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Early electrophysiological markers of atypical language processing in prematurely born infants

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ABSTRACT

Because nervous system development may be affected by prematurity, many prematurely born children present language or cognitive disorders at school age. The goal of this study is to investigate whether these impairments can be identified early in life using electrophysiological auditory event-related potentials (AERPs) and mismatch negativity (MMN). Brain responses to speech and non-speech stimuli were assessed in prematurely born children to identify early electrophysiological markers of language and cognitive impairments. Participants were 74 children (41 full-term, 33 preterm) aged 3, 12, and 36 months. Pre-attentional auditory responses (MMN and AERPs) were assessed using an oddball paradigm, with speech and non-speech stimuli presented in counterbalanced order between participants. Language and cognitive development were assessed using the Bayley Scale of Infant Development, Third Edition (BSID-III). Results show that preterms as young as 3 months old had delayed MMN response to speech stimuli compared to full-terms. A significant negative correlation was also found between MMN latency to speech sounds and the BSID-III expressive language subscale. However, no significant differences between full-terms and preterms were found for the MMN to non-speech stimuli, suggesting preserved pre-attentional auditory discrimination abilities in these children. Identification of early electrophysiological markers for delayed language development could facilitate timely interventions.

1. Introduction

1.1. Neurodevelopmental and cognitive sequelae of premature birth

According to the World Health Organization, 15 million infants are born before term every year. In 2010, the rate of preterm birth (less than 37 gestational weeks) in developed countries was of 8.6% (March of Dimes et al., 2012). It has been clearly shown that premature birth substantially impacts child development. Even in the absence of visible cerebral damage, cognitive and language impairments are among the most frequently reported negative outcomes in prematurely born children (Barre et al., 2011; Cusson, 2003; Guarini et al., 2009; Jansson-Verkasalo et al., 2003; Rizzotto Schirmer et al., 2006; Saigal and Doyle, 2008; Sansavini et al., 2006; Sayeur et al., 2011). Preterm children are at much higher risk for language impairment than their full-term peers: about one out of three shows significant delay in language acquisition at age 3 years (Sansavini et al., 2010). Delayed development of expressive and receptive language in preschool children has been shown to negatively impact interpersonal skills, social functioning, and academic achievement (Durkin and Conti-Ramsden, 2007; Johnson et al., 2011). Furthermore, cognitive and academic problems in preschool- and school-aged preterm children (Baron et al., 2011; Gartstein et al., 2011) have been shown to persist in adolescence and adulthood (Anderson et al., 2003; Hack et al., 2002; Lefebvre et al., 2005; Northam et al., 2012; Saigal et al., 2000; Saigal and Doyle, 2008; Skranes et al., 2007; Wolke et al., 2008). Prematurity is a growing socioeconomic and educational concern. Early intervention therefore appears to be critical in order to limit the negative consequences of prematurity for cognitive, academic, and social functioning.

1.2. Electrophysiological indicators of auditory and speech processing in infants

Recently, high-density electroencephalography (EEG) and auditory event-related potentials (AERPs) have been increasingly

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used to study cognitive development in infants and young children (Thierry, 2005; Picton and Taylor, 2007). AERPs are produced by neural phase synchronization and increases in spectral power following presentation of an auditory stimulus, allowing to measure the timing and strength of the individual cortical responses (Fellman and Huotilainen, 2006; Lippé et al., 2009b). They are used to examine complex cognitive processes such as pre-attentional auditory processes and language discrimination without requiring a specific response or sustained attention from the child (Tampas et al., 2005; Picton and Taylor, 2007). Although, morphology of the AERPs waveform is known to be different in very young children compared to adults due to the immaturity of the auditory cortex, the ability of the infant's brain to discriminate auditory information is thought to be present from the second trimester of fetal life (Moore and Linthicum, 2007). Moreover, the main positive and negative peaks of the infant waveform (P150, N250, P350, and N450) are already identifiable in the first days of life (Kushnerenko et al., 2002a), suggesting that that the generators of the infantile AERP components are already functional at birth. As a function of age, AERPs waveform gradually increases in complexity, the latencies of the AERP components decrease and the amplitudes increase (Cheour et al., 2000; Moore and Linthicum, 2007; Wunderlich et al., 2006).

The mismatch response (MMN) can be elicited very early in infancy and has been used to study speech sound and auditory discrimination in neonates and infants in the first months of life (Cheour et al., 1998a, 1998b, 2002; Martynova et al., 2003). Specifically, mismatch negativity (MMN), which provides an indication of pre-attentional auditory discrimination ability, is a differential negative wave obtained by subtracting brain responses elicited by frequent (or standard) auditory stimuli from those evoked by rare (or deviant) ones (Cheour et al., 2000; Näätänen et al., 2007; Näätänen and Winkler, 1999; Näätänen, 2003; Trainor et al., 2001). In adults, this negativity generally peaks in the frontocentral electrodes at approximately 100–250 ms after stimulus presentation. However, in very young children and infants, a positive rather than negative mismatch at 100–300 ms latency has been reported, suggesting the presence of a pre-attentional discrimination process, albeit immature (Kushnerenko et al., 2002b; Shafer et al., 2010).

1.3. Speech vs. non-speech auditory stimuli

Atypical AERPs and MMN to auditory speech and non-speech stimuli have been documented in prematurely born children, suggesting alterations in cortical processing of auditory information (Bisiacchi et al., 2009; Lavoie et al., 1997; Léveillé et al., 2002). For instance, using non-speech harmonic tones, it was shown that AERPs obtained in preterm children differed from those measured in full-term children during the first year of life (Fellman et al., 2004). Specifically, compared to full-term children, preterm children born with low birth weight showed AERPs of lower amplitude and no significant MMN, whereas preterm children with appropriate birth weight for gestational age showed a positive rather than negative mismatch. Moreover, absent or positive MMN and smaller AERP responses measured at age 12 months were positively correlated with a lower cognitive functioning at age 2 years, corrected for age (Fellman et al., 2004). In a longitudinal follow up, this atypical MMN and P1 responses to non-speech stimuli were also present at age 5 years (Mikkola et al., 2007). In addition to various cognitive impairments observed in these children (lower attention, sensory- and visuo-motor, language and memory scores), the lower amplitude of the AERPs and the MMN components correlated positively with lower language results, suggesting that atypical AERPs can be used as indicators of lower language functioning in infants and children.

To better understand the relationship between language development and auditory processing in preterm children, object naming ability and electrophysiological responses to auditory discrimination of syllables were examined in 4-year-old preterm children (Jansson-Verkasalo et al., 2003). Results showed that preterm children who had specific problems naming objects also had lower MMN amplitudes on a syllable discrimination task. However, no electrophysiological abnormalities were found in children with normal object naming ability (Jansson-Verkasalo et al., 2003). In addition, lower MMN amplitudes in response to speech stimuli subsequently correlated with object naming skills at age 6 years, demonstrating the temporal stability and predictive value of the MMN response (Jansson-Verkasalo et al., 2004). Atypical or longuer AERPs latencies have also been reported in prematurely born infants or in children at risk for specific langage impairements (Cheour et al., 1998a, 1998b; Friedrich et al., 2004; Pasman et al., 1996; Ribeiro and Carvallo, 2008). For instance, Jansson-Verkasalo et al. (2010) found a significantly longuer MMN latency in very prematurely born infants at the age of six months (corrected age) compared to same age full-terms in a native phoneme discrimination task, suggesting slower language discrimination in these infants. Although previous studies mainly reported amplitude differences in AERP and MMN components between preterm and full-term children, latency analysis could also provide valuable information about children's language discrimination processes and pre-attentional development.

Nevertheless, it remains unclear which types of stimuli (speech, non-speech, or both) could better indicate lower cognitive and language development in these children. Previous studies failed to describe the differential maturation of speech and non-speech responses in preterm and full-term born children and their relationship with cognitive and language development. Analyzing cortical responses to speech and non-speech sounds could thus help to clarify cognitive and language development in premature children and early identify impairments incurred following premature birth. The current study therefore aims to identify early electrophysiological markers of language and cognitive impairments in preterm children and to better establish from what age it is possible to detect these impairments by (1) comparing AERP responses to speech and non-speech stimuli in 3-, 12-, and 36-month-old children born prematurely without neonatal brain injury and in children born at term; and (2) assessing the relationship between AERPs and cognitive and language development. Based on the findings by Fellman et al. (2004) and Mikkola et al. (2007), we postulate that preterm children as young as 3-month-old will show atypical AERPs (longer latency and/or reduced amplitude of the P150, N250 and MMN components) in response to speech and non-speech stimuli. We also hypothesize that AERP responses in both groups will be correlated with neurodevelopment outcomes on the BSID-III.

2. Methods

2.1. Participants

The study participants were 74 children aged 3, 12, and 36 months and born prematurely or at term. These age groups were selected based on language developmental milestones in the first years of life to investigate from what age it is possible to identify early AERP abnormalities and their relationship with neurodevelopmental outcomes on the BSID-III (Bates et al., 1992; Gervain and Mehler, 2010). Specifically, the ages of 3 and 12 months were selected because it is possible to start measuring language and cognitive development using standardized tools such as the BSID-III at those ages as opposed to younger ones. Moreover, the age of 36 months was chosen as it becomes possible to objectively assess language delays and impairement at that age. Corrected age was used for 3- and 12-month-old preterm infants, as recommended by the American Academy of Pediatrics,