quickly name a series of items, e.g. pictures or familiar objects), vocabulary, letter knowledge, or phonological awareness (the ability to identify and manipulate the sound units of a word), can already be assessed in preschool and show a medium predictive value (Ehri et al., 2001; Ennemoser et al., 2012; Georgiou et al., 2008). A measure that has been discussed as a possible and very early predictor of dyslexia (and of other psychiatric disorders)

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is the event-related potential (ERP) component with a latency of about 200 ms described as mismatch negativity (MMN).

The MMN is an ERP component that is elicited every time a series of standard stimuli is interrupted by a deviant stimulus and is supposed to reflect change detection ability. To detect the change in the stimulus, (auditory) sensory memory traces of the standard stimulus are necessary (Bartha-Doering et al., 2015). The MMN is calculated by subtracting the response to the deviant from the response to the standard stimulus. The classical experimental design to elicit an MMN, in which standard and deviant stimuli are presented auditorily to the participant, is called the "passive oddball paradigm". As the MMN does not require attention when discriminating between auditory signals, it can be used to measure auditory discrimination capacity as early as in infancy (Alho et al., 1994; Paavilainen et al., 1993). In contrast to adults, in children the MMN can even be measured in sleep (Cheour et al., 2001). In children, however, the MMN frequently does not show a clear negativity (Cheour et al., 2002). In the maturing brain, the electrophysiological response to a mismatch can also be of positive polarity (Maurer et al., 2003b). Even in preschool and school children, different stimulus characteristics can elicit positive mismatch responses (MMR, e.g. Leppänen et al., 2004). The functional properties of the auditory mismatch response (MMN and MMR) and the corresponding brain regions generating this response, however, seem to be similar in children and adults (Lee et al., 2012).

In addition to the "classical" latency of MMN and MMR (approx. 150–250 ms after the onset of the deviant stimulus), a second later mismatch component, called late mismatch negativity (lMMN) or late discriminative negativity (LDN), has been found (Dehaene-Lambertz and Gliga, 2004; Korpilahti et al., 1995). It typically occurs at a latency range of 400–500 ms, but has also been observed at much later latencies, with peaks until around 750 ms (Putkinen et al., 2012). Like the MMN/MMR, the LDN is elicited in response to deviant stimuli appearing in a series of repetitive standard stimuli and can be observed as early as the neonatal period (Alonso-Búa et al., 2006; Hommet et al., 2009). The exact function of the LDN is not known yet, but it also seems to reflect change detection (Korpilahti et al., 2001; Putkinen et al., 2012). Moreover, it has been supposed to reflect some form of further, higher-order processing of auditory mismatch that takes place after the sensory detection and evaluation of that mismatch (reflected by the MMN) has been concluded (Ceponiene et al., 1998; Ceponiene et al., 2002; Kushnerenko et al., 2001) or to reflect a reorientation of attention after a distracting stimuli (Horváth et al., 2009). Whereas the MMN/MMR amplitude seems to be relatively stable during development (Ceponiene et al., 2004), the LDN amplitude appears to decrease during childhood (Cheour et al., 1998a; Cheour et al., 2000) and is more often reported in children than in adults. It has been suggested that MMN and LDN might reflect consecutive and related phases of auditory change processing, although it is still not clear how they are connected (Kraus et al., 1993).

In this review, we report mismatch responses with early and late latencies and with negative and positive polarity. It has been suggested to use MMR profiles which include all those components in the investigation of speech perception development (Liu et al., 2014). In accordance with the literature, for this review we use *MMN*/*LDN* only when the deflection shows a negative polarity. *MMR* is used as an umbrella term for all mismatch components (positive and negative polarity and early and late latencies).

Cortical mismatch responses have been observed in response to deviant speech stimuli (e.g. vowels, syllables) and non-speech stimuli (tones). There are two main theories about the nature of the underlying processing deficit in dyslexia. The *phonological deficit theory* assumes that a specific deficit in dyslexia lies in the representation, storage and/or retrieval of speech sounds (Ceponiene et al., 2004). Lower mismatch responses (e.g. reduced amplitude) in response to speech stimuli but not to non-speech stimuli in children with dyslexia would indicate a specific speech deficit as postulated by the phonological deficit theory. Consistent with this assumption, several studies have found attenuated MMN amplitudes in response to speech stimuli (Bonte et al., 2007; Stanovich, 1988, Sharma et al., 2006) but not to non-speech stimuli (Schulte-Körne et al., 1998) in children with dyslexia. However, differences in response to changes (frequency, duration or intensity) in non-speech stimuli have also been found repeatedly (e.g. Sharma et al., 2006, for a review, see Bishop, 2007). These findings point to a more general auditory deficit. A non-speech-specific auditory deficit in dyslexia, though only in the perception of rapid changes in auditory cues, is assumed by the *rapid auditory processing theory* (Corbera et al., 2006; Bruder et al., 2011; Lachmann et al., 2005; Meng et al., 2005; Zhang et al., 2012).

Interestingly, attenuated MMN amplitudes in response to general auditory stimuli have also been found in schizophrenia (Javitt et al., 2000; Baldeweg et al., 2002). Studies investigating speech stimuli are still limited, but also point to attenuated MMN amplitudes (Kasai et al., 2003). Furthermore, in some patients with schizophrenia, significant phonological awareness and reading deficits, comparable to those in dyslexia, have been found (Arnott et al., 2011; Revheim et al., 2006; Revheim et al., 2014). Similarities in speech and phonological deficits found in patients with dyslexia and schizophrenia have brought up the idea of a common etiology underlying the difficulties associated with both disorders, e.g. in form of a temporal processing deficit (Condray, 2005).

The participants of the so far cited studies about MMN in dyslexia are school children. The finding of group differences in MMR (e.g. attenuated amplitudes) in this age group does not allow one to determine whether the lower MMR was generated as a consequence of the reading problems or whether it was present before the manifestation of dyslexia (and might be less influenced by the reading development). Studies focusing on children before they enter school enable to exclude the effect of reading acquisition on the generation of the MMR. In order to analyze the prediction of developing dyslexia, research often focusses on children at familial risk of dyslexia and compares them with children without familial risk. Some of the studies follow the infants or children until school age to find out if later reading or spelling ability is related to the mismatch responses measured in infancy or at preschool age.

A number of reviews exist about, or including, MMR measures in children and adults with dyslexia (e.g. Hämäläinen et al., 2013b; Schulte-Körne and Bruder, 2010; Tallal, 1980; Temple et al., 2000). However, to our knowledge, no review about MMR in children at risk of developing dyslexia has been published so far. The studies which found MMR differences in at-risk children compared to control children *before* the onset of reading instruction, and therefore before dyslexia can be diagnosed, seem especially promising. Such differences could be a neurophysiological predictor of later reading problems, which could, in addition to behavioral measures, contribute to more reliable risk identification. In the present review we therefore summarize the current state of research with the aim of evaluating if MMR measures can be used as (part of) an early risk screening. In view of the major methodological differences between the studies, it is important to take these differences into account in an attempt to identify how the MMR can best be used as a neurophysiological predictor.

To evaluate a possible clinical use of the MMR, we systematically review relevant studies investigating 1) if children (aged 0–7 years) at risk of developing dyslexia show different MMR amplitudes compared to children without such a risk, and 2) if these measures correlate with later reading or spelling ability (in a combined group of at-risk and not-at-risk children).

2. Methods

2.1. Eligibility criteria

For the study selection, we used the following inclusion criteria: We searched for studies 1) reporting MMR, MMN, or LDN amplitude (or

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