The interplay between prenatal speech input and brain maturation in early language development

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Our main question is: How does GDM brain immaturity affect skills that are critical for later language development? To answer this question, we will assess two skills in GDM infants and compare them to term controls in two independent (separate)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON54637

Source
ToetsingOnline

Brief title
PrenaTaal

Condition

- Other condition

Synonym
gestational diabetes, maternal diabetes

Health condition

Taalontwikkeling, auditieve ontwikkeling

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: NWO

Intervention

Keyword: brain development, gestational diabetes, premature birth, prenatal speech input

Outcome measures

Primary outcome

EEG event-related potentials indicating maturation of general auditory

perception and speech-specific perception

Secondary outcome

N.A.

Study description

Background summary

By listening to speech, infants acquire perceptual skills needed to acquire their native language (L1). The development of these skills starts at week 20 of pregnancy, when fetuses begin perceiving speech (Gervain, 2018). The maternal abdomen filters acoustic information and only allows vowel sounds (e.g. /ei/ and /i/ in *baby*) and variations in pitch, duration, and intensity (*prosodic cues* for short) to reach the fetus. This prenatal experience promotes the development of preferences for, and specific neural responses to the mother*s voice and L1 as compared to unfamiliar voices and rhythmically different languages (Beauchemin et al., 2011; Gervain, 2015, 2018; Kisilevsky, Gilmour, Stutzman, Hains, & Brown, 2012; Nazzi, Floccia, & Bertoncini, 1998; Vouloumanos & Werker, 2007). Neonates show language-specific neural responses to native speech but not to non-speech, indicating speech-specific functional neural organization (Gervain, 2018; Sato et al., 2012; Vannasing et al., 2016). Thus, prenatal experience with speech creates memories of the mother*s voice and L1, and promotes speech-specific neural organization needed for language acquisition (Kisilevsky, 2016).

Although the role of prenatal speech input in neonatal speech perception is becoming clearer, little is known about the consequences of atypical prenatal experiences with speech on language development. Conditions such as preterm birth (i.e. before week 37 of pregnancy), growth restriction, and maternal gestational diabetes (GDM) are associated with altered prenatal responsiveness to the mother*s voice and with deficits in long-term language development (Kisilevsky, 2016). For example, compared to typically developing (TD) infants, growth-restricted fetuses respond less strongly to the mother*s voice, do not prefer their mother*s voice at birth, and display language deficits by 15 months (Kisilevsky, 2016). Preterms, who have had limited exposure to speech in the womb, perform poorly in linguistic rhythm and stress pattern discrimination (i.e. prosodic perception) postnatally, which may be causally related to later language delays (Barre et al., 2011; Gonzalez-Gomez & Nazzi, 2012; Putnick et al., 2017; van Noort-van der Spek et al., 2012). These findings suggest that atypical prenatal experiences with speech affect early postnatal prosodic processing, which in turn has negative consequences for language development.

An underlying cause for atypical prenatal experience with speech may be protracted development of the brain (Kisilevsky, 2016). Brain immaturity results in less efficient processing and storing of information, ultimately resulting in reduced impact of prenatal experience with speech despite exposure similar to that of unaffected fetuses. However, how brain immaturity reduces the impact of prenatal speech experience on language development is unclear. For example, brain immaturity may affect prenatal experience with speech through altering the sensorineural threshold for prenatal input (i.e. fetal perception), or through changes in the auditory recognition memory (Kisilevsky, 2016), which affects language development differently. A clear understanding of how prenatal experience with speech interacts with brain immaturity is needed to determine the role of prenatal speech input in language development.

In order to gain this understanding, the linguistic capacities of prematurely born children may be studied. In Europe, between 8 and 9%, and worldwide between 9 and 13% of all births occur prematurely (Blencowe et al., 2012). By definition, the central nervous system is less developed at birth in preterm neonates, compared to fullterm neonates. Previous research on the role of prenatal speech input in language development has shown that this neural immaturity can lead to language delay at a later stage (Barre et al., 2011; Gonzalez-Gomez & Nazzi, 2012; Putnick et al., 2017; van Noort-van der Spek et al., 2012). Also treatment in neonatal intensive care units (NICUs), which exposes neonates to other adverse conditions (e.g. abnormal postnatal stimulation and stress) may contribute to this delay (Vohr, 2014). However, linguistic skills in prematurely born children have been investigated mostly at a later age, often after the first year of life. Very few studies have focused on language processing in preterm infants at birth. In order to understand the effects of neural underdevelopment on prenatal speech perception, it is necessary to examine the abilities of preterm neonates to recognize and process linguistic input at birth. Because rapid development of the neural auditory system takes place within the third trimester of pregnancy (Moore & Linthicum, 2007), these abilities may vary between preterm babies born at different gestational ages. Therefore, a comparison between the language processing capacities of these different groups can be made in order to gain insight into prenatal linguistic development. In addition, the interaction between prenatal language experience and brain immaturity may be studied by investigating linguistic processing in full-term infants from mothers with GDM (GDM infants). GDM occurs in 9-25% of pregnancies and has neurocognitive implications for the children. GDM fetuses react less strongly to the mother*s voice than low-risk controls, and habituate less to vibro-acoustic stimulation (Kisilevsky et al., 2012), which indicates sensorineurological immaturity. Compared to controls, GDM infants score lower on cognitive and language tests (Adane et al., 2016; Battin et al., 2018), perform poorly in verbal communication, and are twice as likely to have a language impairment in childhood (Dionne et al., 2008). Due to the high prevalence of GDM and high risk for language impairments, many children may experience language deficits, which may have significant negative consequences for their emotional, academic, and social functioning later in life. Early language interventions are thus strongly called for. However, little is known about their early language development.

The present research project aims to determine how neural immaturity affect early language development by examining specific auditory, speech, and language processing skills in GDM neonates and preterm neonates. Specifically, general auditory and speech-specific perceptual skills will be compared between term GDM infants and matched controls, tested within 72 hours after birth. Furthermore, language perception will be compared between preterm neonates born at different gestational ages, tested within one week after birth.

GDM experiments (within 72 hours after birth):
One reason for GDM fetuses being unable to recognize their mother*s voice may be that GDM delays fetal neural maturation, which may affect their ability to process auditory input. We hypothesize that if the brain is unable to properly process prenatal input, it is unable to use that information to prepare the language network before birth. This is a critical, fundamental first step in language acquisition. In this experiment, we aim to find out what auditory input babies are able to process at birth, and how that is affected by prenatal neural development and by prenatal input to speech.

To get a more detailed picture on how GDM babies process auditory stimuli, we will measure neural activity as a result of auditory stimuli using multi-channel EEG in event-related potentials (ERP) paradigms. This experiment will take place within 72 hrs after birth. This was chosen to minimize the amount of time the baby is exposed to language and speech postnatally, which may impact ERPs. Due to practical and logistical reasons, this experiment will take place within 72 hours after birth while mother and child are still in the hospital. To examine the auditory neural maturation, we will use EEG in two steps in one session.

First, we target domain-general auditory neural processing. Here, we test whether GDM delays neural maturation of the auditory system. In particular, we will examine whether the neonates can process quick successive non-speech auditory stimuli (i.e. rapid auditory processing). The development of this ability develops prenatally and does not require exposure to speech. Although it develops independently of speech input, it is an essential skill for the discriminating and learning of speech sounds, which starts as soon as a baby is born. If a baby*s hearing is deficient in temporal resolution, this will negatively affect language outcome. For example, rapid auditory processing not only predicts 39-41% of the variance in later language outcome but it has also shown to predict possible future language impairments such as developmental language disorder (Benasich et al., 2002; Molfese & Molfese, 1997).

Second, we examine the outcome of prenatal development of speech-specific auditory processing at birth. Fetal experience with speech promotes the development of the basic architecture of the language neural network, which can be tested when the babies are born (Gervain, 2015, 2018; Sato et al., 2012). To test whether this neural network has started to develop, we will test whether the neonatal brain distinguishes between speech and non-speech. The distinction between domain-general auditory processing and speech-specific auditory processing allows for a better discrimination between the effects of GDM on general neural immaturity and the specific effects on the prenatal experience with speech.Preterm experiment (within 1 week after birth):
If brain immaturity affects the ability to perceive and analyze prenatal linguistic input in GDM fetuses, the question arises how healthy fetuses are able to properly process the same acoustic information without any linguistic experience, while their neural auditory systems are still developing. Specifically, since it is mostly prosodic information that reaches the intra-uterine environment of the fetus, it is unclear how and at what developmental stage this type of language-specific information can be recognized and learned. We hypothesize that fetuses have innate knowledge of so-called *prosodic boundaries*, i.e. prosodically marked endings of phrases in speech streams. In other words, any developing fetus is equipped with a priori knowledge that enables it to recognize and process the type of linguistic information it can hear within the maternal womb. If this is the case, then preterm newborns who are born between 28 and 33 weeks gestational age should have similar abilities in processing prosodic information at birth, despite the neural immaturity associated with preterm birth. At this stage in prenatal development, fetal hearing is established but language experience is at a minimum. If preterm newborns are nevertheless able to process prosodic information in speech at birth, it would suggest that this ability is driven by innate linguistic mechanisms.

In order to test this hypothesis, neural responses to the presentation of linguistic stimuli will be measured in two groups of healthy, prematurely born infants, who are born at different gestational ages, using multi-channel EEG in an ERP paradigm. Perceiving and processing prosodic boundaries is associated with a specific ERP response, called the *Closure Positive Shift* (CPS) (Steinhauer et al., 1999). These neural responses will be measured in one group of infants born at 28, 29 or 30 weeks of gestation (in this study: *early preterm neonates*), and in one group of infants born at 31, 32 or 33 weeks of gestation (*late preterm neonates*). These different age groups are included since it is not clear at what age CPS may be appear as a response to processing prosodic boundaries. At 28-30 weeks, the infants will have very little linguistic experience, but perhaps they may possess underdeveloped neural mechanisms for demonstrating higher cognitive ERP components. At 31-33 weeks, these neural mechanisms will be more developed. However, at this age, the prosodic abilities of the infants may be influenced by their increased experience with the ambient language, which would make it difficult to assess the role of innate knowledge. To keep a balance between early neural development on the one hand and linguistic experience on the other hand, these two age groups are included. Testing will take place within a week after birth, in order to minimize postnatal linguistic influence. Responses matching the CPS component will be taken as evidence for innate prosodic processing principles, which may guide prenatal linguistic development in typically developing fetuses, but which may fail in GDM fetuses through impaired handling of auditory stimuli.

Study objective

Our main question is: How does GDM brain immaturity affect skills that are critical for later language development?
To answer this question, we will assess two skills in GDM infants and compare them to term controls in two independent (separate) experiments (Experiment 1 and 2, respectively), in correspondence with our first two primary objectives.

In addition, prenatal development of preterm neonates will be studied in one independent experiment (Experiment 3) by assessing linguistic skills in two groups of prematurely born neonates, in correspondence with our third primary objective.

Primary Objectives:
1. to determine the differences between GDM and TD neonates in the general maturation of auditory perception, as measured with multi-channel EEG in an ERP paradigm.
2. to determine the differences between GDM and TD neonates in the maturation of speech perception, as measured with multi-channel EEG in an ERP paradigm.
3. to determine the differences in the maturation of speech perception between early preterm neonates, born at a gestational age of 28-30 weeks and late preterm neonates, born at a gestational age of 31-33 weeks, as measured with multi-channel EEG in an ERP paradigm.

Study design

This study is an observational cross-sectional study with multiple (independent) outcomes.

Intervention

The mother will fill in questionnaires and the child will partake in behavioral and neuroimaging experiments.

Study burden and risks

Gestational diabetes has long-term adverse effects on the child*s cognitive functioning, e.g. on their language abilities. We hypothesize that this is related to prenatal neural immaturity and their experience with speech/language. Considering that the first 1001 days of a child*s life from conception is the most critical for their neurodevelopment due to heightened neural plasticity, neural immaturity may change the fetal sensitivity to auditory stimuli, which then affects to what extent the child learns from this auditory stimulation. To have a better understanding what exactly is affected, more knowledge is needed about their prenatal, perinatal, and postnatal cognition and auditory maturation. The second and third objectives are related to the increase of our understanding of how the prenatal environment affects early language development in general. There is an increasing amount of evidence that fetuses learn from the sounds they hear prenatally, but it is yet unknown whether these experiences with sounds are required for early language development.

There are no known risks associated with any of the experiments in this study. In all the experiments, the child will be presented with auditory stimuli at a volume that is safe for their hearing and thus will cause no harm. EEG is a non-invasive method to measure brain activity. EEG requires the use of a special hat which carries the sensors to measure brain activity. This hat is especially made for neonates and is thoroughly tested for their sensitive heads for this purpose. The sensors are made to only receive electrical information that are produced internally by the brain. EEG therefore does not send off electricity itself and is safe for usage. All researchers involved in this study will be trained prior to their first contact with a study participant.

Although there are no risks, there is some burden that the parents/guardians and child may experience. First, one or both parent(s)/guardian(s) will be present during each of the experimental sessions, which they may consider to be boring. They will also have to answer questions, e.g. on their socioeconomic status, which they may be uncomfortable with. However, we will make sure that it is clear to the parents/guardians that all provided information will be confidential and protected. Second, the child will be tested twice in one session in the fullterm experiments and once in the preterm experiment. They may find this bothersome. However, the experiments have been designed in such a way that the baby can be asleep; an activity that a newborn already does most of the day. This allows for more comfort during the experiment.

We have also tried to minimize the burden that falls upon parents/guardians and child by planning the testing moments when the mother and child are already at the hospital or by testing at home. Therefore, they do not have to spend extra time to come to the lab.

In light of the vast amount of knowledge we will gather from this study, we believe that the relatively low burden that the parents/guardians and the child face are negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Experiments 1 and 2:
At-risk group:
- Born at >37 weeks.
- Consent signed by the parents/guardians at 30 weeks of gestation or within 24h after birth
- Mother diagnosed with gestational diabetes
Control group:
- Born at >37 weeks.
- Consent signed by the parents/guardians at 30 weeks of gestation or within 24 h after birth

Experiment 3:
Early preterm group:
- Born between 28-30 weeks
- Consent signed by the parents/guardians within 1 week after birth
- Normal birth weight for the postconceptional age

Late preterm group:
- Born between 31-33 weeks
- Consent signed by the parents/guardians within 1 week after birth
- Normal birth weight for the postconceptional age

Exclusion criteria

Experiments 1 and 2:
- Suspected or proved genetic neural disorders
- Congenital malformations
- Severe perinatal complications
- No consent from the parents/guardians
- Bilingual home (< 70% exposure to Dutch)
- Deaf mothers
- Mother diagnosed with a different type of diabetes

In addition, subjects will be withdrawn from the study if:
- Born pre-term (<37 weeks of gestation)
- Impaired hearing abilities
- Withdrawn parental/guardian consent
- Unacceptable adverse events

Experiment 3:
- Suspected or proved genetic neural disorders
- Congenital malformations

- Severe perinatal complications
- No consent from the parents/guardians
- Bilingual home (< 70% exposure to Dutch)

In addition, subjects will be withdrawn from the study if:
- Mother diagnosed with (gestational) diabetes
- Impaired hearing
- Withdrawn parental/guardian consent
- Unacceptable adverse events

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-02-2023
Enrollment:	190
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	03-02-2021
Application type:	First submission

Review commission: METC NedMec

Approved WMO
Date: 02-08-2022

Application type: Amendment

Review commission: METC NedMec

Approved WMO
Date: 13-04-2023

Application type: Amendment

Review commission: METC NedMec

Approved WMO
Date: 17-04-2024

Application type: Amendment

Review commission: METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	**ID**
CCMO	NL72280.041.20