Clinical Neurophysiology 119 (2008) 796–804

www.elsevier.com/locate/clinph

Neonatal and fetal response decrement of evoked responses: A MEG study

Carolin J. Sheridan [a,b,*], Hubert Preissl [a,b], Eric R. Siegel [c], Pamela Murphy [a], Maureen Ware [a], Curtis L. Lowery [a], Hari Eswaran [a]

[a] *Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot # 518, Little Rock, AR 72205, USA*

[b] *MEG Center, Eberhard-Karls-University of Tuebingen, Tuebingen, Germany*

[c] *Division of Biostatistics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

Accepted 6 November 2007
Available online 28 January 2008

Abstract

Objective: To investigate the response decrements of visual evoked responses (VER) in newborns and assess the applicability of this paradigm to fetuses in magnetoencephalographic (MEG) recordings.

Methods: Twelve newborns with no known risks or complications participated at chronological ages between 6 and 22 days. They constituted the follow-up group to a prenatal study conducted on a sample of 25 fetuses whose gestational age (GA) varied between 29 and 37 weeks at the time of recording. Trains of four light flashes with an interstimulus interval of 2 s followed by 10 s without stimulation were delivered to record VER.

Results: Nine of the 12 newborns responded to the stimulation and showed response decrements in amplitude from the first to the last light flash. Furthermore, the response latency increased significantly from the first to the last stimulus. The remaining three recordings were discontinued early. Even though the prenatal visual evoked response rate was only 29%, the fetuses exhibited a response decrement after the first stimulus.

Conclusions: The amplitude of VERs can be used to elicit a response decrement in newborns and, with limitations, even in fetuses. This paradigm might be a useful tool for a direct non-invasive assessment of neonatal and prenatal brain development and CNS functioning.

Significance: The proposed method might be a first step towards an early detection of developmental deficits in newborns and fetuses.

Keywords: Evoked responses; Habituation; Response decrement; Fetus; Prenatal development; Newborn; Neonatal development; Magnetoencephalography

1. Introduction

The developing prenatal and neonatal brain is more vulnerable to physiological insult than the more mature brain of older subjects. Moreover, events in these early periods can negatively affect brain development and therefore lead to motor, sensory and cognitive disabilities. Hence, detecting brain impairment at very early stages could contribute to the prevention of subsequent developmental delays and the implementation of intervention methods. Habituation is one of the primary phenomena utilized to assess neurological integrity of the newborn and normal central nervous system (CNS) functioning (Leader et al., 1984; Madison et al., 1986a,b). It is defined as the decrease of an elicited response as a result of repeated stimulation (Thompson and Spencer, 1966). Several ultrasound studies have shown fetuses to exhibit habituation (Madison et al., 1986a,b; Kuhlman et al., 1988; Shalev et al., 1989; Smith

* Corresponding author. Address: Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot # 518, Little Rock, AR 72205, USA. Tel.: +1 501 526 4334; fax: +1 501 603 1544.

E-mail address: carolin.sheridan@gmail.com (C.J. Sheridan).

1388-2457/$32.00
doi:10.1016/j.clinph.2007.11.174

et al., 1991; Groome et al., 1993; Van Heteren et al., 2001a,b; Bellieni et al., 2005). Moreover, there is evidence that younger fetuses (below 28 weeks GA) habituate at a slower rate than those at advanced gestational ages (older than 32 weeks GA) (Kuhlman et al., 1988; Groome et al., 1993; Doherty and Hepper, 2000). However, some studies could not reproduce this gestational age dependency (Madison et al., 1986b; Bellieni et al., 2005).

In the past, habituation paradigms performed with ultrasound have been used to differentiate also between high- and low-risk conditions in the fetus (Leader et al., 1982a,b; Leader and Baillie, 1988; Hepper and Shahidullah, 1992). Maternal conditions such as diabetes (Doherty and Hepper, 2000), depression (Allister et al., 2001) and stress (Sandman et al., 2003) have been shown to affect the fetal habituation in a negative way, indicating developmental delays which may be linked to impaired function of the cerebral cortex (Morokuma et al., 2004). Therefore, the prenatal detection of adverse habituation could be used as an indicator for the re-evaluation of maternal high-risk conditions. Regarding normal brain development, the degree of habituation has been shown to be a possible predictor of postpartum cognitive development (Madison et al., 1986b; Gaultney and Gingras, 2005).

Previous studies on prenatal habituation used mostly vibroacoustic (Leader et al., 1982a,b; Madison et al., 1986a,b; Smith et al., 1991; Groome et al., 1993; Kuhlman et al., 1988; Groome et al., 1993; Doherty and Hepper, 2000; Van Heteren et al., 2001a,b; Gaultney and Gingras, 2005; Bellieni et al., 2005) or sound stimulation (Shalev et al., 1989; Hepper and Shahidullah, 1992) to elicit a response. The outcome measures were mainly fetal body movements (Madison et al., 1986a,b; Groome et al., 1993; Doherty and Hepper, 2000; Van Heteren et al., 2001a,b) or blink-startle reflex (Bellieni et al., 2005) observed by ultrasound and/or heart rate acceleration (Smith et al., 1991; Goldkrand and Litvack, 1991). These measures are based on reflexes of the motor system, and are believed to indicate cortical stimulus perception (Hepper, 1995; Bellieni et al., 2005; Morokuma et al., 2004). However, all of these responses are indirect observations of brain responses, and have to be interpreted carefully since it is not clear whether the development of fetal motor skills influences these observations (Hepper, 1997). These studies used a long-term habituation paradigm in which the stimulus was presented repeatedly until response cessation. The number of stimuli leading to a termination of the response is called the habituation rate.

No previous study has investigated habituation in fetuses via direct detection of brain response. In adult electroencephalography (EEG) and MEG studies, habituation has been tested with a paradigm called short-term habituation (Rosburg et al., 2006; Vanhanen et al., 1996; Noguchi et al., 2004; Lasky et al., 1996). Lasky (1997) conducted this paradigm with auditory stimulation on newborns and adults. It differs from the above-mentioned long-term habituation as follows. First, the number of stimuli presented is fixed from the beginning, and therefore independent of the strength of an elicited response. Second, the interstimulus interval (ISI) is usually shorter. Third, in order to enforce dishabituation, the train of stimuli is followed by a longer break or a deviant stimulus. Hence, the criterion for the occurrence of habituation is the decrease in response latency and/or amplitude from the first to the second stimulus rather than cessation of the response. In case a paradigm does not fulfill all the criteria to distinguish habituation from receptor fatigue (Thompson and Spencer, 1966), it is more appropriate to call the phenomenon "response decrement" (Kuhlman et al., 1988). Nevertheless, studies using this paradigm on adults have shown its usefulness in the initiation of habituation in healthy adults (Amochaev et al., 1989; Lasky et al., 1996) as well as in the differentiation between cognitively impaired and normal subjects (Vanhanen et al., 1996).

Previous studies with a fetal magnetoencephalography (fMEG) system called SARA (SQUID Array for Reproductive Assessment, VSM Med Tech Ltd., Canada) have shown its capability to detect neonatal and fetal evoked brain responses elicited by visual and auditory stimulation (Eswaran et al., 2002; Lowery et al., 2006). Therefore, this device could add a new perspective on fetal habituation. It enables the direct observation of brain responses, their latencies, amplitudes and response patterns in normal and abnormal development.

This study is designed to investigate the usefulness of MEG technology for the application of a short-term habituation paradigm in newborns and fetuses to assess response decrement with visual stimulation. Since there are no known reports of response decrement of neonatal evoked responses to flash stimuli assessed with MEG technology, our first step was to evaluate the results of this visual paradigm on newborns before assessing its applicability to fetuses. In the next step, we investigated the application of this paradigm to the results from the same subjects during their fetal stage of life. The investigation on the fetuses was planned as an observational study.

Overall, this study might be the first step towards an improved assessment of human pre- and postnatal brain development, and therefore contribute to a more accurate detection of early developmental delays.

2. Methods

2.1. Subjects and methods

In order to investigate the newborns and further assess the applicability of the habituation paradigm on the fetuses, we recruited the subjects at the fetal stage of life and performed follow-up recordings after birth. The mothers were advised to bring the newborns for a follow-up study within 3 weeks after delivery. The study was approved by the local Institutional Review Board and each mother or their legal representative signed an informed consent form. Two mothers were under the age of 18,