Detection of abnormal neural enconding of speech sounds at birth using the frequency-following response

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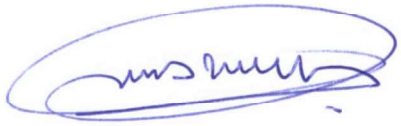

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ABSTRACT

In humans, auditory system is functional at the end of the second trimester of pregnancy and its correct development is crucial to receive auditory inputs from our acoustic environment, exposure which, in turn, is essential for the language acquisition. Although the auditory system formation is influenced by genetic factors that program anatomic and physiologic changes, is also susceptible to environmental agents and the intrauterine period is the most vulnerable stage. Previous studies described that an unfavorable intrauterine environment could conditionate structurally and functionally the auditory system. Taking into account that birth weight represents the fetus growth during pregnancy and is a correlate of the intrauterine environment state, the present thesis aims to explore if an altered fetal growth is associated which abnormal neural encoding of speech sounds at birth.

Neonates born with an unexpected birth weight for their gestational age are at high risk of short- and long-term complications. According to the Gaussian distribution of birth weight, there are two groups of babies located at each end that require special attention: neonates born small-for-gestational age (SGA) or affected by fetal growth restriction (FGR) and neonates born large-for-gestational age (LGA). Since the prevalence is approximately 9% for each group (SGA/FGR and LGA), reaching a combined incidence of 18% of total births in developed countries and being even higher in developing countries, the clinical and societal impact of an altered fetal growth cannot be ruled out. International health organizations claim the need to improve SGA/FGR and LGA detection techniques and objective tools that enable the early identification of those cases at greatest health risk. Therefore, to contribute to this goal, we would like to explore whether essential language skills such as voice perception at birth could be affected by altered fetal growth through an auditory evoked potential called frequency-following response (FFR). FFR reproduces with great fidelity the spectro-temporal features of the complex auditory stimulus such as music or speech.

Due to the small number of studies in which the neonatal FFR has been recorded, the first objective of the present doctoral thesis was to describe in depth the neonatal FFR and to corroborate the possibility of recording this electrophysiological response as part of the clinical routine. In the first study, we achieved this specific goal and a normative database describing neonatal FFR standards was published. Once the possibility of recording neonatal FFR was confirmed, we explored whether newborns affected by fetal growth restriction — a population traditionally associated with a high risk of communication disorders — were more likely to exhibit alterations in the encoding of voice-pitch through the FFR that their healthy peers. The

second study revealed that FGR neonates had an altered perception of voice-pitch in the vowel region, an alteration that was consistent with the effects of white matter reported by radiological and animal studies. Finally, in the third study, we investigated whether those newborns located at the opposite end of the birth weight continuum, the so-called large-for-gestational age (LGA), have an altered voice-pitch encoding. The results showed that being born LGA was associated with altered voice-pitch perception, and it was suggested that elevated adipose tissue could functionally limit, through proinflammatory agents, the brain structures involved in encoding complex sounds. Therefore, in the present thesis we have observed that being born with altered fetal growth is associated with altered coding of voice-pitch. However, more studies are needed with larger cohorts and longitudinal approaches that make it possible to corroborate the FFR's predictive power on language skills assessed by neurobehavioral tests.

RESUM

En humans, el sistema auditiu és funcional al final del segon trimestre de l'embaràs i el seu correcte desenvolupament és crucial per rebre aportacions auditives del nostre entorn acústic, exposició que, al seu torn, és essencial per a l'adquisició del llenguatge. Tot i que la formació del sistema auditiu està influenciada per factors genètics els quals programen canvis anatòmics i fisiològics, també és susceptible als agents ambientals, i el període intrauterí és l'etapa més vulnerable. Estudis previs han descrit que un entorn intrauterí desfavorable podria condicionar estructuralment i funcionalment el sistema auditiu. Tenint en compte que el pes al naixement representa el creixement del fetus durant l'embaràs i és un correlat de l'estat del medi intrauterí, la present tesi té com a objectiu explorar si un creixement fetal alterat s'associa a una codificació neuronal anòmala de la parla en néixer.

Els nounats nascuts amb un pes al naixement no esperat per a la seva edat gestacional tenen un risc elevat de complicacions a curt i a llarg termini. Segons la distribució gaussiana del pes al naixement, es distingeixen dos grups de nadons situats un a cada extrem de la distribució que reclamen especial atenció: els nounats nascuts petits per la seva edat gestacional (PEG) o afectats per una restricció del creixement fetal (FGR) i els nounats nascuts grans per la seva edat gestacional (GEG). Atès que la prevalença és del 9% aproximadament per a cada grup (PEG / FGR i GEG), arribant a una incidència conjunta del 18% del total de naixements als països desenvolupats i sent, fins i tot, superior als països en desenvolupament, l'impacte clínic i social d'un creixement fetal alterat no es pot descartar. Les organitzacions internacionals de salut reclamen la necessitat de millorar les tècniques de detecció de PEG / FGR i GEG i eines objectives que possibilitin la identificació precoç d'aquells casos en major risc de salut. Per tant, per contribuir a aquesta finalitat, ens proposem explorar si les habilitats lingüístiques essencials com la percepció del to de veu en néixer podrien veure's afectades per un creixement fetal alterat mitjançant un potencial evocat auditiu anomenat resposta de seguiment de freqüència (RSF). La RSF reprodueix amb una gran fidelitat els trets espectro-temporals de l'estímul auditiu complex que l'ha evocat. Per tant, recentment es suggereix aquesta resposta electrofisiològica com un correlat neuronal de la codificació de sons com la música o la parla.

Degut al nombre reduït d'estudis en què s'ha registrat la RSF en nadons, el primer objectiu de la present tesi doctoral va ser descriure amb profunditat la RSF neonatal i corroborar la possibilitat de registrar aquesta resposta electrofisiològica com a part de la rutina clínica de l'hospital. En el primer estudi, vam assolir aquest objectiu específic i es va publicar una base de dades normativa que descrivia els estàndards de la RSF neonatal. Un cop confirmada la possibilitat de registrar el

RSF neonatal, vam explorar si els nounats afectats per restricció de creixement fetal -una població tradicionalment associada a un alt risc de trastorns de la comunicació- tenien una probabilitat major de presentar alteracions en la codificació del to de veu per mitjà de la RSF que els seus companys sans. El segon estudi va revelar que els nounats FGR tenien una percepció del to alterada a la regió vocal, alteració que era compatible amb les afectacions de la substància blanca reportades per estudis radiològics i animals. Finalment, al tercer estudi vam investigar si aquells nounats situats a l'extrem oposat del continu de pes al naixement, els anomenats nounats grans per la seva edat gestacional (GEG), presenten una codificació del to de veu alterada. Els resultats van mostrar que el fet de néixer GEG es va associar amb una percepció de to alterada i es va suggerir que el teixit adipós elevat podria limitar funcionalment, per mitjà d'agents proinflamatoris, les estructures cerebrals implicades en la codificació de sons complexos. Per tant, en la present tesi hem observat que néixer amb un creixement fetal alterat s'associa amb una codificació alterada del to de veu. No obstant això, es necessiten més estudis amb cohorts més grans i enfocaments longitudinals que facin possible corroborar el poder predictiu del FFR sobre les destreses lingüístiques avaluades per proves neuroconductuals.

FOREWORD

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LIST OF ORIGINAL PUBLICATIONS

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STUDY II

Ribas-Prats, T., Arenillas-Alcón, S., Lip-Sosa, D. L., Costa-Faidella, J., Mazarico, E., Gómez-Roig, M. D., & Escera, C. (2021). Deficient neural encoding of speech sounds in term neonates born after fetal growth restriction. *Developmental science*, e13189. https://doi.org/10.1111/desc.13189

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ABBREVIATIONS

AABR	Automated Auditory Brainstem Response
ABR	Auditory Brainstem Response
AGA	Adequate-For-Gestational Age
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
CC	Corpus Callosum
CNS	Central Nervous System
EEG	Electroencephalogram
EHDI	Early Hearing Detection and Intervention
ERP	Event-Related Potential
F_0	Fundamental Frequency
F_1	First Formant
F_2	Second Formant
FFR	Frequency-Following Response
FFT	Fast Fourier Transform
FGR	Fetal Growth Restriction
GA	Gestational Age
GWG	Gestational Weight Gain
IOM	Institute of Medicine
IQ	Intelligence Quotient
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
LGA	Large-For-Gestational Age
MMN	Mismatch Negativity
MRI	Magnetic Resonance Imaging
NSG	Neurosonography
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small-For-Gestational Age
SLI	Specific Language Impairment
SNR	Signal-To-Noise Ratio

TEOAE	Transient Evoked Otoacoustic Emissions
UNHS	Universal Newborn Hearing Screening
WHO	World Health Organization

INTRODUCTION

Auditory system development trough pregnancy

An appropriate human auditory system development is crucial to receive, encode, interpret and respond to complex auditory stimuli, such as the sounds of language and music (Stanley et al., 2008). The auditory system is ready to process auditory inputs already before birth (Mehler et al., 1994; Moore, 2002). Around 25-28 weeks of gestational age (GA), fetuses' responses to vibro-acoustic stimulation delivered across the maternal ventral region have been described by means of overall fetal activity (Hepper & Shahidullah, 1994), eye-blink (Birnholz, & Benacerraf, 1983) and heart rate (Birnholz & Benacerraf, 1983; Gagnon, 1989). More recent studies at the same GA described fetal auditory event-related fields to several types of auditory stimulation, including white noise (Muenssinger et al., 2013), amplitude modulated tones (Draganova et al., 2018) and syllables (Hartkopf et al., 2016).

The emergence of behavioral and physiological responses to auditory stimulation at this age is roughly explained by the beginning of the myelination process in the cochlear nerve (Moore & Linthicum, 2001), in the brainstem pathway (Moore et al., 1995) and in the axons running from the inferior colliculus to the medial geniculate body (Langworthy, 1933; Yakovlev & Lecours,1967). The cochlea and cochlear nerve are structurally formed by 13 weeks of GA, yet the cochlear outlet through the brainstem and up to the auditory thalamus are not myelinated until the third trimester of pregnancy (Moore & Linthicum, 2007). From week 34, exponential neural connections between the cochlea and the auditory brainstem are formed and start to extend to the auditory cortex (Hall, 2000; Hepper & Shahidullah, 1994; Pujol & Lavigne-Rebillard, 1992), and evoked potentials to sound become more robust. In this critical period, the state of the fetal environment is crucial to allow an appropriate development of the auditory system (Lahav & Skoe, 2014). Adverse intrauterine conditions like oxygen or nutrients supply deprivation (Amin et al., 2010), the presence of toxins such as alcohol (Church, 1987; Yoshida et al., 2018), and smoking (Weitzman et al., 2013) could have permanent negative consequences on the auditory system.

Since in the intrauterine life, high frequency exogenous sounds are strongly attenuated by the maternal womb (Gerhardt & Abrahms, 1996; Hepper & Shahidullah, 1994; Lahav & Skoe, 2014; Parga et al., 2018) and the low-frequency endogenous sounds such as maternal voice and heartbeat sounds dominates the acoustic environment (Gerhardt & Abrams, 2000), birth represents an explosion of accoustic stimulation whose effects on the newborn's brain are unequivocal. It has been widely demonstrated that a varied and organized auditory stimulation

that includes speech, music and meaningful sounds from the environment is essential for the appropriate neural development of the hearing system (American Academy of Pediatrics, Joint Committee on Infant Hearing, 2007, 2019).

Universal Newborn Hearing Screening (UNHS) implementation

To ensure the potentiality of the auditory system to perceive the acoustic environment, the Universal Newborn Hearing Screening (UNHS) was developed. The UNHS is a clinical strategy that aims to identify newborns with congenital deafness and hearing loss (Wroblewska-Seniuk et al., 2017). The UNHS is currently conducted by means of two independents and interchangeable tests: the transient evoked otoacoustic emissions (TEOAE) and the automated auditory brainstem response (AABR). The TEOAE measures the "echoes" produced by the cochlea when a series of clicks is presented with a small microphone placed at the external ear canal. The AABR evaluates the auditory pathway integrity measuring neuroelectric events generated within the auditory pathway, from the eighth cranial nerve up to the inferior colliculus, with electrodes located on the infant's forehead and neck in response to click or chirps delivered through earphones (Wrightson, 2007). These physiological, noninvasive, automated screening tests are commonly performed at the bedside in term and pre-term newborns (Patel & Feldman, 2011).

The implementation of the UNHS has had a strong impact in the worldwide public health. Hearing impairment is one of the most prevalence congenital anomaly (Biernath et al., 2010; Nikolopoulos, 2015; Papacharalampous et al., 2011) with an incidence estimated between 1 and 3 per 1,000 live births (Erenberg et al., 1999; Mehl & Thomson, 1998). Thus, the establishment of the UNHS has saved thousands of babies from deafness, providing the opportunity for a timely intervention that reduces the dramatic consequences of hearing loss (Patel & Feldman, 2011; Yoshinaga-Itano, 2003). After a positive UNHS result, diagnostic confirmation of hearing loss before 3 months of age and implementation programs at 6 months of age are common practices in developed countries (American Academy of Pediatrics, Joint Committee on Infant Hearing, 2007, 2019). Several studies have shown that early diagnosis and interventions lead to significant improvements in vocabulary, receptive language, expressive language, syntax, oral expression and social and emotional development (Yoshinaga-Itano, 2003).

Language impairment without the presence of hearing loss

Despite being born healthy and passing the UNHS, a large number of babies will face communication and language disabilities. A systematic review conducted by Law and collaborators (2000) suggest that the prevalence of speech and language delays and disorders in children aged between 2 to 5 years old is estimated between 5% and 12% (median, 6%) and is associated with poor school achievement (Catts et al., 2002; Durkin et al. 2009), emotional function (Spackman et al., 2006) and lower socio-economic outcome (Armstrong et al., 2017) when compared to healthy peers. The high prevalence of these disorders -which has an important genetic component (Graham & Fisher, 2013; Newbury et al., 2010)- and their negative consequences for child development, highlight the importance of early identification of children who may present any sign of communication difficulty (National Institutes of Health, 2000; Schatschneider & Torgesen, 2004).

In the last decades, to better understand the neural underpinnings of communication disorders and following the interest in finding potential objective biomarkers allowing an early and objective diagnosis and intervention, the number of neuroimaging and neurophysiological studies has grown in an astonishing manner (Beeson, 2010; Kuhl, 2010; Mayes et al., 2015). Event-related brain potentials (ERPs), derived from the electroencephalogram (EEG), are the neurophysiological technique most used to explore auditory and speech processing (e.g., Näätänen et al., 2007). EPRs are electrical brain responses time-locked to a specific sensory stimulus or event (Luck, 2005). The precise time resolution (in order of milliseconds) and the possibility to record them without attention, motivation or language skills make them optimal for exploring human speech through the lifespan in normal and clinical populations. From their discovery, a wide range of auditory evoked potentials (AEPs) have been proposed to explore language impairments (see Barman et al., 2021; Friederici, 2006; Luck, 2005). Some AEPs, such as the N1/P2/N2 complex, P300, and mismatch negativity (MMN), are widely used but present a prominent variability, a small rate of replicability and slow voltage fluctuations occurring hundreds of milliseconds after the evoking sound was elicited. All these limitations question their role as renderings of the acoustics of the stimulus (Kraus & Nicol, 2014). But, recently, a variant of the auditory brainstem responses called *Frequency-following response (FFR)* have been proposed as a promising tool that deal with all the limitations exposed to examine complex sounds encoding.

The frequency-following response as a neural correlate of speech encoding

In contrast to other sound-evoked neuroelectric responses which their morphology shows an arbitrary relationship with the eliciting-stimulus waveform, the FFR faithfully mimics the temporal and spectral features of the eliciting complex auditory stimuli, allowing to examine the accuracy of fine-grained speech-sound neural encoding along the entire auditory system (Coffey et al., 2019; Gorina-Careta et al., 2021). This transparency is the main reason why the FFR have been suggested as a promising clinical tool for understanding the neural underpinnings of communication disorders (see Figure 1). Traditionally, the FFR sources have been attributed to the subcortical auditory system (Moushegian et al., 1973). Yet, based on multimodal source modeling studies (Bidelman, 2018; Coffey, et al., 2016, 2017; Gorina-Careta et al., 2021) and EEG signal decomposition techniques (Galbraith, 1994; Stillman et al., 1978; Zhang & Gong, 2017) raised the conception of the FFR as a summation of responses from subsequent auditory system stages, including the auditory nerve, cochlear nucleus, inferior colliculus, thalamus and auditory cortex in a frequency-specific manner, with frequencies below 150 Hz originating primarily from subcortical sources.

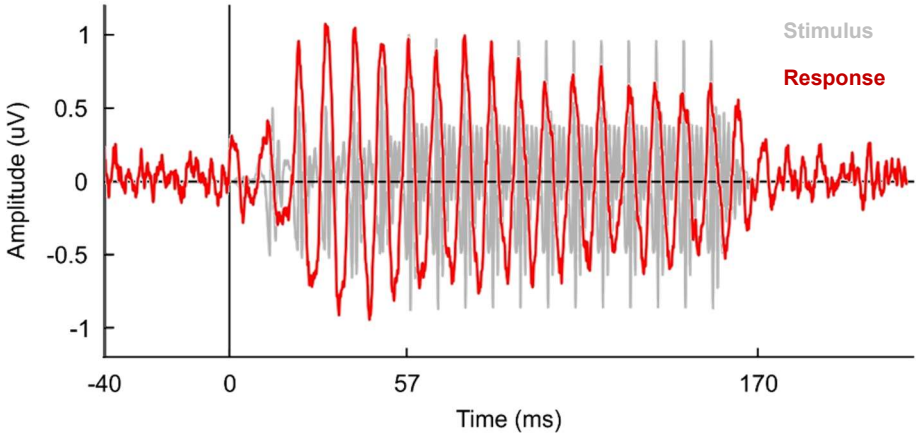

Figure 1. Temporal neural representation of the consonant-vowel /da/ in the neonate's auditory brain. Stimulus waveform (/da/) is represented in gray and in red the grand-averaged FFR waveform computed from 46 helathy neonates (adapted from Ribas-Prats et al., 2019).

The FFR can be recorded with the same electrode montage used to record the auditory brainstem response (ABR), by replacing the click or chirp traditionally used in the UNHS with complex sounds such as music or speech. Whereas clicks or chirps are characterized by the short duration and the broad frequency spectrum along their entire duration (Chertoff et al., 2010), complex sounds are longer periodic sounds composed by a set of frequencies that maintain a mathematical relationship of proportionality. For that reason, several studies suggest that responses to complex sounds like speech could not unavoidably be predictable from ABR to click

or chirps stimuli (Johnson et al., 2008; Palmer & Shamma, 2004; Skoe & Kraus, 2010; Song et al., 2006).

Within the frequency components of complex sounds (see in figure 2B the evoked FFR waveform to the /oa/ stimulus section and in 2C the frequency components for the /o/ region and for the /a/ region and steady F_0), the lowest frequency represents the rate at which the vocal folds open and close and it is usually termed fundamental frequency (F_0) (indicated with a black dotted line in Figure 2C). The perception of F_0 is the pitch, which plays a key role in language acquisition (Háden et al., 2009) as it allows speaker recognition, contains emotional information which, in turn, facilitates the establishment of the first social interactions (Benavides-Varela et al., 2012) and facilitates the segmentation of continuous speech into word-form units (François et al., 2017). The integer multiples of the F_0 constitute the harmonics (indicated with grey lines in Figure 2C), whose amplitudes are modulated by the supraglottal cavities for which the air passed when it is flowing out (Viegas et al., 2019). These cavities work as a filter attenuating certain harmonics and amplifying other ones (Ericsson, 2020). The amplified harmonics are known as the formants (indicated with dark grey lines in Figure 2C) and are also essential for language development because their encoding contributes to phoneme discrimination (Carlson et al., 1975; Hillenbrand et al., 1995; Peterson & Barney, 1952).

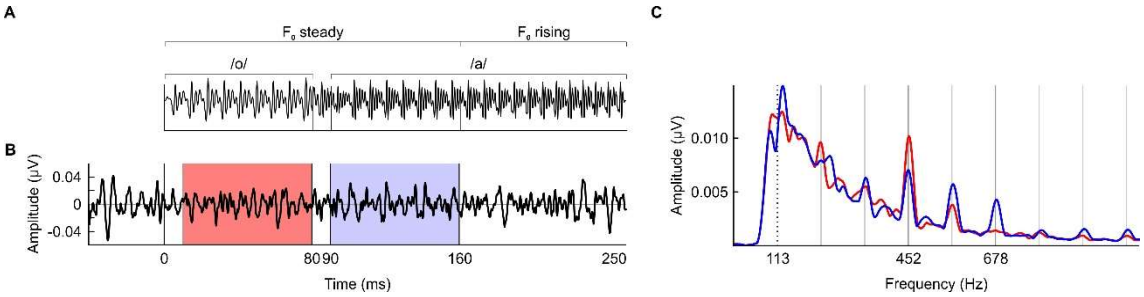

Figure 2. Temporal and spectral representation of the stimulus /oa/. (**A**) Time waveform of the /oa/ stimulus. (**B**) Grand averaged time-domain waveform from an adult cohort obtained by subtracting the neural responses to the two stimulus polarities. (**C**) Amplitude FFR spectra extracted from the /o/ vowel section (red) and the /a/ vowel section (blue). Adapted from Arenillas-Alcón et al. (2021)

Thus, the study of the FFR allows us to explore the precision and strength with which these acoustic signals are encoded in quiet and in noise environments, and the fidelity with which changes in these accoustic cues are tracked throughout the stimulus duration.

FFR and neural plasticity

The auditory system is a complex and integrated circuit that has an impressive ability to modulate the way in which incoming sounds are processed (Kraus & White-Schwoch, 2015). This

experience-dependent capacity is crucial to adapt our function to our changing environments but also to make feasible the improvement or restoration of perceptual abilities after the implementation of compensative strategies (Sharma et al., 2013).

Given the neuroplasticity of the auditory system, several studies explored the astonishing effects of higher-level cognitive activities such as language and music experience in shaping the auditory processing of complex sounds in human beings (Krishnan et al., 2005; Musacchia et al., 2007; Wong et al., 2007; Xu et al., 2006). The FFR, as a faithful snapshot of the neural encoding of periodic sounds, has been proposed a valuable tool to explore and quantify the impact of these practices on the perceptual-cognitive skills. The FFR modulations are described after short- (Carcagno & Plack, 2011; Escera, 2017; Russo et al., 2005; Song et al., 2008) and long-term (Krishnan et al., 2005; Musacchia, et al., 2007; Reetzke et al., 2018; Wong et al., 2007) auditory experiences along the lifespan.

Russo and colleagues (2005) found an improvement in the FFR to speech stimuli presented with background noise in nine children aged between 8 and 12 years old diagnosed with language-based learning problems following an 8-week commercially available auditory speech training program. In adults, the modulation of the FFR was also observed after a short-term linguistic training (Song et al., 2008) and, even, after ten hours on a pitch discrimination task (Carcagno & Plack, 2011). Although these findings in adult populations showed neurophysiological changes restricted to specific speech stimuli, an improvement in overall sensory encoding non-stimulus dependent and detected even after 8 weeks post-training, has been recently disclosed following an intensive training characterized by the combination of high-talker variability stimuli and reinforcement-driven learning using trial-by-trial feedback (Reetzke et al., 2018).

The impact of long-term language experience on the FFR have also been investigated. Krishnan and collaborators (2005) recorded the FFR to four mandarin monosyllables in fourteen native speakers of Mandarin and thirteen native speakers of American English and found that native Mandarin-speaking participants showed more accurate pitch pattern encoding relative to native English-speaking subjects.

The effects of musical experience on the FFR have also been widely investigated (Musacchia et al., 2007; Parbery-Clark et al., 2009, 2012a, 2012b, 2013; Strait et al., 2009, 2012, 2014; Tierney et al., 2015; Wong et al., 2007). In a recent study, the FFR was recorded in twenty-nine adults, sixteen of them musicians and thirteen no musicians (Musacchia et al., 2007), showing that musicians, who declared to play an instrument before the age of 5 and had more than 10 years

of experience with intensive practice, had earlier and more robust FFR to speech and music stimuli than non-musician controls. The interplay between music and speech were corroborated in another study in which the FFR to different linguistic pitch patterns were recorded in ten amateur musicians who had at least 6 years of musical training and ten nonmusicians (Wong et al., 2007). Both groups had no previous exposure to a tone language. Musicians showed stronger overall F_0 amplitude and a higher stimulus-to-response correlation values compared to the non-musician group. Also, a significant correlation between the ability of tracking pitch changes and the music experience were found.

Strait and colleagues (2009, 2012, 2014) conducted a series of studies in which assessed the effects of musical training in speech processing at different time ranges by recording the FFR to consonant-vowel presented in quiet and in noise condition. These studies corroborated the association between music training and a greater competence in communication skills (Strait et al., 2014), better representations of frequency components important for the perception of pitch and timbre (Strait et al., 2009), and an increased tolerance to background noise (Strait et al., 2012). The specific effects of musical training were shown by a study conducted with teenagers (Tierney et al., 2015). Tierney and colleagues (2015) disclosed that music learning begun in high school enhanced in a greater way the stability of subcortical complex-sound processing compared to other training program not focused on auditory skills. Taking together, these findings suggest that long-term experience with language or music via corticofugal pathway could improve the early sensory processing at the subcortical level (Ahissar & Hochstein, 2004; Kraus & Banai, 2007).

Thus, the FFR provides a window to explore the effects of the individual auditory experiences on the auditory system function, making it possible to examine the modulations sculped by music (Musacchia et al., 2007; Parbery-Clark et al., 2009, 2012a, 2012b, 2013; Strait et al., 2009, 2012, 2014; Tierney et al., 2015; Wong et al., 2007), and language experience (Krishnan et al., 2005; Zhao & Kuhl, 2018) but also from other factors such as aging (Anderson et al., 2021; Roque et al., 2019), education and socioeconomic status (SES) (Skoe et al., 2013) and reading and learning disorders.

FFR and neurodevelopmental disorders

The FFR allows to identify the fine-grained auditory processing deficits associated with communication skills. Hence, an extant body of research described disruptions in the FFR associated with specific language impairment (SLI; Barman et al., 2020; Basu et al., 2010), autism

spectrum disorder (ASD; Chen et al., 2019; Font-Alaminos et al., 2020; Jones et al., 2020; Otto-Meyer et al., 2018; Russo et al., 2008, 2009), dyslexia and other reading and learning disabilities (Banai et al., 2005, 2009; Cunningham et al., 2001; Hornickel et al., 2009, 2011, 2012; Lam et al., 2017; Wible et al., 2004).

Children with SLI showed a poorer FFR waveform morphology with shallower peaks and a delayed onset compared with the typically developing children (Barman et al., 2020; Basu et al., 2010). In children with ASD, a reduced neural synchrony and phase locking to speech cues were described (Russo et al., 2009), showing an impoverished encoding of pitch changes along the entire stimulus duration (Russo et al., 2008), a major vulnerability to the presence of background noise (Russo et al., 2009) and a more unstable response compared to controls (Otto-Meyer et al., 2018). Also, Font-Alaminos et al. (2020) found a defective sensory encoding to auditory repeated information, underpinned by an increase of the FFR amplitude with stimulus repetition in children with ASD compared to their peers. In learning disabilities (e.g., dyslexia), delayed FFR responses with an impoverished representation of stimulus harmonic content (Banai et al., 2005, 2009; Hornickel et al., 2011, 2012) and a reduced representation of stimuli differences (Hornickel et al., 2009) were disclosed. Recently, a poor reading fluency has also been linked to unstable FFR (Lam et al., 2017).

The association between the FFR and language impairments described in the previous lines suggests the potential clinical use of the FFR as an early biomarker of future communication skills. To test the predictive value of the FFR, White-Schwoch, Woodruff Carr, et al. (2015) analyzed the FFRs recorded from a group of 3-4 years old children and disclosed that the precision and stability with which consonants presented in noise were encoded in a 30-min neurophysiological assessment predicted performance on reading readiness test one year after the neurophysiological assessment.

Thus, the consideration of the FFR as a potential predictor of communication skills and the possibility to modulate this electrophysiological response through specific training motivated us to investigate the FFR during the first days of life, when plasticity of the underpinning neurophysiological machinery is maximum and the effectiveness of early intervention programs is highest (Foorman et al., 2003; Schatschneider & Torgesen, 2004; Vellutino et al., 2004; Willcutt & Pennington, 2000).

FFR in newborns

In contrast to the abundant literature on school-age children, much less is known about the characteristics of the FFR during the neonatal period, and whether there exist differences or particular traits for newborns at risk of neurodevelopmental or language delay. Gardi et al. (1979) recorded for the first time the neonatal FFR. He investigated this electrophysiological response from neonates aged between 1-3 days old to 10 ms tone bursts. This study disclosed, on the one, hand the possibility to record the FFR during the first days of life, and on the other hand, the similarities with the adult FFR amplitude and waveform morphology.

Despite this seminal electrophysiological finding, it was not until three decades later when the neonatal FFR research field expanded. In the early 2010s, Jeng and colleagues conducted a series of studies on newborns, infants and adults using speech sounds in which the feasibility to record the neonatal FFR was confirmed (Jeng et al., 2011). Also, the universal and innate voice-pitch encoding were disclosed after recorded similar FFRs in American and Chinese newborns during their three first days of live to different Mandarin tones (Jeng et al., 2011; Jeng, Lin, & Wang, 2016); the effect of linguistic experience was corroborated, showing better neural responses in Chinese adults than in Chinese newborns (Jeng et al., 2011). These findings provided a significant conceptual advancement and the basis for further examination of the developmental maturation of neural representation of speech features.

Thus, since the possibility to record the FFR during the first days of life and the conceptualization of this electrophysiological response as a biological snapshot of the integrity of sound encoding along the auditory pathway, the implementation of the neonatal FFR in clinical routines was suggested as a possible promising contribution from the hearing and neurosciences fields to the public health such as it was the UNHS (Kraus & White-Schowoch, 2016). Indeed, a similar intervention program proposed by Joint Committee on Infant Hearing to detect congenital hearing loss, the Early Hearing Detection and Intervention (EHDI) plan, was suggested for detecting communication disorders. In an idealized scenario, a neonatal FFR recording is suggested after passed the UNHS only changing the click or chirp stimuli by more complex sounds such as music or speech. After that, the detection of a disrupted FFR could trigger out the implementation of an early intervention plan guided by an interdisciplinary group who tries to minimize the speech encoding disruption consequences to the language outcomes based on the idea that early auditory abilities impact on language development (Jusczyk, 1997; Leppänen et al., 2010; Mueller et al., 2012; Tsao et al., 2004;). However, before the FFR can be used in clinical settings, normative values need to be established. Thus, the first goal of this PhD thesis

was to collect and analyze the FFR from a large number of healthy newborns at 1-3 days after birth offering reference values from an extensive number of FFR parameters.

Neonatal FFR in clinical conditions

The following step of this PhD thesis concerned establishing the potential clinical use of the neonatal FFR. A previous study conducted by Musacchia and colleagues (2020) explored if the FFR could identify neurotoxicity levels in neonates affected by hyperbilirubinemia with more accuracy than click-evoked ABRs. To test that, they recorded the click-evoked ABRs and the FFR to the /da/ speech syllable in 3 groups of neonates: Group I were composed by 13 healthy neonates, Group II comprised neonates before phototherapy treatment and Group III consisted of these same individuals after treatment. A total of 28 infants were included in Group II and III. Regarding click-evoked ABRs, no group differences were observed neither in latency nor amplitude. Regarding FFR, first formant (F_1) amplitudes were less robust in Group II compared with Group I. And also, those infants who presented high-bilirubin levels and were treated with phototherapy, Group III, showed greater F_1 amplitudes than Group II. Thus, they suggested that the neonatal FFR could reflect in a more specific manner the neurotoxicity in neonates in infants with hyperbilirubinemia.

Recently, Madrid and colleagues (2021) aimed to extend normative FFR values to the premature population. To that end, they recorded the FFR in preterm infants aged between 33 to 64 weeks of GA to the consonant-vowel /da/. The preterm FFR showed a remarkable similarity in waveform morphology to that reported in previous studies conducted with newborns born at term. Also, a shortening of the FFR onset time with increasing age was described in line with neonatal and infant FFR literature (Anderson et al., 2015; Arenillas-Alcón et al., 2021; Ferreira et al. 2020; Pinto & Martinelli, 2020; Van Dyke et al., 2017). This finding is interpreted as a mirror of the myelination pattern experimented by the auditory pathway (Moore et al., 1995; Sano et al., 2007).

Regarding frequency cues encoding, Madrid et al. (2021) reported a significant higher F_0 and F_1 spectral amplitude with increasing weeks of GA. However, the representation of the higher harmonics was similar across age. Other neurophysiological research groups investigating the developmental trend of the FFR during the first year of life, reported a robust and stronger representation of the F_0 during the first months of life and although an improved representation of the F_0 and the fine structure were observed, significant differences were only found in the neural encoding of the fine structure (i.e., formant-related harmonics; Anderson et al., 2015;

Van Dyke et al., 2017). A similar pattern of results was found recently in our laboratory by comparing the neonatal FFR with that from an adult cohort (Arenillas-Alcón et al., 2021). In this study, although higher spectral amplitude to the F_0 were found in the adult group, these differences vanished once the F_0 spectral amplitude was normalized by dividing it by adjacent "off-frequency" bins in which no response energy is expected. Related to the fine structure encoding, a frequency-dependent pattern was disclosed, showing a smaller spectral amplitude of the newborn FFR compared to the adult FFR in harmonics lower than 500 Hz, whereas newborns signal was undetectable in harmonics higher than this cutoff value (Arenillas-Alcón et al., 2021), roughly corresponding to the frequency limits of the natural filter of the mother's bomb (Gerhardt & Abrahams, 1996; Lahav & Skoe, 2014) until the end of pregnancy (Bench, 1968; Draganova et al., 2005; Gerhardt, 1989; Gerhardt et al., 1990; Gerhardt & Abrams, 2000; Hepper & Shahidullah, 1994; Jardri et al., 2008). It was suggested that the lack of signal for frequencies higher than this limit could be explained by the low exposure to high frequencies and the evidence of experience-dependent auditory learning present before birth (Lahav & Skoe, 2014; Krueger & Garvan, 2014; Kujala et al., 2003; Partanen et al., 2013).

Thus, the feasibility to record the neural representation of F_0 is demonstrated also in control and clinical population, at least for the 100 Hz range, during the first hours of life regardless of nationality or mother tongue (Jeng et al., 2011). In addition, pitch -as a perceptual correlate of F0 (Oxenham, 2012)- is an acoustic cue that contains emotional information, facilitates speaker recognition, promotes the first social interactions (Benavides-Varela et al., 2012) and contributes to the segmentation of continuous speech into word-form units (François et al., 2017). Pitch representation could offer a neural synchrony route onto which other speech features could attach as pieces that would, finally, fit together and become a coherent entity (Arenillas-Alcón et al., 2021; Eggermont, 2001). Taking into account the innate capacity of F_0 encoding, the essential role of pitch for language acquisition (He et al., 2007) and the sensitivity of the auditory system to the fetal environment status, we deemed relevant to analyze whether an anomalous intrauterine nutrition, exploring the two phenotypes which represents both ends of the birth weight continuum (fetal growth restriction (FGR) and large-for-gestational age (LGA)), could negatively impact the auditory system's functionality in encoding speech sounds during the first days of life by means of the FFR-F_0 .

Hazards to fetal development: fetal growth restriction

As mentioned above, a number of pathological or environmental conditions can challenge normal fetal growth, hence compromising auditory system development and resulting in turn, in a high risk for neurodevelopmental delays. One such condition is fetal growth restriction (FGR). FGR is defined as the impossibility to achieve the genetic growth potential (Lee et al., 2013) and its prevalence accomplish between 6 and 10% of all deliveries (Marsál, 2002). In low-income countries, this percentage is even greater and, currently, the worldwide FGR affection exceeds 30 million of cases per year (Bernstein et al., 2000; Chauchan & Magann, 2006; De Onis et al., 1998; Fang, 2005; Figueras & Gratacos, 2014; Lackman et al., 2001;). Growth restricted infants represent a high-risk population for perinatal and long-term morbidity and mortality (Gardosi et al., 2013; McIntire et al., 1999). Adverse neurobehavioral outcomes have also been found throughout life (Arcangeli et al., 2012; Baschat, 2014; Dubois et al., 2008; Løhaugen et al., 2013; Viggedal et al., 2004).

The causes of FGR are diverse, and generally classified into maternal, fetal and placental. The most relevant maternal factors are weight, smoking, use of recreational drugs, socioeconomic status, advanced maternal age, nulliparity, previous pregnancy with preeclampsia, history of gestational hypertension, family history of intrauterine growth restriction (IUGR) or previous IUGR pregnancy, intra-uterine fetal death (IUFD), inherited or acquired thrombophilia, anemia, high altitude living, autoimmune disorders (phospholipid syndrome, lupus erythematosus), antepartum diabetes mellitus, chronic diseases such as chronic pulmonary disease or cyanotic heart disease. Placental causes are related to those cases in which insufficient oxygen and nutrients transfer to placental site is occurred, such as in placenta previa, placental infarct, circumvallate placenta, chorioangiomas or velamentous cord insertion. Finally, fetal causes are related to those cases in which the maternal substrate arrives appropriately to the placenta but is not consumed by the fetus. Some examples of fetal risk factors are chromosomal anomalies (trisomy 13/18/21) or congenital malformations such as cardiovascular disease or renal disease (Malhotra et al., 2019; Manandhar et al., 2018).

Placental insufficiency is the most commonly cause of FGR (Burton & Jauniaux, 2018) and is associated with chronic hypoxia which, in turn, triggers an adaptive mechanism known as brain sparing (McMillen et al., 2001). This compensatory response consists in a redistribution of cardiac output to increase the cerebral perfusion to the brain. However, the benefits derived

from blood flow redistribution does not guarantee normal brain growth over a prolonged period (Malhotra et al., 2017; Miller et al., 2016).

An intricate assortment of neuropathologies is observed in FGR infants and white matter injury is one of the principal affectations (Castillo-Melendez et al., 2015). Zhu et al. (2016) investigated with Magnetic Resonance Imaging (MRI) the expected circulatory redistribution associated to hypoxia in FGR fetuses. They observed an abnormal placental oxygen delivery and a limited oxygen consumption as a fetus adaptative response to this limited oxygen supply which, in turn, results in a poor rate of fetal growth. Also with MRI, alterations in fetal brain metabolism (Sanz-Cortés et al., 2010, 2015; Simões et al., 2015) and microstructure (Sanz-Cortes et al., 2014; Sanz-Cortés, Figueras et al., 2013; Sanz-Cortes, Ratta et al., 2013), have been also disclosed. Other radiological studies described macroanatomic affections such as changes in gyrification (Egaña-Ugrinovic et al., 2013) and insular cortical morphometry (Egaña-Ugrinovic, Sanz-Cortes, Figueras et al., 2014). Connectivity alterations as a low global and local efficiency (Batalle et al., 2012) and a disrupted resting-state network (Batalle et al., 2016) were also reported. Finally, due to the detection of some of the brain disruptions disclosed in the previous lines are difficult to implement in the clinical routines, several studies focused on the corpus callosum (CC) as expression of white matter development and analyzed it by fetal MRI (Egaña-Ugrinovic, Sanz-Cortés, Couve-Pérez et al., 2014) or fetal neurosonography (NSG) (Eganã-Ugrinovic et al., 2015). These latter found that IUGR babies have thinner and shorter CC and the growth rate of CC is lower compared to the experimented by the control group.

Although the evidence of neuroradiological affections, detection and management of FGR neonates are contentious (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2019; McCowan et al., 2018). At the present, FGR neonates born at term without any other perinatal complications such as admission to the neonatal intensive care unit are discharged without further follow-up (Baschat, 2014; Clayton et al., 2007). Thus, neurodevelopmental disruptions are typically identified too late, even at school age (Chen et al., 2016). The heterogeneous phenotypes of growth restriction affection makes it difficult to find accurate biomarkers to help clinicians to detect those at the highest risk (Sanz-Cortes, et al., 2014).

Since one of the major areas affected is language, with an incidence of 30% of the FGR population (Low, 1994), we suggest that the FFR recorded at birth -as part of an exhaustive screening and intervention plan- could help identifying those FGR neonates at the highest risk with language encoding limitations at birth. Taking into account the white matter affections

reported by radiological studies (Nitsos & Rees, 1990; Olivier et al., 2007; Tolcos et al., 2011), the significant relationship between FFR–F_0 strength and white matter affections (Coffey et al., 2017), we hypothesize that the fine-grained central nervous system (CNS) microstructure required for an accurate speech sound processing at birth will be affected and these limitations will be sculpted in the FFR recordings of FGR newborns. Thus, the second aim of my thesis was to explore if neonates affected by fetal growth restriction -a population associated with cognitive impairments being language one of the areas affected-, present deficits in speech encoding at birth.

Hazards to fetal development: neonatal overweight (large-for-gestational babies)

While the lower end of the birth weight continuum (<10th percentile), under the term fetal growth restriction (FGR) or small-for-gestational-age (SGA), have been clearly associated with adverse perinatal outcomes and poor neurobehavioral attainment, the other end of the distribution, commonly defined as large-for-gestational-age (LGA, >90th percentile) has yielded contradictory results. Indeed, in spite LGA has been also associated with negative perinatal conditions such as mortality, obesity, type 2 diabetes, cardiovascular diseases, and metabolic syndrome (Boney et al., 2005; Johnsson et al., 2015; Rich-Edwards et al., 1997; Sack, 1968; Yu et al., 2011), the risk of negative neurocognitive outcomes is not clear.

Sørensen and collaborators (1997) investigated the relation between birthweight and cognitive function in a retrospective cohort study. They administered the Boerge Prien cognitive test to 4300 young adult Danish born between 1973 and 1975 and concluded that although test scores improved with a birth weight of <2500 g to 4200 g, a decrement of cognitive function was observed with a birth weight above 4200 g. Richards et al. (2001) in a longitudinal study measured cognitive function at ages 8, 11, 15, 26 and 43 years old in 3900 males and females born in 1946. After split birth weight into five categories (< 2.51 kg, 2.51-3.00 kg, 3.01-3.50 kg, 3.51-4.00 kg, and 4.01-5.00 kg), an increasing mean cognitive function with increasing birth weight by the first four subgroups and a declining at the highest birthweight category were disclosed at ages 8, 11, 15, 26, and weakly at 43 years old. These results confirmed the Sørensen findings and suggested that the non-linear association in the upper end of the birthweight continuum could be detected at 8 years of age. Similar findings were disclosed in education achievement suggesting a possible functional implication of the association between birth weight and cognition.

Regarding academic achievement, Kirkegaard and colleagues (2006) follow 5319 children for 11 years and explored the relation between birth weight, GA and their school performance. The results disclosed the existence of a U shaped relationship between birth weight and learning difficulties, particularly with reading and arithmetic competence. After adjusting for GA, the results changed slightly but the association persisted. Similar results were found by Cesur & Kelly (2010), who explored two different datasets, a cohort of young men and women of the National Longitudinal Survey of Youth and the kindergarten cohort of the Early Childhood Longitudinal Study. They found that a 250 g weight increase from 4500 g was associated with a reduction in math and reading recognition scores by approximately 0.1% after correcting for potential confounders.

Other studies disclosed that being born with high birth weight was associated with a major risk of cerebral palsy (Jarvis et al., 2003), ASD (Moore et al., 2012), attention problems (van Mil et al., 2015), social disorder symptoms (Alati et al., 2009) and externalizing behavior problems (Van Lieshout et al., 2011). However, other studies failed to show these associations or even revealed a positive relationship. Paulson et al. (2014) compared cognitive functioning in 271 children born with ≥90% BW for GA vs 2659 children with a 5-89% at 4 time points: 9 months, and 2, 3.5, and 5.5 years, and they found that cognitive performance was not statistically different, and that this pattern of results did not change through early childhood. Frank et al. (2018) reported a lack of association between being born LGA and are at increased risk for poor verbal ability or externalizing behavior problems. Khambalia et al. (2017) compared 49439 LGA (>90th percentile for birthweight, GA and sex) and 400418 appropriate size for gestational age (AGA; 10th–90th percentile) infants and disclosed that LGA infants show positive long-term health, development and educational outcomes, specifically in reading performance (in year 3) compared with AGA after adjusted by potential confounders.

The lack of international consensus on terminology and criteria, with different cutoff values and the use of absolute birth weight or its normalization by GA, hampers to integrate previous literature in a whole. A further limitation of neurodevelopmental studies conducted with LGA is that they did not explored the first years of life, when neuroplasticity is maxima and possible confounding factors such as postnatal nutritional exposure and growth trajectories during childhood are not present. From animal studies, different models disclose a plausible association between LGA and poor cognitive outcomes. Fetal growth is conditioned by complex interactions between genetic information and intrauterine environment, so that an adverse fetal environment could translates into being LGA (Chiavaroli et al., 2016).

Although there is a lack of studies exploring the pathophysiological mechanisms which could contribute to understand the incongruities found in the neurofunctional alteration at birth in LGA neonates, previous works reported an association between maternal pre-pregnancy body mass index (BMI) and maternal gestational weight gain (GWG) with offspring's neurodevelopmental impairment. Gage et al. (2013) explored the impact of maternal weight gain in the cognitive outcomes across childhood from age 4-16 years, and one of their findings was that offspring of women who gained more than recommended by the 2009 Institute of Medicine (IOM) guidelines had poorer academic achievement at age 16 years than those born from mothers who experimented an adequate GWG during pregnancy. Huang et al. (2014) investigating the consequences of the maternal pre-pregnancy BMI on the child neurodevelopment, found that the upper end of the maternal pre-pregnancy BMI spectrum was associated with a poor child IQ, and an excessive weight gain accelerated the association. Recently, Van der Burg et al. (2016) suggested an integrative model to explain the pathway with which maternal obesity could limit children neurodevelopment and suggested that maternal and fetal inflammation derived from maternal obesity were the main cause. A recent study suggested that neonatal adipose tissue not mother-related may also induce an inflammatory response (Hernandez-Trejo et al., 2020). Thus, the third aim of my thesis was to explore if being born LGA is associated with an altered speech encoding at birth by using the FFR as neural correlate.

OBJECTIVES

The present PhD thesis aimed at exploring the possibility to detect abnormal neural encoding of speech sounds at birth using the frequency-following response (FFR) in neonates affected by an altered fetal growth. To test the clinical potential of the FFR during the first hours of life, the specific aims of each study that compile in the present thesis are the followings:

STUDY I

In the first study we aim to establish a normative database depicting the standard variability found in different measurements extracted from the FFR recorded in healthy newborns. With that, we would like to offer a characterization of this electrophysiological response during the first days of life including all the parameters used in previous neonatal studies and those included in childhood studies conducted with healthy and control groups.

STUDY II

In the second study we aim at exploring whether neonates affected by fetal growth restriction (FGR), a population associated with high risk of cognitive impairments, with language as the most affected function, present deficits in speech encoding indexed by the neonatal FFR. Given the diffuse central nervous system alterations observed in FGR affecting mainly white matter connectivity, and the sensitivity of the FFR to the rapid spectro-temporal fluctuations of speech sounds requiring a precise functional neuronal architecture, we hypothesize to find an impaired neural encoding of complex sounds in FGR neonates born at term compared to their healthy peers.

STUDY III

In the third study, we aim to investigate the presence of altered neural encoding of speech sounds in large-for-gestational-age newborns by means of FFR disruptions and to shed light on the existent disparity in neurodevelopmental studies conducted with LGA populations. Given the affections of the white matter caused by neuroinflammatory agents linked to the accumulation of maternal and/or neonatal adipose tissue and the association between a white matter affection and disrupted F_0 encoding indexed by the FFR , we expect to find a disrupted speech encoding in LGA neonates.

STUDY I:

The frequency-following response (FFR) to speech stimuli: A normative dataset in healthy newborns

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Research Paper

The frequency-following response (FFR) to speech stimuli: A normative dataset in healthy newborns

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ABSTRACT

The Frequency-Following Response (FFR) is a neurophonic auditory evoked potential that reflects the efficient encoding of speech sounds and is disrupted in a range of speech and language disorders. This raises the possibility to use it as a potential biomarker for literacy impairment. However, reference values for comparison with the normal population are not yet established. The present study pursues the collection of a normative database depicting the standard variability of the newborn FFR. FFRs were recorded to /da/ and /ga/ syllables in 46 neonates born at term. Seven parameters were retrieved in the time and frequency domains, and analyzed for normality and differences between stimuli. A comprehensive normative database of the newborn FFR is offered, with most parameters showing normal distributions and similar robust responses for /da/ and /ga/ stimuli. This is the first normative database of the FFR to characterize normal speech sound processing during the immediate postnatal days, and corroborates the possibility to record the FFRs in neonates at the maternity hospital room. This normative database constitutes the first step towards the detection of early FFR abnormalities in newborns that would announce later language impairment, allowing early preventive measures from the first days of life.

1. Introduction

Auditory brainstem responses (ABR) and otoacoustic emissions (OAE) to simple auditory stimuli are used in clinical practice to assess auditory pathway integrity (Hoth et al., 2009; Moller, 1999; Stuart et al., 1996). Universal newborn hearing screening based on the ABR or OAE has provided the earliest possible diagnosis for infants with permanent hearing loss (Moeller et al., 2006). ABRs can also be elicited with more complex stimuli such as speech or music. Studying brainstem responses to complex stimuli has revealed that the subcortical auditory system is more than a set of relay stations transmitting information from the peripheral sensory epithelium to the cerebral cortex (Song et al., 2008). Subcortical contributions to the neural representation of sound can hence be reliably studied using a variant of the ABR, the so-called Frequency-Following Response (FFR).

The FFR is a non-invasive electrophysiological measurement that reflects the encoding of the temporal and spectral characteristics of complex evoking sounds in a cortico-subcortical auditory network (Bidelman, 2018; Kraus and White-Schwoch, 2015; Skoe and Kraus, 2010). Disruptions in the FFR are found in children with deficits in phonological awareness, reading and abnormal timing resolution (Abrams et al., 2006; Banai et al., 2009, 2005; Basu et al., 2010; Hornickel et al., 2012, 2011; 2009; Johnson et al., 2007; King et al., 2002; Kraus et al., 1996; Wible et al., 2004). Children with reading or language disorders have significantly slower neural response timing, weak neural encoding of formant-related stimulus harmonics and less robust tracking of frequency contours than typically developing children (Banai et al., 2005; Basu et al., 2010; Billiet and Bellis, 2010; Hornickel et al., 2009;

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The frequency-following response (FFR) to speech stimuli: a normative dataset in healthy newborns[1]

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Abbreviated title: Normative FFR in neonates

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Highlights

- Frequency-following responses (FFR) were recorded on 46 newborns
- Seven objective FFR parameters were retrieved in time and frequency domains
- A normative data-base is offered to guide future clinical studies

Abstract

The Frequency-Following Response (FFR) is a neurophonic auditory evoked potential that reflects the efficient encoding of speech sounds and is disrupted in a range of speech and language disorders. This raises the possibility to use it as a potential biomarker for literacy impairment. However, reference values for comparison with the normal population are not yet established. The present study pursues the collection of a normative database depicting the standard variability of the newborn FFR. FFRs were recorded to /da/ and /ga/ syllables in 46 neonates born at term. Seven parameters were retrieved in the time and frequency domains, and analyzed for normality and differences between stimuli. A comprehensive normative database of the newborn FFR is offered, with most parameters showing normal distributions and similar robust responses for /da/ and /ga/ stimuli. This is the first normative database of the FFR to characterize normal speech sound processing during the immediate postnatal days, and corroborates the possibility to record the FFRs in neonates at the maternity hospital room. This normative database constitutes the first step towards the detection of early FFR abnormalities in newborns that would announce later language impairment, allowing early preventive measures from the first days of life.

Keywords: auditory brainstem response, FFR, auditory processing, speech encoding, hearing screening, human neonates, language impairments, cognition.

1. Introduction

Auditory brainstem responses (ABR) otoacoustic emissions (OAE) to simple auditory stimuli are used in clinical practice to assess auditory pathway integrity (Hoth et al., 2009; Moller, 1999; Stuart et al., 1996). Universal newborn hearing screening based on the ABR or OAE has provided the earliest possible diagnosis for infants with permanent hearing loss (Moeller et al., 2006). ABRs can also be elicited with more complex stimuli such as speech or music. Studying brainstem responses to complex stimuli has revealed that the subcortical auditory system is more than a set of relay stations transmitting information from the peripheral sensory epithelium to the cerebral cortex (Song et al., 2008). Subcortical contributions to the neural representation of sound can hence be reliably studied using a variant of the ABR, the so-called Frequency-Following Response (FFR).

The FFR is a non-invasive electrophysiological measurement that reflects the encoding of the temporal and spectral characteristics of complex evoking sounds in a cortico-subcortical auditory network (Bidelman, 2018; Kraus and White-Schwoch, 2015; Skoe and Kraus, 2010). Disruptions in the FFR are found in children with deficits in phonological awareness, reading and abnormal timing resolution (Abrams et al., 2006; Banai et al., 2009, 2005; Basu et al., 2010; Hornickel et al., 2012, 2011, 2009; Johnson et al., 2007; King et al., 2002; Kraus et al., 1996; Wible et al., 2004). Children with reading or language disorders have significantly slower neural response timing, weak neural encoding of formant-related stimulus harmonics and less robust tracking of frequency contours than typically developing children (Banai et al., 2005; Basu et al., 2010; Billiet and Bellis, 2010; Hornickel et al., 2009; Wible et al., 2004).

In addition, neurodevelopmental disorders characterized by impaired communication and literacy skills such as dyslexia or autism spectrum disorder (ASD) have been associated with abnormal subcortical representation of speech sounds. Hornickel and Kraus (2013) described that children with dyslexia are characterized by delayed and harmonically impoverished responses from the auditory brainstem (Banai et al., 2009; Basu et al., 2010; Hornickel et al., 2012, 2011) and reduced subcortical representation of stimulus differences (Banai et al., 2005; Hornickel et al., 2009). In children with ASD, Russo et al. (2009) reported deficits in timing and frequency encoding of speech sounds at brainstem level. ASD individuals also exhibited a subcortical neural response which was more vulnerable to background noise in comparison to typically developing children. Another recent study described more variable FFRs in children with ASD compared to their healthy peers (Otto-Meyer et al., 2018).

Moreover, White-Schwoch and colleagues (2015a) examined the FFRs recorded from a group of 3-4 years old children and reported that the precision and stability of the neural encoding of

consonants in noise predicted performance on reading readiness tests one year after the neurophysiological assessment. In infants with ages between 3 to 10 months, Anderson et al. (2015) found a robust fundamental frequency representation while the amplitudes of the first formant and higher harmonics in the FFR increased with age. Thus, the FFR may offer a neurophysiological marker of the efficient encoding of speech sounds related to literacy abilities (Hornickel and Krauss, 2013).

In spite of the potential of the FFR to anticipate reading and literacy impairments, little is known about the neural transcription of speech sounds in newborns. Recently, Kraus and White-Schwoch (2016) suggested an idealized scenario where the FFR could be registered after the hearing screening test was passed using the same equipment, with only replacing the typical click or burst stimulus used for ABR with a speech sound. Their claim was that FFR screening could help identifying newborns at risk of developing literacy impairments in the future, so that they could be referred to appropriate specialists for a more exhaustive examination.

The interest to improve our knowledge in the early maturation of complex sound processing at brainstem level is further encouraged by the plasticity of neural tissues in subcortical structures (Johnson et al., 2008; Krisham et al., 2009, 2005; Musacchia et al., 2007; Russo et al., 2005; Song et al., 2008; Strait et al., 2009; Wong et al., 2007). Recent studies have shown that the FFR is sensitive to language (Krishnan et al., 2009, 2005; Krizman, 2015; Xu et al., 2006), musical experience (Bidelman et al., 2014; Jonhson et al., 2008; Lee et al., 2009; Musacchia et al., 2007; Strait et al., 2009; Weiss and Bidelman, 2015; Wong et al., 2007) and short- and long-term auditory adaptation and training (Escera, 2017; Russo et al., 2005; Song et al., 2008). Evidence of brainstem response modulation by musical training has been shown with a few years of lessons (Parbery-Clark et al., 2012; Strait and Kraus, 2014; Zuk et al., 2013) and observed in very young musicians of 3 years of age (Skoe and Kraus, 2013; Strait et al., 2014, 2013, 2012). After a revision of a number of phonologic intervention studies, Handler et al. (2011) confirmed the effectiveness of phonologic training implementation during the first years of life in reading impaired children as compared to those who were not identified or helped until years later (Foorman et al., 2003; Lyon et al., 2010; National Institutes of Health, 2000; Schatschneider and Torgesen, 2004; Vellutino et al., 2004; Willcutt and Pennington, 2000). Hence, detecting early FFR abnormalities in newborns that would announce later language impairment would allow installing early preventive measures such as music enrichment programs (Kraus et al., 2014).

The possibility to record FFR in newborns has been suggested in no more than ten studies so far, showing a remarkable similarity between the adult and newborn responses (Gardi et al., 1979; Jeng et al., 2016, 2013, 2011b). In addition, Jeng et al. (2016, 2013, 2011b) reported similar FFRs in American and Chinese newborns indicating an early and universal maturation of voice-

pitch processing at brainstem level in neonates at 1-3 days after birth. However, before the FFR can be used in the clinics, normative values need to be established. The aim of the present study was the collection of a normative database depicting the standard variability observed in different relevant parameters retrieved from the newborn FFR.

2. Methods

2.1. Participants

Fifty term newborns (24 females, aged 14-125 hours after birth) were recruited from Sant Joan de Déu Hospital in Barcelona (Catalonia, Spain). By medical reports, all newborns were low-risk gestations without neither obstetric pathologies nor risks factors for hearing impairment as determined by the Committee on Infant Hearing as a "high-risk registry" (Joint Committee on Infant Hearing, 1994). All the participants had a high Apgar score (>7) at 1 and 5 minutes of life.

All newborns passed the standardized hearing screening of peripheral auditory health using an automated auditory brainstem response system (ALGO 3i, Natus Medical Incorporated, San Carlos, CA), before the experiment. Each newborn also passed a normal click-evoked auditory brainstem response collected with a standard SmartEP platform (Intelligent Hearing Systems, Miami, Fl). Standard click ABR was recorded in response to a 100 μs square-wave click stimulus presented at 55 dB SPL according to standard procedures to the Joint Committee on Infant Hearing (2007). Mean latency and amplitude of wave V were 8.90 (± 0.79 SD) ms and 0.27 (± 0.15 SD) μV, respectively (Fig. 1), being comparable to the norms published by Stuart et al. (1994). Four newborns were excluded from the final sample because their wave V could not be reliably identified.

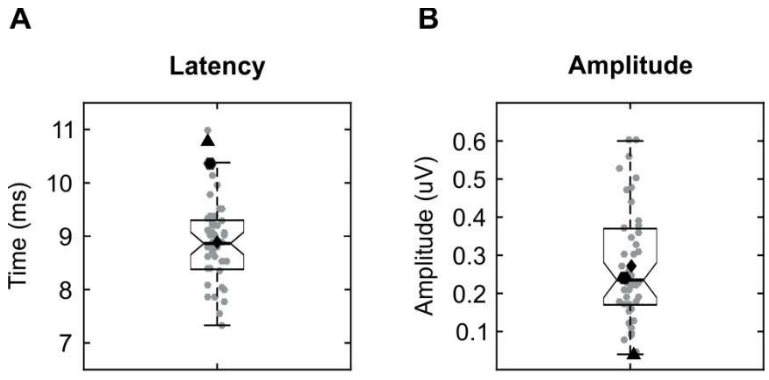

Fig. 1 Distribution of Wave V parameters. Scatter plots depicting all tested newborns (light color filled circles) within box plots for (**A**) latency, and (**B**) amplitude. In the scatter plots, dark filled circle and dark filled triangle indicate data corresponding to the individual newborns selected for illustration in successive figures, with high and low SNR respectively. In each box plot, thick black line and black filled diamond indicate the median and mean, respectively.

Informed consent was obtained from legal guardians of the newborns assessed in accordance with the Declaration of Helsinki after the study has approved by the Ethical Committee of Clinical Research (CEIC) of the Sant Joan de Déu Foundation.

2.2. Stimuli

The complex auditory stimuli used were the syllables /da/ and /ga/ created with a Klatt-based synthesizer (Klatt, 1976) and modified by Praat (Boersma and Weenink, 2013) to have a fundamental frequency (F_0) of 113 Hz in both syllables. The use of F_0 of 113 Hz instead of the very common F_0 at 100 Hz was motivated to avoid contamination by harmonics of the 50 Hz electric line in Europe. The stimuli had a duration of 170 ms, including a 10 ms onset period, a 47 ms consonant transition and a 113 ms steady state vowel. These sounds differed only by the trajectory of their second formant (F2) during the consonant transition (/da/: 1438-1214 Hz; /ga/: 1801-1214 Hz). In the vowel region, all the formants were stable in both syllables. Stimuli were presented at 55 dB SPL in alternating polarities with a 100.27 ms inter-stimulus interval (presentation rate of 3.7 Hz) to the right ear through Etymotic shielded earphones of 300 ohms (ER, Elk Grove Village, IL, EEUU) connected to Flexicoupler® (Natus Medical Incorporated, San Carlos, CA) adaptor.

2.3. Procedure

All newborns were tested in the hospital room where they were resting with their mother once the newborn hearing screening was already passed. For the recording, each newborn was asleep in its own bassinet and the researcher interrupted the experiment to any sign of sleep disruption, to restart the recording as soon as the newborn was calm again. The total mean duration of a test session was 26.09 (± 3.56 SD) min (51.81 ms x 2000 sweeps x 1 condition + 270.27 ms x 2000 sweeps x 2 conditions + duration of sweeps rejected + time needed to check electrodes impedances + time for the newborn restored the sleep in case that it was disrupted). If the recording time

Fig. 2 Recording setup. Four disposable snap Ag/AgCl electrodes were placedin a vertical montage: the active electrode was located at Fpz (white electrode), references at each ear (red and blue, right and left respectively), and ground electrode at the forehead (black electrode). Only the ipsilateral reference (right electrode) was used in the analysis. The reproduction of the participant's picture is with the written consent of her mother.

exceeded this duration, the session was canceled and postponed for several hours or until the next day.

2.4. Data adquisition

FFRs were collected with a SmartEP platform including the *cABR* and *Advanced Hearing Research* modules (Intelligent Hearing Systems, Miami, Fl, EEUU). Auditory brainstem responses to click and to the syllables /da/ and /ga/ were recorded using disposable snap Ag/AgCl electrodes placed in a vertical montage (the active electrode was located at Fpz, references at each ear, and ground at the forehead) with impedances < 5 kΩ (Fig. 2). Only the ipsilateral reference was used in the analysis (Hornickel et al., 2009). The continuous EEG was online bandpass filtered from 30-3000 Hz and acquired with a sampling rate of 13333 Hz. Responses were collected by alternating polarity and averaged ((Org.+Inv.)/2) to isolate the neural response by minimizing stimulus artifact and cochlear microphonic (Aiken and Picton, 2008). Any activity exceeding ±30 μV was rejected online as an artifact, and a total of 2000 artifact-free responses were averaged for each syllable and newborn. Rejection was smaller than 15% of sweeps per condition.

2.5. Data processing and analyses

Neural responses to /da/ and /ga/ were averaged separately and epoched into 270.27 ms windows (including 40 ms pre-stimulus period). After averaging, data were filtered off-line with a spectral bandpass filter with infinite slope from 80 to 3000 Hz to isolate brainstem responses (Chandrasekaran and Kraus, 2009).

After a review of the analytic techniques used to characterize the FFR in different populations (Anderson et al., 2015; Banai et al., 2009; Basu et al., 2010; Hornickel et al., 2012, 2011, 2009; Hornickel and Kraus, 2013; Jeng et al., 2013, 2011a, 2011b, 2010; Jonhson et al., 2008, 2007; Liu et al., 2015; Musacchia et al. 2007; Neef et al., 2017; Russo et al., 2005; 2004; Skoe et al., 2011; Strait et al., 2014; White-Schwoch et al., 2015a and 2015b; White-Schwoch and Kraus, 2013), an extensive number of parameters are included in this study to offer an accurate description of FFR properties in newborns. In the time domain, cross-correlation between the stimulus and the neural response, the neural lag and the signal-to-noise ratio (SNR) are reported. Pitch error and pitch strength, extracted from a sliding time-window autocorrelation approach, were also evaluated. In the spectral domain, the amplitude of the fundamental frequency and its harmonics was calculated based on fixed time-windows. Signal-to-noise ratio variation along the stimulus duration, computed as points below noise floor using a sliding time-window approach, is also reported. All analyses were performed under Matlab R2015b (Mathworks) using routines provided by Intelligent Hearing Systems (Miami, Fl, EEUU) and custom scripts developed in our

laboratory. The following sections describe the rationale and procedure to obtain each of these measures.

2.5.1. Time domain

To examine the FFR in the time domain, a cross-correlation between each syllable stimulus and the neural response was computed. For the purpose of comparison, each syllable was resampled to the sampling rate of the EEG recording (13333 Hz), and bandpass filtered between 80 – 3000 Hz. The magnitude of the first maximum cross-correlation peak and its lag are reported. In addition, the signal-to-noise ratio (SNR) of the FFR was computed in three time windows, corresponding to three different regions of the acoustic stimulus: consonant transition (10 – 57 ms), vowel (57 – 170 ms) and entire response (0 – 170 ms). In the following lines, each of these objective parameters is briefly described.

2.5.1.1. Stimulus-to-response cross-correlation. The cross-correlation magnitude shows how faithfully the FFR reproduces the stimulus waveform as a function of the time shift between the two (Russo et al., 2004). The maximum cross-correlation value was obtained within a response time lag of 3 to 10 ms, in line with previous studies (Jeng et al., 2010).

2.5.1.2. Neural lag. The neural lag is an estimation of the transmission delay between stimulus and response. It was retrieved as the time lag that produced the maximum stimulus-to-response cross-correlation magnitude computed as described above.

2.5.1.3. Signal-to-noise ratio (SNR). Root mean square (RMS) amplitude (in μV) indicates the overall magnitude of neural activity over time (Liu et al., 2015). RMS is calculated by squaring each point in a region of the response waveform, computing the mean of the squared values and then computing its square root. The RMS amplitudes of the FFR to the consonant transition, the vowel and the entire stimulus were computed separately and divided by the RMS amplitude of the pre-stimulus period (-40 – 0 ms) (Anderson et al., 2015; Russo et al., 2004). In order to account for individual response-to-stimulus delays, the individual neural lag retrieved from the stimulus-response cross-correlation analysis was added to each of the selected regions (except to the pre-stimulus region).

Additionally, we computed the autocorrelation function of the entire FFR recording in a sliding time-window approach, using short bins of 40 ms (Hanning tapered) with 1 ms step size. In each bin, the periodicity of the F_0 was estimated as the frequency (inverse of the lag) yielding the maximum autocorrelation value (Boersma, 1993) within a predefined frequency range, fixed from 103 to 123 Hz, leaving a 10 Hz buffer at each side of the F_0 frequency of the stimulus (113 Hz) (Jeng et al., 2013, 2011b, 2010). The F_0s from each bin were concatenated to construct the F_0

contour of the FFR recording. The same procedure was applied to the stimulus waveforms /da/ and /ga/. Two objective parameters were extracted using this method, as described next.

2.5.1.4. Pitch error. Pitch error (in Hz) is a measure of pitch encoding accuracy of the FFR along the syllable presentation. Once the syllable was shifted the time equivalent to the average of the individual neural lag, the absolute Euclidian distance between the syllable F_0 and the response F_0 from each bin was calculated and averaged together (Liu et al., 2015; Song et al., 2008).

2.5.1.5. Pitch strength. Pitch strength is a measure of periodicity that reflects the robustness of the response's phase-locking to the syllable F_0 contour (Jeng et al, 2013). It was computed as the average across bins of the normalized autocorrelation values at the signal's F_0.

2.5.2. Frequency domain

To examine the FFR in the frequency domain, we computed a Fast Fourier Transform (FFT; Hamming windowed) separately for the three different regions of the stimuli as described above (*see 2.5.1*), each region adjusted for each newborn to account for the individual neural lag. In order to avoid artifact differences in power estimates due to different window lengths, the Welch's averaging method (Welch, 1967; *pwelch.m* Matlab function) was applied to estimate the power spectrum of the demeaned signal corresponding to the consonant transition, the vowel and the entire response (segments of 40 ms, equivalent to the window length of the pre-stimulus region; Hamming windowed; 82.5% overlap; spectrum type specified as 'power').

2.5.2.1. Spectral amplitude. The spectral amplitude indicates the magnitude of neural phaselocking at a certain frequency (White-Schwoch et al., 2015b). In order to compare our results with the previous literature, a square root of power estimates was applied to convert them to spectral amplitude. Spectral amplitude corresponding to the F_0 (113 Hz) and its integer harmonics up to 1500 Hz (i.e., $HH_{2\text{-}13}$) were computed as the mean over a ± 5 Hz frequency window centered at each individual peak. Two values are reported: 1) the F_0 spectral amplitude; and 2) a composite value for all F_0 harmonics, resulting from averaging the spectral amplitudes of $HH_{2\text{-}13}$ (Krizman et al., 2015; Parbery-Clark et al., 2009).

2.5.2.2. Points below noise floor. In addition, we computed the spectrogram of the entire FFR recording in short bins of 40 ms (Hanning tapered) with 1 ms step size. Spectral amplitudes were computed with FFTs after zero-padding each FFR bin to 1s to increase spectral resolution, and Hanning windowed. This method allowed extracting the points below noise floor, which is an objective index that describes how the signal could be discerned and differentiated from the noise. It is computed dividing the F_0 spectral amplitude of each bin by the F_0 spectral amplitude

computed in the pre-stimulus region (Song et al., 2008). The total number of bins in which the spectral amplitude of F_0 is smaller in the post- vs. the pre-stimulus region is reported.

2.6. Statistical analyses

SPSS 22.0 was used for statistical analysis. Descriptive statistics for each parameter computed for each syllable (/da/, /ga/) are presented as mean and standard deviation (SD) or median and interquartile range (IQR), after assessing normality distribution by Kolmogorov-Smirnov Statistic with Lilliefors' Significance.

The initial statistical approach was a 2x2 repeated measures analysis of variance (RMANOVA), with syllable (/da/, /ga/) and region (consonant transition, vowel) as factors. However, in the objective indices where the results were obtained only in one response region (i.e., stimulus-to-response cross-correlation, neural lag, pre-stimulus RMS amplitude, pitch error, pitch strength and points below noise floor), a t-test or Wilcoxon test was computed according to the assumption of normal distribution. In the spectral amplitude analyses, a third factor was included (harmonic: F_0, average amplitude $HH_{2\text{-}13}$). The Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. A result was considered significant when $p<0.05$ using a two-tailed analysis. Bonferroni correction was used to adjust p-values for all multiple pairwise contrasts.

3. Results

Grand-average FFR waveforms for both syllables (/da/, /ga/) and the corresponding amplitude spectra of the consonant transition and the vowel regions of the response are shown in Fig. 3A. Individual waveforms and corresponding amplitude spectra from a typical newborn with high SNR (NF 029) and from another newborn with very low SNR (NF 038) are plotted in Fig. 3B and 3C, respectively. Grand-average spectrograms are presented in Fig. 4A, and those from the same individual newborns as in Fig. 3 are shown in Fig. 4B and 4C. As Fig. 4 shows, the newborn FFR contains clear energetic content in the F_0 contour of the syllable, but not in its harmonic frequencies, in agreement with Jeng et al. (2016, 2013, 2011b). Below, we provide a series of descriptive statistics extracted from the values obtained to all computed parameters. In addition, we provide a statistical comparison of parameter values across stimulus types (syllable /da/ vs. /ga/).

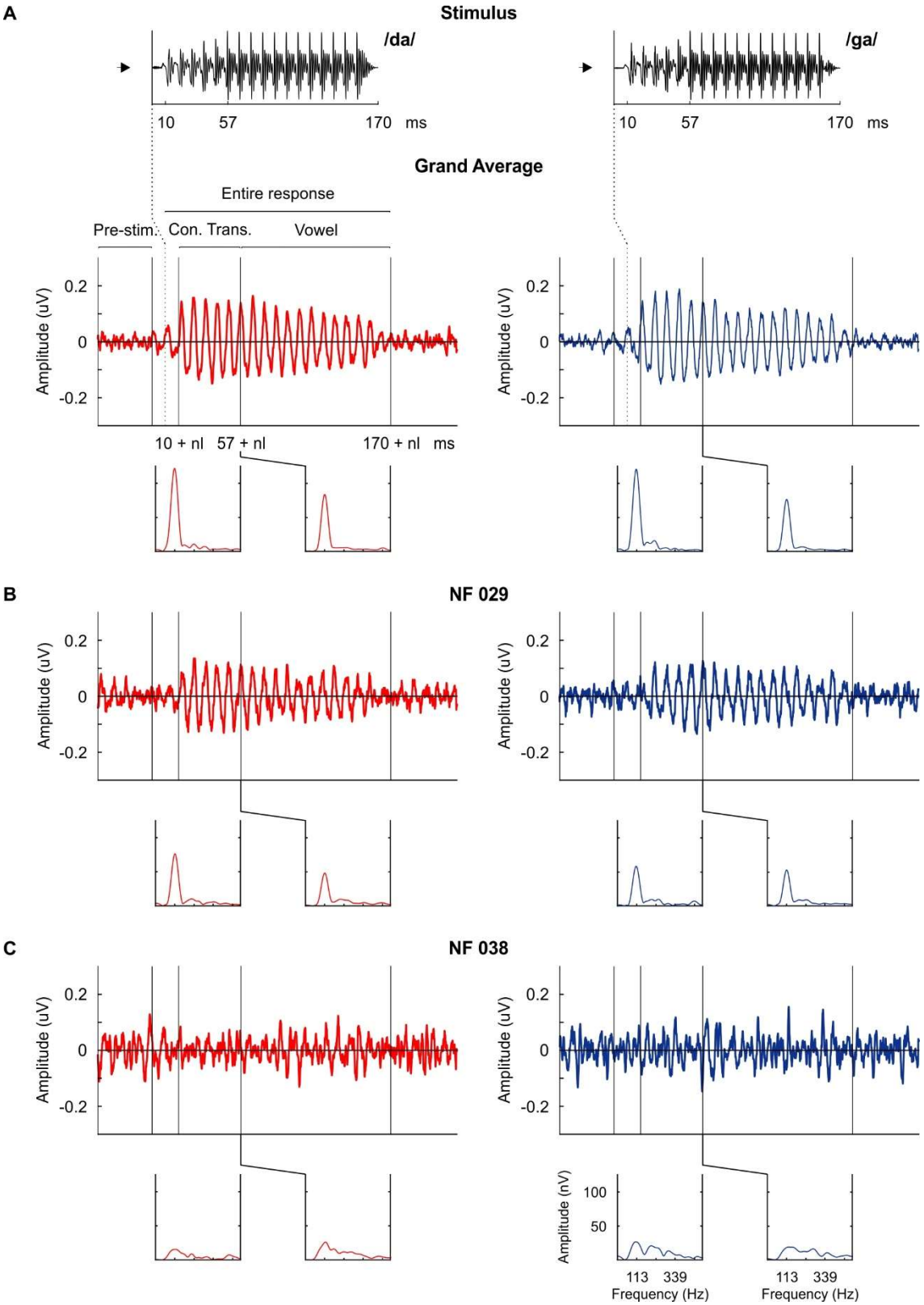

Fig. 3 Spectral and temporal neural representation of the syllables /da/ and /ga/ in the newborn's auditory brain. (**A**) Stimulus waveforms (/da/, /ga/) plotted in black, and grand averaged time-domain FFR waveforms and amplitude FFR spectra extracted from the consonant transition and the vowel stimulus regions to /da/ and /ga/ ploted in red and blue, respectively. (**B**) Time-domain FFR waveforms and amplitude FFR spectra from an individual newborn with high SNR (NF 029) and (**C**) from another newborn with low SNR (NF 038).

3.1. Time domain

In the time domain, a normal distribution was observed for most of the parameters assessed. Only the values of the SNR computed for the consonant transition when the syllable /da/ was presented and the values of the SNR calculated for the vowel and the entire response when the syllable /ga/ was presented did not follow a normal distribution. The corresponding descriptive statistics are reported in Table 1. Fig. 5 illustrates the distribution of the values obtained in all time-domain parameters for each syllable (/da/, /ga/) and indicates the response region assessed (consonant transition and vowel) for SNR. Pitch tracking and pitch strength obtained from the grand-average waveforms and from the individual newborns depicted in Fig. 3 with high and low SNR are shown in Fig. 6 and 7, respectively.

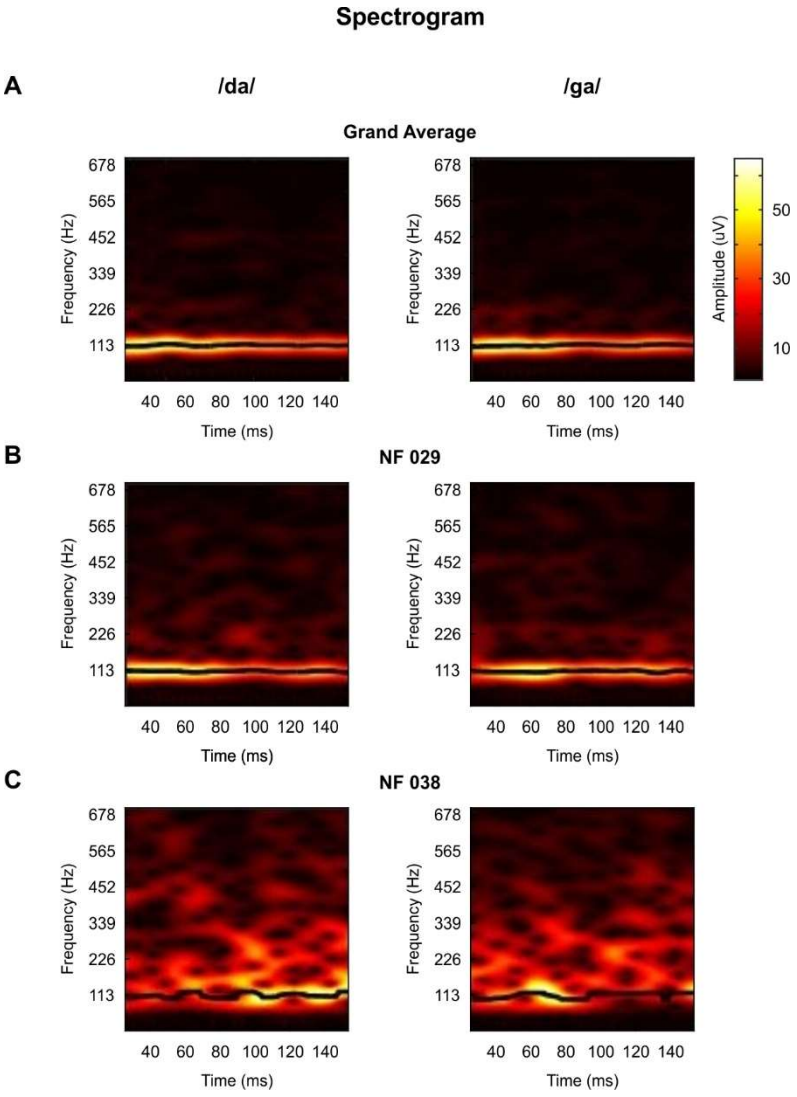

Fig. 4 Spectrograms from FFRs elicited to syllables /da/ and /ga/. (**A**) Spectrograms extracted from the grand-averaged FFRs. (**B**) and (**C**) spectrograms corresponding to the same individual newborns with high and low SNR depicted in Fig. 3. The color scale from black to white indicates the spectral amplitude in µV, with light colours depicting highest amplitude values (top right).

Table 1

Time-domain parameters. Descriptive statistics of stimulus-to-response cross-correlation, neural lag, RMS amplitude calculated from the pre-stimulus region, SNR computed from the consonant transition, vowel and entire response, pitch error and pitch strength for each syllable presented.

Measure	**/da/** **M (SD)**	**/ga/** **M (SD)**
Cross-correlation (Pearson's r)	0.15 (0.04)	0.15 (0.03)
Neural lag (ms)	5.87 (1.11)	5.90 (1.16)
Pre-stimulus RMS (μV)	0.03 (0.01)	0.03 (0.01)
SNR		
Consonant transition (10 – 57 ms)	1.58 (0.75) †	1.82 (0.66)
Vowel (57 – 170 ms)	1.48 (0.41)	1.44 (0.48) †
Entire response (0 – 170 ms)	1.53 (0.44)	1.46 (0.69) †
Pitch error (Hz)	4.89 (2.01)	5.29 (1.78)
Pitch strength (r)	0.61 (0.18)	0.63 (0.17)

† Median (IQR, interquartile range)

A comparison of the time-domain parameter values obtained to the /da/ and /ga/ syllables showed no significance differences in stimulus-to-response cross-correlation values ($t(45) = 0.032$, $p = 0.974$) nor in neural lag ($t(45) = -0.251$, $p = 0.803$). RMS amplitudes during the pre-stimulus baseline period were not significantly different either ($t(45) = 1.860$, $p = 0.069$). Thus, any difference observed in response to the /da/ and /ga/ stimuli could not be attributed to variation in pre-stimulus spontaneous activity. However, no differences were observed in SNR between syllables ($F(1,45) = 1.630$, $p = 0.208$, $\eta^2 = 0.239$). Regarding response region, in contrast with previous studies, the SNR of the vowel was smaller than that of the consonant transition, irrespective of the syllable ($F(1,45) = 32.385$, $p < 0.001$, $\eta^2 = 1$). Finally, pitch measurements, extracted from a sliding time-window autocorrelation approach applied to the entire FFR recording, did not show any significant differences between

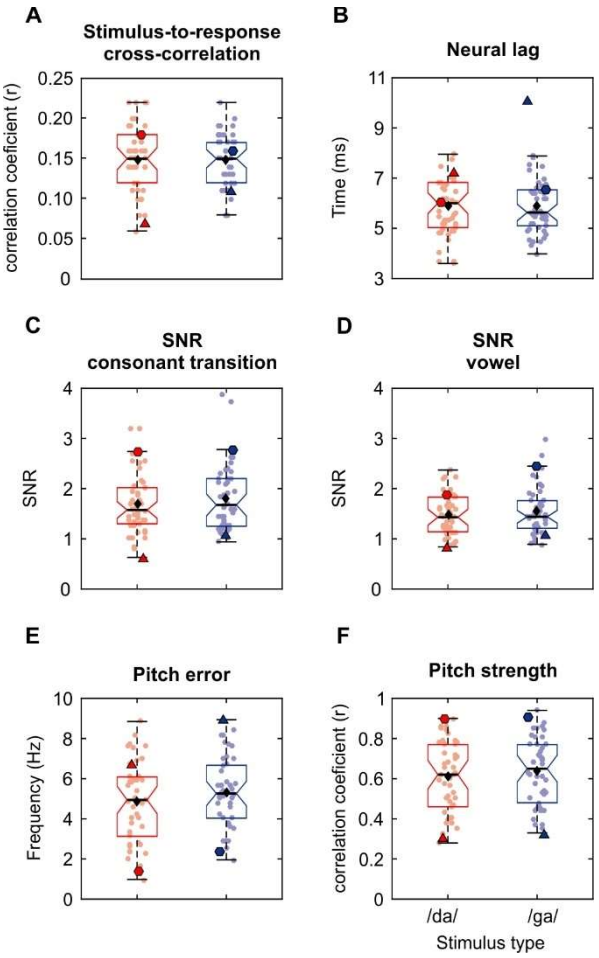

Fig. 5 Distribution of each of the objective indices retrieved in the time domain. Scatter plots depicting all tested newborns (light color filled circles) within box plots for (**A**) stimulus-to-response cross-correlation; (**B**) neural lag; (**C**) signal-to-noise-ratio (SNR) of the consonant transition and (**D**) of the vowel; (**E**) pitch error; and (**F**) pitch strength measurements to /da/ and /ga/ syllables (depicted in red and blue, respectively). In the scatter plots, dark filled circles and dark filled triangles indicate data corresponding to the individual newborns with high and low SNR, respectively, as depicted in Fig. 3. In each box plot, the thick black line and the black filled diamond indicate the median and mean, respectively.

syllables either (pitch error: t(45) = -1.440, p = 0.157; pitch strength: t(45) = -1.187, p = 0.242).

3.2. Frequency domain

In the frequency domain, spectral amplitude values followed a normal distribution for most of the conditions assessed. However, points below noise floor values did not pass the Kolmogorov-Smirnov test. Descriptive statistics are reported in Table 2. Fig. 8 illustrates the distribution of spectral amplitude values across response regions (consonant transition, vowel), harmonics (F_0, HH_{2-13}) and syllables (/da/, /ga/), as well as the distribution of points below noise floor values

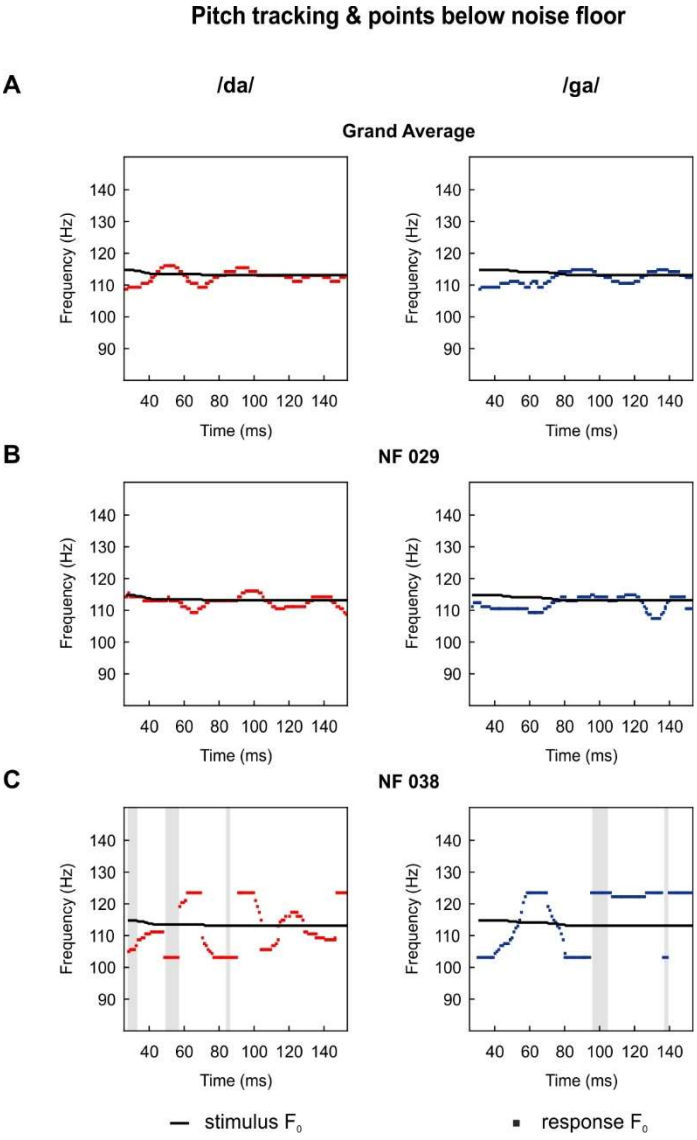

Fig. 6 Pitch tracking and points below noise floor obtained from (**A**) the grand average; (**B**) and (**C**) obtained from the individual newborns depicted in Fig. 3 with high and low SNR, respectively. F_0s were extracted separately from the FFRs to /da/ (*left column*) and /ga/ (*right column*), as well as from the stimuli (*black solid lines*) in overlapping steps of 40 ms using an autocorrelation based approach. Light grey areas indicate the bins in which the F_0 spectral amplitude was lower than the F_0 spectral amplitude in the pre-stimulus region (points below noise floor).

across syllables. Fig. 6 shows the points below noise floor computed from the grand-average waveforms and from the individual newborns depicted in Fig. 3 with high and low SNR.

A three-factor RMANOVA (syllable: /da/, /ga/; region: consonant transition, vowel; harmonic: F_0, $HH_{2\text{-}13}$) performed on all spectral amplitude values showed no significance differences between syllables ($F(1,45) = 0.038$, $p = 0.846$, $\eta^2 = 0.054$). Regarding response region, spectral amplitudes were larger to the consonant transition than to the vowel ($F(1,45) = 22.008$, $p < 0.001$, $\eta^2 = 0.996$) in agreement with previous studies (White-Schwoch et al., 2015b). Regarding the harmonic factor, an expected significant effect was found in spectral amplitude ($F(1,45) = 274.123$, $p < 0.001$, $\eta^2 = 1$), being larger for the F_0 than for its harmonics. A significant interaction between the region and the harmonic was observed as well ($F(1,45) = 23.631$, $p < 0.001$, $\eta^2 = 0.997$). Post-hoc analyses showed a slightly higher difference in spectral amplitudes between the

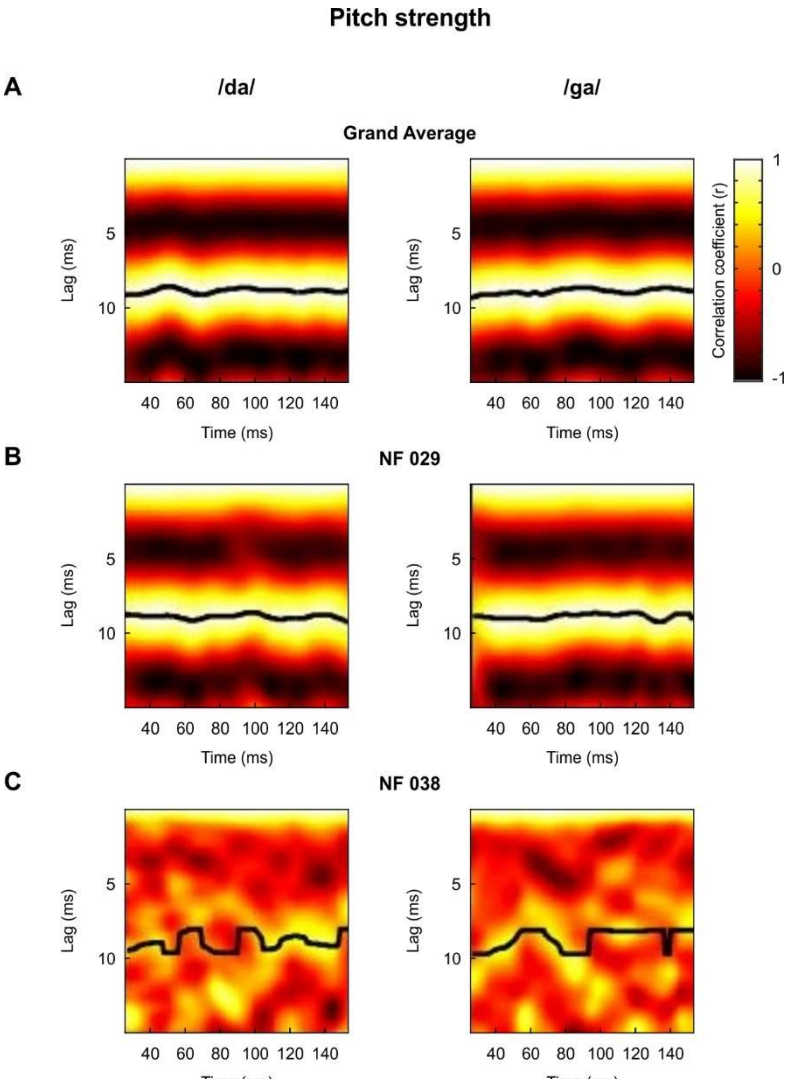

Fig. 7 Pitch strength obtained from (**A**) the grand averaged FFRs; (**B**) and (**C**) from the individual newborns depicted in Fig. 3 with high and low SNR, respectively. The figures depict the autocorrelation values (*r*; from -1 in *black* to 1 in *white*) computed separately from the FFRs to /da/ (*left column*) and /ga/ (*right column*) as a function of time and lag. The maximum autocorrelation value per unit of time is marked in black. Notice that the emerging black line is equivalent to the pitch tracking profiles observed in the Fig. 6.

F_0 and those of the HH_{2-13} in the consonant transition (mean F_0 = 43.293 nV, SE = 2.801; mean HH_{2-13} = 2.892 nV, SE = 0.110) than in the vowel portion (mean F_0 = 35.212 nV, SE = 1.902; mean HH_{2-13} = 2.917 nV, SE = 0.101). Finally, no significant differences were observed in points below noise floor across syllables (Z = -1.116, p = 0.264).

Table 2

Frequency-domain parameters. Descriptive statistics for spectral amplitude across response syllables, stimulus regions and harmonics and for points below noise floor for each syllable presented.

Measure	/da/ M (SD)	/ga/ M (SD)
Spectral Amplitude (nV)		
Consonant transition (10 – 57 ms)		
F_0	40.65 (27.82) †	44.01 (21.45)
HH_{2-13}	3.01 (0.86)	2.52 (0.99) †
Vowel (57 – 170 ms)		
F_0	35.43 (13.55) †	34.47 (14.42)
HH_{2-13}	2.88 (1.16) †	2.73 (0.66)
Entire response (0 – 170 ms)		
F_0	38.29 (13.98)	38.11 (14.84)
HH_{2-13}	3.19 (0.89)	2.83 (0.65)
Points below noise floor	2.5 (24.75) †	0 (13.25) †

† Median (IQR, interquartile range)

4. Discussion

We here provide the first normative database of the newborn FFR, thus demonstrating the feasibility to record this electrophysiological response from bedside, in the maternity unit where newborns are delivered, during their first hours of life.

In order to obtain a comprehensive database, two syllables with different stop consonants (/da/, /ga/) were presented to 50 newborns aged 14-125 hours. Descriptive statistics of each of the parameters assessed were obtained (see Table 1-2). Normal distribution was confirmed for most of them, for which mean and standard deviation are reported. In those cases in which parameter values did not follow a normal distribution, median and interquartile range are reported instead. The representation of the distribution of all values using quartiles opens the possibility to determine the location of an individual's scores and to assess if her/his results are included into the central 50% of values. In general, comparing our results with previous literature, we found smaller values in all measures (Skoe et al., 2013; Strait et al., 2013; White-Schwoch et al., 2015b) except in pitch error and pitch strength (Jeng et al., 2010). The lower values obtained, according to Skoe et al. (2013) could be attributed to age differences.

For each of the objective parameters assessed, no differences between /da/ and /ga/ syllables were observed, indicating that these two stimuli could be used interchangeably to obtain a potential snapshot of pitch representation in the newborn's brain before they are discharged. However, differences were found between parameter values extracted from distinct portions of the FFR,

which corresponded to different stimulus regions, and from different harmonic components of the frequency spectrum. For instance, higher SNR and spectral amplitude values were found in the consonant transition compared to the vowel, possibly due to response adaptation. In contrast, White-Schwoch et al. (2015b) showed higher SNR values for the vowel region than for the consonant transition, although comparable results in spectral amplitude. Regarding the harmonic content, higher spectral amplitude values were observed for the F_0 in comparison to higher harmonics (see Fig. 8), in line with previous observations (Anderson et al., 2015; Banai et al., 2009; Jeng et al., 2016, 2013, 2011b; White-Schwoch et al., 2015b). While we cannot rule out that this may be a particular characteristic of the newborn FFR, the procedure used to obtain it, by averaging responses to opposite polarities, may have exerted a major influence. In fact, while this operation enhances envelope representation, which is not polarity dependent, it eliminates the temporal fine structure of the signal, drastically reducing the spectral energy of the present harmonics (Aiken and Picton, 2008). This explanation may account as well for the lack of differences found in parameter values across syllables.

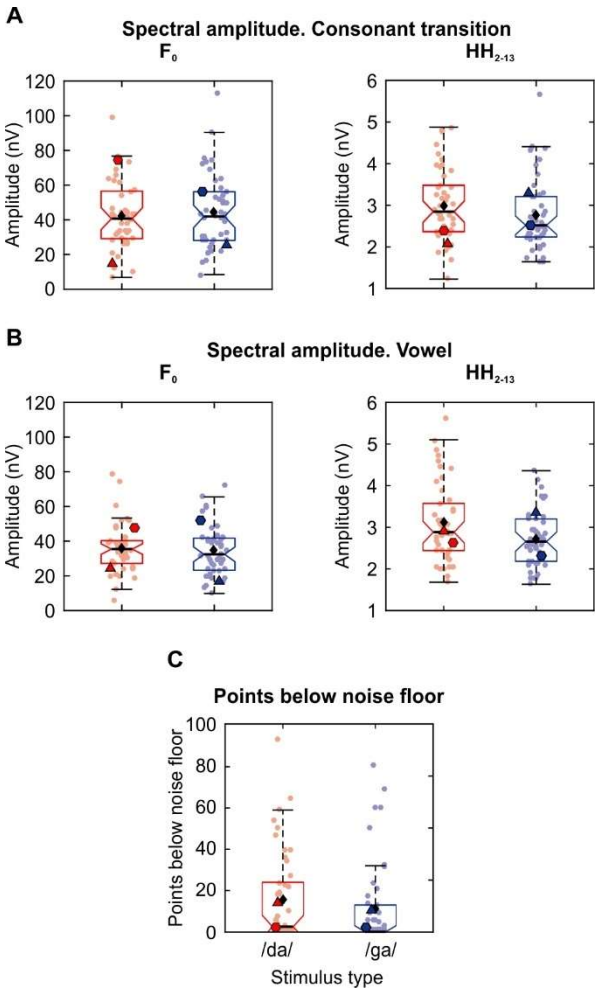

Fig. 8 Distribution of each of the objective indices retrieved in the frequency domain. Scatter plots depicting all tested newborns within box plots for: (**A**) F_0 and averaged HH_{2-13} spectral amplitudes during the consonant transition, and (**B**) the vowel; and (**C**) points below noise floor measurements, all computed for each syllable separately. The layout is equal to that used in Fig. 5.

The results obtained here are in line with those of Jeng and colleagues (2016, 2013, 2011b) who corroborated that the newborn FFR (age: 1-3 days) could be registered during the first days of life (Gardi et al., 1979). In addition to finding evident spectral energy content at the F_0 in the newborn FFR spectrograms, differences in the F_0 spectral energetic content across the individual newborns assessed were observed (Jeng at al., 2016, 2013, 2011b), as in our study. However, descriptive statistics of the different FFR parameters as the ones computed in the present study were only published in Jeng et al. (2010), specifically for measurements related to pitch tracking. They found similar FFRs to voice pitch between infants of 5.7 months mean age and adults using a Chinese

monosyllabic stimulus that mimics the English vowel /i/ with a rising pitch (117 to 166 Hz). Mean and standard deviation of pitch error and pitch strength recorded from the infant group were slightly smaller than those found in the present study. In spite of the differences in group age and the stimulus materials, our results, together with those of Jeng et al. (2010), confirm that pitch is accurately processed during the first stages of life.

We believe our study contributes a step forward towards achieving the ideal scenario proposed by Kraus and White-Schwoch (2016). Taking the universal newborn hearing screening (UNHS) as a reference, they proposed the implementation of a cognitive screening after the UNHS is passed, by using the same recording system where only the classical click stimulus would be replaced by a speech sound. In this study, FFRs were recorded in the hospital room where newborns were resting with their mothers after the auditory screening was passed. Auditory pathway integrity was corroborated by Wave V identification to a click presentation (Fig. 1) using the same portable equipment employed afterwards to record the FFR to the syllables /da/ and /ga/. As the specific hearing screening protocol recommended by the Joint Committee of Infant hearing (2007) to promote the early identification and intervention of children with hearing loss, we suggest, according to Kraus and White-Schwoch (2016), the establishment of a protocol with which the identification of a disrupted newborn FFR would prompt the child to be referred to a coordinated team for follow up, in seeking intervention strategies to improve his/her literacy abilities. Several studies support that spectro-temporal encoding mechanisms could be improved after short- (Song et al., 2012) and long-term (Hornickel et al., 2012) training protocols using the FFR as a fingerprint reflecting these improvements. The neural plasticity of the subcortical auditory system during the first days of life highlights the importance to this period to detect as earlier as possible an abnormal FFR.

The speech tokens selected (/da/ and /ga/) are extensively used in the literature because several studies suggest that stop consonants are an important constraint in populations with literacy impairments (Kraus et al., 1996; Tallal and Stark, 1981; Turner et al., 1992). However, recent studies suggest that the identification of the speech in noise is especially compromised in populations with specific language impairment (Cunningham et al., 2001; Hornickel et al., 2009, White-Schwoch et al., 2015a, 2015b, 2013). To complement the present normative database, future studies using different stimulus materials, for example including speech in noise, and achieving other potential objective indices retrieved from the FFR are needed.

In any case, this study offers valuable information relative to a specific lifetime that was not included in previous normative database research and remained to be described. Skoe and colleagues (2013) characterized the auditory brainstem response of 586 healthy participants

across an extensive age range (from 3 months to 72 years). With our data we contribute to fill the gap in the research focused on the FFR trends along the lifetime. In addition, an age-appropriate normative database is critical to establish a reference with which to compare the results of an individual from a population that presents risk factors to develop literacy impairments (Jeng et al., 2016; Skoe et al., 2013).

Albeit the potential clinical utility attributed to the FFR, its small amplitude at the scalp in contrast with the high background noise constraints the quality of the recordings to translate the use of the FFR from brain research to clinical applications. The averaging method is usually used in clinical practice to assess how the signal is discernible to the noise recorded as a function of the number of sweeps presented (Jeng et al., 2011a). Recent studies offered different threshold criterion depending on the statistical approach used and population assessed (Bidelman et al., 2018, 2014; Jeng et al., 2018, 2013, 2011a). Thus, before the FFR could be considered a universal clinical test, a consistent predetermined threshold to verify a distinguishable FFR is required for each specific lifetime (Jeng et al., 2016).

In summary, the present study shows the possibility to record newborn FFR during the first postnatal hours at the maternity unit before discharge and contributes to approximate the FFR to clinical context. In agreement with Jeng et al. (2016), our study promotes longitudinal research in which the newborns that present normal and abnormal FFR were followed up to elucidate whether an FFR recorded during the first days of life could become a biomarker to prevent future literacy disorders.

Acknolwedgements.

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PAPER

Deficient neural encoding of speech sounds in term neonates born after fetal growth restriction

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Abstract

Infants born after fetal growth restriction (FGR)—an obstetric condition defined as the failure to achieve the genetic growth potential—are prone to neurodevelopmental delays, with language being one of the major affected areas. Yet, while verbal comprehension and expressive language impairments have been observed in FGR infants, children and even adults, specific related impairments at birth, such as in the ability to encode the sounds of speech, necessary for language acquisition, remain to be disclosed. Here, we used the frequency-following response (FFR), a brain potential correlate of the neural phase locking to complex auditory stimuli, to explore the encoding of speech sounds in FGR neonates. Fifty-three neonates born with FGR and 48 controls born with weight adequate-for-gestational age (AGA) were recruited. The FFR was recorded to the consonant-vowel stimulus (/da/) during sleep and quantified as the spectral amplitude to the fundamental frequency of the syllable and its signal-to-noise ratio (SNR). The outcome was available in 45 AGA and 51 FGR neonates, yielding no differences for spectral amplitudes. However, SNR was strongly attenuated in the FGR group compared to the AGA group at the vowel region of the stimulus. These findings suggest that FGR population present a deficit in the neural pitch tracking of speech sounds already present at birth. Our results pave the way for future research on the potential clinical use of the FFR in this population, so that if confirmed, a disrupted FFR recorded at birth may help deriving FGR neonates at risk for postnatal follow-ups.

KEYWORDS
auditory brainstem response, auditory processing, fetal growth restriction, FFR, newborns, speech encoding

Deficient neural encoding of speech sounds in term neonates born after fetal growth restriction[2]

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Deficient neural encoding of speech sounds in term neonates born after fetal growth restriction

Research Highlights

- The present study discloses that term neonates affected by fetal growth restriction (FGR) show impaired speech pitch processing.
- Deficits in speech encoding have been tracked in FGR neonates by the auditory evoked potential named frequency-following response (FFR).
- A neonatal FFR recording could offer valuable information to guide the inclusion of FGR neonates in early intervention programs.

Abstract

Infants born after fetal growth restriction (FGR) --an obstetric condition defined as the failure to achieve the genetic growth potential-- are prone to neurodevelopmental delays, with language being one of the major affected areas. Yet, while verbal comprehension and expressive language impairments have been observed in FGR infants, children and even adults, specific related impairments at birth, such as in the ability to encode the sounds of speech, necessary for language acquisition, remain to be disclosed. Here, we used the frequency-following response (FFR), a brain potential correlate of the neural phase locking to complex auditory stimuli, to explore the encoding of speech sounds in FGR neonates. Fifty-three neonates born with FGR and 48 controls born with weight adequate-for-gestational age (AGA) were recruited. The FFR was recorded to the consonant-vowel stimulus (/da/) during sleep and quantified as the spectral amplitude to the fundamental frequency of the syllable and its signal-to-noise ratio (SNR). The outcome was available in 45 AGA and 51 FGR neonates, yielding no differences for spectral amplitudes. However, SNR was strongly attenuated in the FGR group compared to the AGA group at the vowel region of the stimulus. These findings suggest that FGR population present a deficit in the neural pitch tracking of speech sounds already present at birth. Our results pave the way for future research on the potential clinical use of the FFR in this population, so that if confirmed, a disrupted FFR recorded at birth may help deriving FGR neonates at risk for postnatal follow-ups.

Keywords: auditory brainstem response, FFR, auditory processing, speech encoding, newborns, fetal growth restriction

INTRODUCTION

Fetal growth restriction (FGR) is defined as the failure to achieve the genetic growth potential (Lee et al., 2013) and affects 6-10% of all deliveries (Marsál, 2002). Growth restriction poses a higher risk of perinatal and long-term morbidity and mortality (Gardosi et al., 2013; McIntire et al., 1999) and is associated with adverse neurobehavioral outcomes at different stages of development (Arcangeli et al., 2012; Baschat, 2014; Dubois et al., 2008), spanning until early adulthood (Løhaugen et al., 2013; Viggedal et al., 2004). Detection of FGR and management of FGR neonates are controversial (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2019; McCowan et al., 2018), as unless adverse perinatal outcomes, such as preterm birth, fetal distress, neonatal acidosis, or admission to the neonatal unit (Baschat, 2014; Clayton et al., 2007; National Guideline Alliance, 2017; Stewart et al., 2019), these neonates are discharged with no established follow-up protocol, so that neurodevelopmental alterations are typically spotted too late, at early childhood (Levine et al., 2015) and even at school age (Chen et al., 2016). One major problem is that the pathophysiological mechanisms underpinning the heterogeneous expressions of growth restriction remain unknown, so that candidate biomarkers to identify cases at the highest risk still pose some concerns (Sanz-Cortes, et al., 2014). Suboptimal outcomes are not exclusive to preterm FGR, since neuroradiological studies conducted with FGR fetuses born at term have shown hemodynamic (Zhu et al., 2016), metabolic (Sanz-Cortés et al., 2010, 2015; Simões et al., 2015), microstructural (Sanz-Cortés, Figueras et al., 2013; Sanz-Cortes et al., 2014; Sanz-Cortes, Ratta et al., 2013), macroanatomic (Egaña-Ugrinovic et al., 2013, Egaña-Ugrinovic, Sanz-Cortes, Figueras et al., 2014) and connectivity (Batalle et al., 2012, 2013, 2016) alterations, with the corpus callosum (CC) measured with fetal MRI (Egaña-Ugrinovic, Sanz-Cortés, Couve-Pérez et al., 2014) or fetal neurosonography (NSG) (Eganã-Ugrinovic et al., 2015) as a prominent hallmark.

One of the most neurodevelopmental areas affected in FGR is language, displaying disruptions in up to 30% of the FGR population (Low, 1994). Altered literacy skills such as verbal comprehension and expressive language in FGR children aged between 2 and 5 years have been disclosed (Gutbrod et al., 2000; Low et al., 1982; Vohr et al., 1988), and speech and language clarity and richness affections remained at 10 years of age (Leitner et al., 2007). Since a deficient language development might have far reaching consequences on other areas of early childhood development, monitoring language skills during the first years of life is needed. Yet, no studies to date have identified any specific language disabilities in FGR population already present at birth, which could condition future language development. In the present study, we disclose for the first time an alteration in the neural encoding of speech sounds of FGR neonates born at term. This alteration was revealed with a variant of the auditory brainstem response (ABR) used in universal newborn hearing screening, the so-called *frequency-following response* (FFR).

While classical click-elicited ABR informs about the integrity of neural transmission through the auditory nerve up to the inferior colliculus, the FFR mimics with striking similarity the temporal and spectral features of the eliciting complex auditory stimulus, allowing to examine the accuracy of fine-grained speech-sound encoding along the entire auditory system (Coffey et al., 2019; Gorina-Careta et al., 2021). Abnormal FFRs have been consistently observed in children with disorders characterized by impaired communication, such as dyslexia, specific language impairment and autism (Banai et al., 2005, 2009; Basu et al., 2010; Cunningham et al., 2001; Font-Alaminos et al., 2020; Hornickel & Kraus, 2013; Otto-Meyer et al., 2018; Russo et al., 2008). Moreover, the FFR has been shown to predict literacy test scores obtained one year after being recorded in children aged 3-4 years (White-Schwoch, Woodruff Carr, et al., 2015). In neonates, the feasibility to record the FFR has been established (Arenillas-Alcón et al., 2021; Gardi et al., 1979; Jeng et al., 2011, 2016; Ribas-Prats et al., 2019), and a recent study showed its clinical potential to monitor the neurophysiological status of neonates with progressive moderate hyperbilirubinemia in the maternity unit (Musacchia et al., 2020). While the ABR was insensitive to transcutaneous bilirubin levels, this study revealed that the FFR paralleled bilirubin variation, and allowed tracking the reduction in neurotoxicity after phototherapy (Musacchia et al., 2020).

Taken together, these findings suggest that the FFR may provide an insight into the functional brain alterations of neonates born at term with FGR. In the present study we obtained the FFR elicited to a standardized speech token –the syllable /da/ (Krizman & Kraus, 2019; Ribas-Prats et al., 2019)— in a sample of 101 neonates split in two groups (adequate-for-gestational age –AGA, and FGR). Given the diffuse central nervous system alterations observed in FGR affecting mainly white matter connectivity (Batalle et al., 2012, 2013, 2016; Eganã-Ugrinovic et al., 2015; Egaña-Ugrinovic, Sanz-Cortés, Couve-Pérez et al., 2014; Sanz-Cortés, Figueras et al., 2013; Sanz-Cortes et al., 2014; Sanz-Cortes, Ratta et al., 2013), and the sensitivity of the FFR to the rapid spectro-temporal fluctuations of speech sounds, requiring a precise functional neuronal architecture (Kraus & White-Schwoch, 2015; Tzounopoulos & Kraus, 2009), we hypothesized impaired neural encoding of complex sounds in FGR neonates born at term without any major adverse perinatal outcome.

METHODS

Sample size

Sample size was calculated based on the signal-to-noise ratio (SNR) values of the FFR from a previous study (Ribas-Prats et al., 2019). In that study, a normative dataset of different parameters retrieved from the FFR recorded in 46 healthy neonates was reported. Assuming a standard deviation of .93 units, a total sample size of 100 is required, 50 in each group, for detecting a true difference in means between the test and the reference group of .526 units, with a power of 80% and a level of significance of 5% (two sided).

Participants

A sample of 101 mother-neonate pairs were recruited from the SJD Barcelona Children's Hospital (Catalonia, Spain) between April 2019 and January 2020, with 48 of the fetuses born adequate-for-gestational age (AGA) and 53 born with fetal growth restriction (FGR). Fetuses with AGA growth or FGR were defined as those with an estimated and postnatally confirmed fetal weight >10th and <10th centile, respectively (Figueras & Gratacós, 2014). Biparietal diameter, head and abdominal circumferences, and femur length using the Hadlock formula (Hadlock et al., 1985), were used to obtain the estimated fetal weight (EFW). Following the delivery, all of them at term, birth weights were recalculated in centiles to ascertain the cases. EFW and birth weight centiles were calculated using local reference curves, adjusted for the gestational age and neonatal sex (Figueras et al., 2008). AGA neonates were selected among low-risk pregnancies delivered at term with a normal birth weight (between 10^{th} and 91^{th} centile). Thirty-two of the 53 neonates were diagnosed as FGR during pregnancy and confirmed at birth. However, the remaining 21 (39.6%) received the FGR diagnosis at birth, as they were not identified as such during pregnancy. Exclusion criteria were multiple gestations, preterm delivery, chromosomal or major structural abnormalities or risk factors associated with hearing impairment (American Academy of Pediatrics, Joint Committee on Infant Hearing, 2019). From the initial 101 recorded neonates, five were excluded (three AGA, two FGR) because the FFR signal could not be detected (i.e., SNR computed in the consonant transition and/or vowel regions < 0; see below). Thus, a final sample of 96 neonates, 45 AGA (21 females, 0.5-3.3 days old) and 51 FGR (27 females, 0.7-67.4 days old), was analyzed. All parents filled in a sociodemographic questionnaire and signed the informed consent in accordance with the Declaration of Helsinki after the study protocol had been approved by the Ethical Committee of Clinical Research (CEIC) of the Sant Joan de Déu Foundation (Approval ID: PIC-53-17).

Stimuli

In this study two different stimuli were used: a click stimulus to elicit the ABR and the consonant-vowel /da/ to elicit the FFR. Both stimuli, click and /da/, were delivered in alternating polarities to the right ear at 60 dB SPL though ER3C shielded earphones of 300 Ω (Etymotic Research Inc., Elk Grove Village, IL, USA) connected to Flexicoupler® (Natus Medical Incorporated, San Carlos, CA) adaptor.

Click stimulus

The ABR was elicited to a square wave click stimulus with a duration of 100 μs presented at a rate of 19.30 Hz (silent inter-stimulus interval of 51.71 ms), following the procedure of a previous newborn FFR study (Arenillas-Alcón et al., 2021).

/da/ stimulus

As for the speech stimulus for eliciting the FFR, we opted for the consonant-vowel /da/ as it is the most common used in FFR newborn research (Lemos et al., 2021; Richard et al., 2020). This complex stimulus was created by Klatt-based synthesizer (Klatt, 1980) and modified by Praat (Boersma & Weenink, 2019). The stimulus duration was 170 ms (10 ms onset period, 47 ms for the consonant transition and 113 ms for the vowel region) and the presentation rate 3.7 Hz (silent inter-stimulus interval of 100.27 ms). The fundamental frequency (F_0) was 113 Hz along the stimulus duration. During the consonant transition, the first and second formants (F_1, F_2) varied from 553 to 688 Hz and 1438 to 1214 Hz, respectively, remaining constant in the vowel region.

Recording procedure

Once the universal hearing screening was passed as part of the hospital's routine (ALGO 3i, Natus Medical Incorporated, San Carlos, CA), each neonate was recorded in its cradle during natural sleep from an active electrode placed at Fpz location of the International 10-20 EEG system (Klem et al., 1999), with a ground electrode at the forehead and reference electrodes at the mastoids. In the present analysis, only the ipsilateral reference to stimulus presentation (i.e., the right mastoid electrode) was used (Figure 1A). Owing to the impossibility to conduct the recording during the time of hospitalization, eight FGR neonates were recorded during the first two months of age. Stimulus generation, recording and data storage were carried out by the portable SmartEP equipment, incorporating the *cABR* and *Advanced Hearing Research* modules (Intelligent Hearing Systems, Miami, Fl, USA). For the experiment, a total of six blocks were collected: two blocks of 2000 artifact-free ABRs to a click stimulus (100 μs square; 60 dB SPL), and four blocks of 1000 artifact-free responses to the consonant-vowel /da/, according to a previous study (Ribas-Prats et al., 2019). The blocks were always presented in the same order. It has to be mentioned that a block was completed when the total number of required responses (2000 for clicks; 1000

for the /da/ stimulus) free of activity exceeding ±30 μV was acquired. Less than 6% of sweeps were rejected in click or /da/ stimulus blocks. The total recording duration was on average 33.2 ±6.87 SD min (two click blocks of 2000 sweeps and 51.81 ms of stimulus-onset asynchrony (SOA), plus four /da/ stimulus blocks of 1000 sweeps and 270.27 ms SOA, plus the duration of rejected sweeps and the short breaks between blocks to handle system pipelines). The continuous EEG was sampled at 13333 Hz, online bandpass filtered from 30 to 1500 Hz and epoched in sweeps of 51.81 ms (10.93 ms for the baseline and 40.88 for post-stimulus recording period) for the click stimulus, and of 270.27 ms (40.95 ms for the baseline and 229.32 ms for post-stimulus recording period) for the /da/ stimulus. Data epoching, rejection and averaging were performed online. Impedances were kept < 8 kΩ throughout the entire recording, and responses were averaged separately per each stimulus and neonate (Aiken & Picton, 189 2008).

Data analyses

ABR

To assess neural transmission time from the reception of the stimulus at the cochlea up to the inferior colliculus in the auditory midbrain, the latency of wave V elicited to the click ABR was computed. Quantification of wave V in the ABR provides the most reliable objective diagnostic tool of hearing loss in infants and children (Rushaidin et al., 2009). Wave V was identified automatically as the major positive peak between 8 to 9.90 ms (Stuart & Yang, 1994), and reviewed by visual inspection to detect peaks outside this range, and its peak amplitude and latency measured.

FFR

Neural responses to /da/ were filtered off-line with a spectral bandpass filter with infinite slope from 80 to 1500 Hz, as implemented in the IHS equipment. Analysis of the FFR was based on recent recommendations (Krizman & Kraus, 2019) and our experience with the neonate FFR (Ribas-Prats et al., 2019). First, to ensure that any potential group differences in the FFR were not caused by any spontaneous EEG difference (White-Schwoch, Davies, et al., 2015), the pre-stimulus root mean square (RMS) amplitude was calculated. Pre-stimulus RMS provides an estimate of the overall neural fluctuations through the pre-stimulus period. To calculate it, we first averaged the squared data points from -40 ms to stimulus presentation at 0 ms and we computed the square root of the average. In the second place, to account for the neural transmission delay, or neural lag, we estimated the time elapsed since stimulus reception at the cochlea until neural phase locking onset. For computing such neural lag, we cross-correlated the stimulus and response waveforms using a recursive sliding procedure and obtained a correlation value at each lag. The time lag in which the correlation value was maximum within a time window between 3 and 10 ms (Jeng et al., 2010; Liu et al., 2015; Ribas-Prats et al., 2019) was defined as neural transmission

delay (i.e., neural lag). Notice that previous to the cross-correlation computation, the /da/ stimulus was resampled and bandpass filtered according to the signal parameters (i.e., 13333 Hz and 80 – 1500 Hz, respectively).

The encoding of stimulus frequency structure was investigated by means of the fast Fourier transform (FFT; hanning windowed) (Cooley & Tukey, 1965). The analysis was centered on the stimulus F_0 because pitch -as a perceptual correlate of the F_0 (Oxenham, 2012)- is essential for language acquisition in infancy (He et al., 2007). Pitch is an acoustic cue that contains emotional information and facilitates speaker recognition, promoting in turn the first social interactions (Benavides-Varela et al., 2012) and, with them, normal language development (Benavides-Varela et al., 2012; Háden et al., 2009). The spectral amplitude and its normalized transformation at the stimulus F_0 (i.e., its SNR) were retrieved as measures of response strength for the consonant transition and for the vowel regions separately, as these speech categories are accessed at different timepoints in development (Benavides-Varela et al., 2012; Kuhl, 2004; Kuhl et al., 2008). The spectral amplitude at the stimulus F_0 indicates the magnitude of neural phase-locking at that specific frequency range (White-Schwoch, Davies, et al., 2015), and the SNR at F_0 peak estimates the relative spectral magnitude of the response, taking into account not only the amplitude value of the signal at the frequency peak of interest (i.e., 113 Hz) but also the noise level around the peak (Arenillas-Alcón et al., 2021). To carry out the computations, the spectral amplitude was calculated as the mean over a ±5Hz frequency window centered at 113 Hz (i.e., stimulus F_0) following the standards established in previous studies (Ribas-Prats et al., 2019; Arenillas-Alcón, 2021). Its normalization was calculated according to the formula (see Arenillas-Alcón, 2021):

$$SNR = 10*\log10(\text{Signal spectral power}/\text{Noise spectral power})$$

The signal was defined as the frequency window used to calculate the spectral amplitude, and the noise as the mean over two 28 Hz frequency windows located at each side of the signal window (see Figure 2C). The frequency range of the noise was defined from the lower filter limit (i.e., 80 Hz) up to the lower edge of the signal's window (i.e., 108 Hz); for symmetry, the upper band window had also 28 Hz, ranging from 118 to 146 Hz. All signal analyses were performed under Matlab R2019b (Mathworks) using scripts developed in our laboratory and the functions provided by Intelligent Hearing Systems (Miami, FI, EEUU) to access the stimuli and the signal files.

Statistical Analyses

Statistical analyses were conducted by IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY). To assess group differences in demographic data, click ABR and FFR, chi-square test (Cramer's V for effect size) was performed for categorical variables and *t* test (Cohen's d for effect size) or Mann-Whitney *U* tests (using the formula $r = z/\sqrt{N}$, where N = number of cases, for effect size) for continuous variables after assessing normality distribution by Kolmogorov-

Smirnov Statistic with Lilliefors' Significance. To explore if sociodemographic variables could explain the electrophysiological results found, a multiple regression analysis with the stepwise regression algorithm was used. Two-tailed Pearson's or Spearman's correlations (attending to normality distribution criteria) between wave V latency and the FFR parameters were also computed. A p-value <.05 was considered statistically significant. Correction for multiple comparisons using the Bonferroni methods was applied where appropriate.

RESULTS

Maternal and neonatal clinical characteristics

Maternal and neonatal clinical data were obtained from the sociodemographic questionnaire filled in by the parents (Table 1). From the initial 101 neonates recorded, a final sample of 96 neonates, 45 AGA and 51 FGR, was included in the analyses leaving out those cases with an unreliable FFR because their FFR SNR was < 0. Significant differences were found in mother's age, being AGA mothers older than FGR mothers ($t_{(91)} = 2.17$, $P = .03$, $d = 0.45$). A significantly higher rate of smokers during pregnancy and/or during the month before being pregnant in the FGR group was detected ($X^2_{(1)} = 5.16$, $P = .02$, $V = 0.23$). No significant differences were found in body mass index, primiparity and white ethnicity.

Table 1. Maternal characteristics

Measures	AGA (n = 45)	FGR (n = 51)	*t* test	*df*	*P* value	Cohen *d*
Age, y	34.79 (4.51)	32.42 (6.17)	2.17	91	.03*	0.45
Smoker, %	6.7	23.5	5.16†	1	.02*	0.23‡
Body mass index (BMI), kg/m^2	22.97 (3.86)	23.42 (4.43)	-0.53	94	.60	-0.11
Primiparity, %	42.2	56.9	2.05†	1	.15	0.15‡
White ethnicity, %	77.8	78.4	0.01†	1	.94	0.01‡

Results are expressed as mean (SD) or percentage as appropriate. †Pearson's X^2. ‡Cramer's V. *P value < .05. y, years; BMI, Body mass index; kg, kilograms; m^2, square meter.

Regarding the neonatal clinical characteristics (Table 2), significant differences were found in gestational age at birth. FGR neonates were delivered earlier ($U = 860.50$, $P = .04$, $r = -0.22$), with no differences in gestational age at recording time, as determined as the gestational age plus the chronological age at which the recording took place. As expected, FGR neonates presented a significant lower birth weight ($t_{(94)} = 10.52$, $P = <.001$, $d = 2.17$) and birth centile ($t_{(45.06)} = 11.24$, $P = <.001$, $d = 3.35$). Also, a significantly higher rate of labor induction was found in FGR than

in AGA ($X^2_{(1)}$ = 7.07, P = .008, V = 0.27). No differences were observed in gender, emergency cesarean section, neonatal acidosis and Apgar score lower than 7 assessed at 5 minutes of life.

Table 2. Neonatal clinical characteristics

Measures	AGA (n = 45)	FGR (n = 51)	*t* test	*df*	*P* value	Cohen *d*
GA at birth, w	39.57 (2.07)†	38.57 (3.29)†	860.50‡	-	.04*	-0.22§
GA at recording, w	39.88 (2.08)†	39.80 (3.52)†	1123.00‡	-	.86	-0.02§
Birth weight, g	3264.22 (344.89)	2532.35 (336.04)	10.52	94	<.001***	2.17
Birth centile	45.40 (24.59)	3.94 (2.87)	11.24	45.06	<.001***	3.35
Male gender, %	53.3	47.1	0.38¶	1	.54	0.06††
Labor induction, %	35.6	62.7	7.07¶	1	.008**	0.27††
Emergency cesarean section, %	13.3	11.8	0.05¶	1	.82	0.02††
Neonatal acidosis, %‡‡,§§	7.5	12.8	0.61¶	1	.43	0.08††
Apgar score <7 at 5 min, %	0	2	0.89¶	1	.35	0.10††

Results are expressed as mean (SD) or percentage as appropriate. †Median (IQR, interquartile range). ‡Mann-Whitney U test. §Effect size calculated by $r = z/\sqrt{N}$. ¶Pearson's X^2. ††Cramer's V. ‡‡Neonatal acidosis: umbilical artery pH<7.15. §§40 AGA versus 39 FGR. *P value < .05. **P value < .01. ***P value < .001. GA; gestational age; w, weeks; g, grams; min, minutes.

Neurophysiology

ABR. Wave V peak was detected in all participants recruited (i.e., 101 neonates). Grand-average waveforms (Figure 1B) and the distributions of wave V amplitude (Figure 1C) and latency (Figure 1D) values are reported for the final sample included in the FFR analysis (i.e., 96 neonates). Wave V parameters (Table 2) were comparable to the reference values published by Stuart et al. (1994) (i.e., their 8.01 - 9.90 for wave V latency and 0.13 - 0.47 for wave V amplitude). Wave V amplitudes were similar across groups (U = 1136.00, P = .93, r = -0.01), but its peak latency was slightly delayed in FGR compared to AGA ($t_{(94)}$ = -2.12, P = .04, d = -0.44).

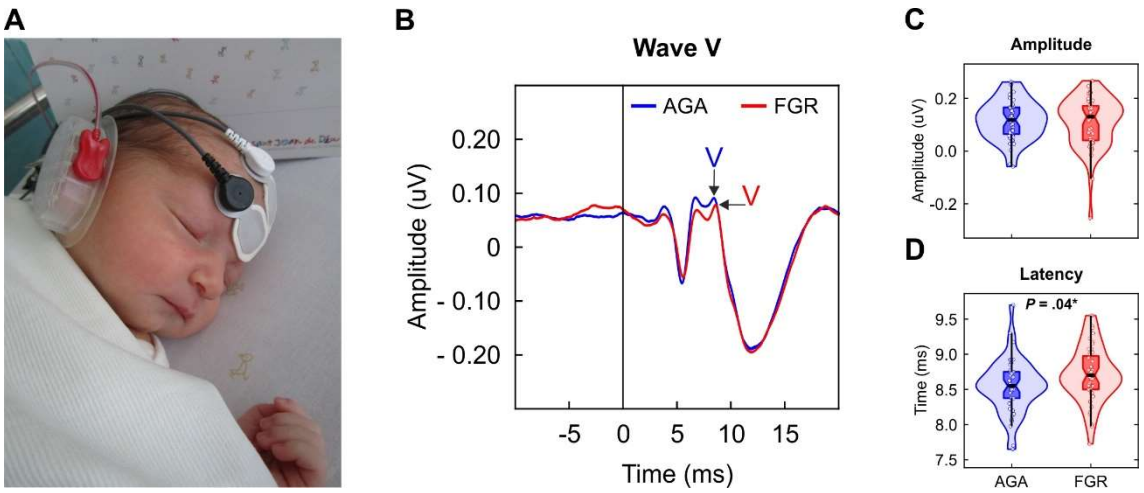

Figure 1 (**A**) Recording setup. Four disposable snap Ag/AgCl electrodes were placed in a vertical montage: the active electrode was located at Fpz (white electrode), references at each ear (red and blue, right and left respectively), and ground electrode at the forehead (black electrode). Only the ipsilateral reference (right electrode) was used in the analysis. The reproduction of the participant's picture is with the written consent of her mother. (**B**) Grand-averaged click ABRs for AGA (blue) and FGR (red) groups, with Wave V peak pointed out. Data distribution (violin plots) for (**C**) wave V amplitude, and (**D**) its latency. The black horizontal line indicates the median, the dark colored box (blue and red for the AGA and the LGA group, respectively) shows the interquartile range (IQR) and the black vertical lines stretched from the box illustrate 1.5 times the IQR. White filled circles indicate data corresponding to the individual neonates and the violin plot outlines illustrate kernel probability density, i.e., the proportion of the data located there. Panel A is reproduced with permission from Ribas-Prats and colleagues (2019; their figure 2).

To explore if sociodemographic factors could explain wave V latency results, we conducted a multiple regression analysis. Seven sociodemographic factors (maternal age, smoker, primiparity, GA at birth, GA at recording time, birth weight, labor induction) met the assumptions required to carry out the multiple regression analysis (e.g., linearity). Once the assumptions were confirmed, the stepwise regression algorithm was used to select the appropriate subset of explanatory variables. One such models identified GA at birth and maternal age, while the other identified GA at birth only, as the factors modulating wave V latency. According to the Akaike information criterion (AIC, Akaike, 1973) and the predictive power for the wave V latency variable, we selected the first model. The resulting regression model, including group, GA at birth and maternal age, accounted for 18.0% of wave V latency variance ($F_{(3, 92)} = 6.71$, $P < .001$, $R^2 = .18$). In the present model, group variable did not reach a significant partial effect ($t = 1.07$, $P = .29$).

Table 3. Descriptive statistics and comparisons between AGA and FGR groups for each wave V and FFR parameter assessed

Measures	AGA (n = 45)			FGR (n = 51)	*t* test	*df*	*P* value	Cohen *d*	Adjusted *P* value
Wave V									
Baseline amplitude, µV	0.06 (0.04)			0.06 (0.04)	-0.48	94	.63	-0.10	-
Amplitude, µV			0.12 (0.11)†	0.13 (0.13)†	1136.00‡	-	.93	-0.01§	-
Latency, ms			8.55 (0.38)	8.71 (0.39)	-2.12	94	.04*	-0.44	.14¶
FFR									
Pre-stimulus RMS, µV			0.02 (0.01)†	0.03 (0.02)†	974.00‡	-	.20	-0.13§	-
Neural lag, ms			5.55 (1.43)†	5.78 (1.28)†	1051.50‡	-	.48	-0.07§	-
Spectral amplitude, nV									
Consonant transition (10 to 57 ms)			32.97 (11.26)	30.94 (10.41)	0.92	94	.36	0.19	.72††
Vowel (57 to 170 ms)	23.60 (12.44)†	21.74 (8.82)†	1043.00‡	-	.44		-0.08§		.89††
SNR, dB									
Consonant transition (10 to 57 ms)	3.34 (0.90)†	3.32 (0.96)†	1053.00‡	-	.49		-0.07§		.98††
Vowel (57 to 170 ms)	8.71 (1.81)†	8.02 (3.08)†	789.00‡	-	.008**		-0.27§		.02††*

Results are expressed as mean (SD). †Median (IQR, interquartile range). ‡Mann-Whitney U test. §Effect size calculated by $r = z/\sqrt{N}$. ¶Multiple regression adjusted for GA at birth. ††Adjusted *P* value after correcting for the number of comparisons conducted within the same parameter. **P* value < .05. ***P* value < .01. ****P* value < .001. µV, microvolts; ms, milliseconds; nV; nanovolts; dB, decibels.

FFR. As it can be seen in Figure 2, the FFR is a neurophysiological signature that reproduces the eliciting stimulus with great fidelity, thus providing a snapshot into the accuracy of neural pitch tracking. Clear FFR waveforms were obtained in the two groups, yet with a visually apparent smaller amplitude through its entire duration in the FGR group compared to AGA (Figure 2B). Notice, however, that the background EEG was nearly identical in the two groups (no group differences in pre-stimulus RMS: $U = 974.00$, $P = .20$, $r = -0.13$; Figure 3A; Table 3). Neural lag was also similar across groups ($U = 1051.50$, $P = .48$, $r = -0.07$; Figure 3B; Table 3).

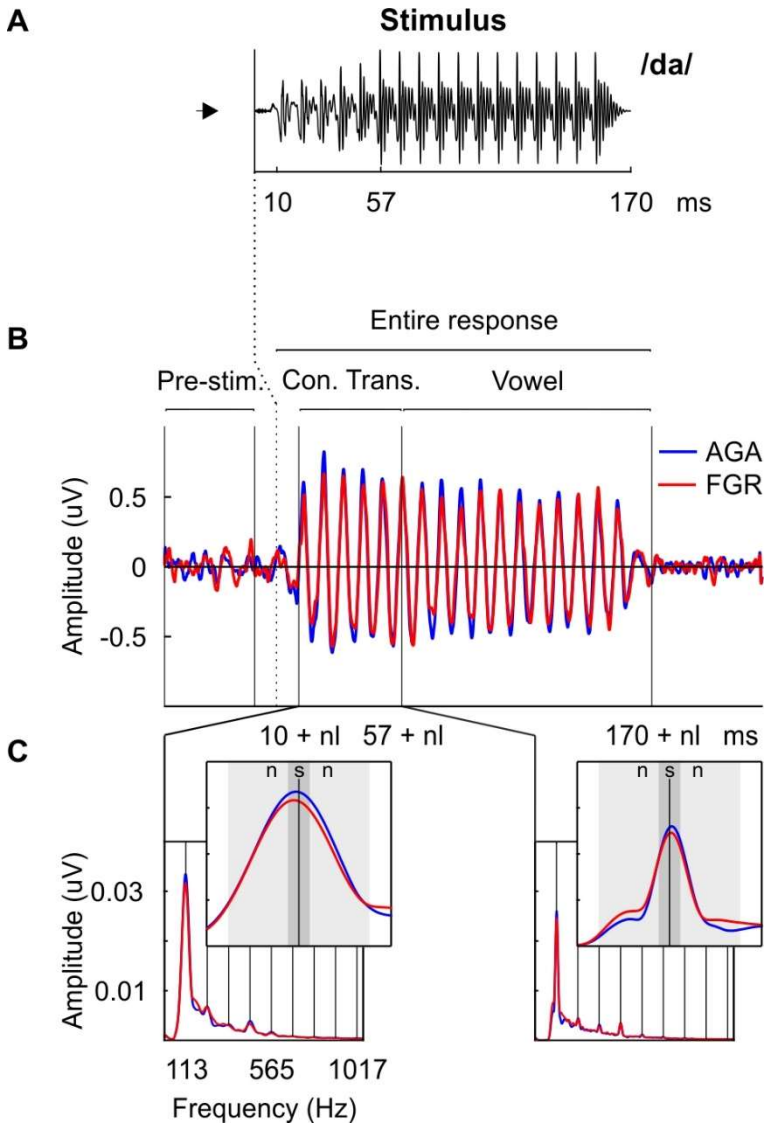

Figure 2 Temporal and spectral neural representation of the consonant-vowel /da/ in the neonate's auditory brain. (**A**) Stimulus waveform (/da/), (**B**) grand-averaged FFR waveform and (**C**) amplitude FFR spectra extracted from the consonant transition and from the vowel sections for AGA (blue) and FGR (red) groups. The signal (s) and noise (n) spectral windows used for quantification of the FFR are marked with dark and light gray rectangles, respectively.

To quantify the FFR, the spectral amplitude at the stimulus' F_0, as well as its SNR, were retrieved by means of an FFT both for the responses to the stimulus consonant transition and vowel regions in each group (Figure 2C; Figure 3C to F). Normalized spectral amplitudes (SNR measures) were strongly attenuated in the FGR group compared to the AGA group for the vowel region (U = 789.00, P = .008, r = -0.27; adjusted P for multiple comparisons = .02). For the consonant transition, no significant differences were found in the normalized spectral amplitudes (SNR measures) (U = 1053.00, P = .49, r = -0.07). On the non-normalized data (i.e., spectral amplitudes), no differences were found either for the consonant transition ($t_{(94)}$ = 0.92, P = .36, d = 0.19) or the vowel region (U = 1043.00, P = .44, r = -0.08). Since eight FGR neonates were

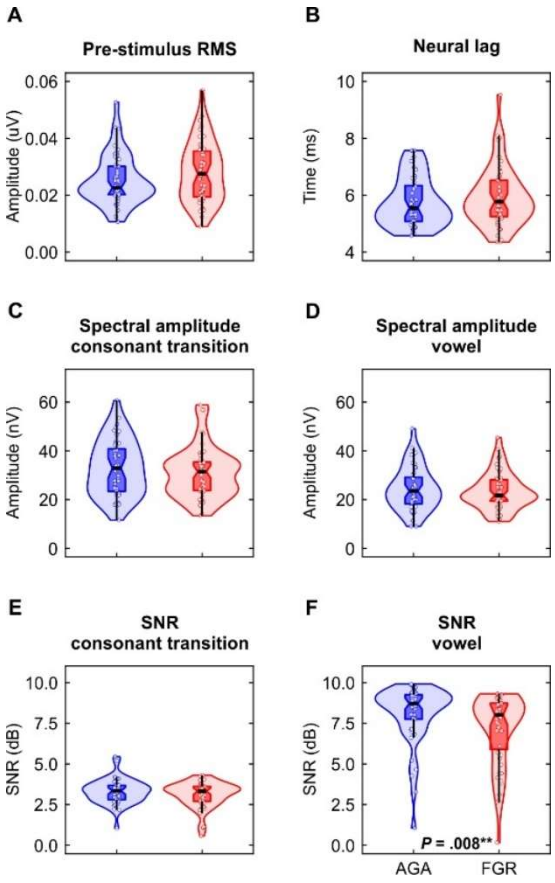

Figure 3 Data distribution (violin plots) of the (**A**) Pre-stimulus RMS, (**B**) Neural lag, (**C, D**) Spectral amplitude and (**E, F**) its normalization (SNR) extracted from the consonant transition and from the vowel. The layout is the same to that used in **Fig. 1** (**C**) and (**D**).

recorded after discharge at a gestational recording age between 2.5 and 9.6 weeks, we repeated the statistical analyses after excluding them from the sample. This approach yielded the same pattern of results, with the SNR of FFR at the vowel region remaining statistically different between groups (U = 645.00, P = .007, r = -0.29; adjusted P for multiple comparisons = .014). We also conducted the SNR vowel analysis leaving out those cases who were outliers according to the definition of any observations that was higher than 1.5 IQR below Q1 or higher than 1.5 IQR above Q3. As a result, five AGA and one FGR individuals were removed, so that 40 AGA neonates and 50 FGR neonates (median (IQR): 8.79 (1.38), 8.05 (2.81)) were included in this additional analysis. As a result, strong significant differences were also found between groups for the SNR of the F_0 of the vowel region (U = 565.00, P = <.001, r = -0.37; adjusted P for multiple comparisons <.001).

We also explored if sociodemographic factors could interfere in the SNR results found in the vowel region. In contrast of wave V latency, only the group factor strongly correlated with the SNR of the FFR. Consequently, no multiple regression models including sociodemographic factors as independent variables were calculated.

ABR-FFR relationships. To explore whether the FFR differences obtained between groups could be attributed to the delayed neural transmission timing observed in FGR, a matrix of correlations between wave V latency and all FFR parameters was computed across the entire final sample (N = 96, see Figure 4). A strong significant correlation between wave V latency and neural lag was found (ρ = 0.36, P <.001), yet all other FFR parameters were unrelated to wave V latency (Figure 4).

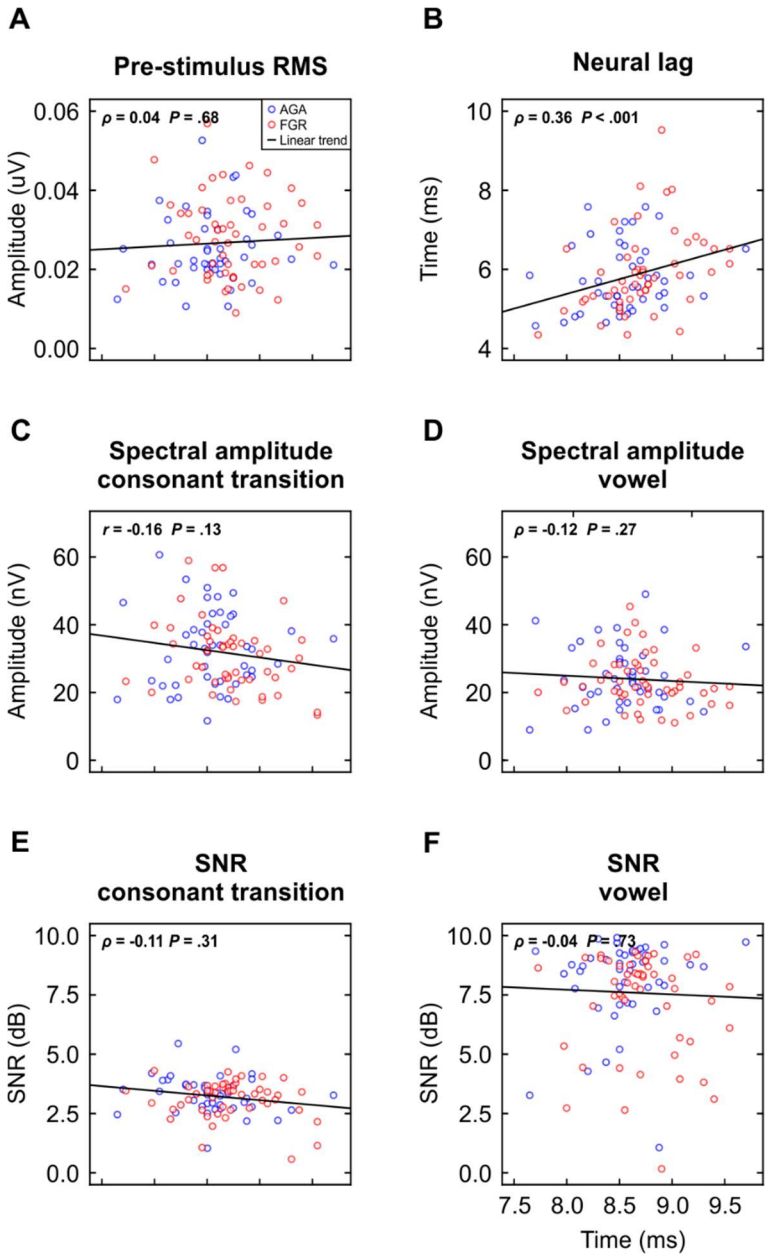

Figure 4 Correlation between the ABR wave V peak latency and each of the FFR parameters assessed. Blue and red dots illustrate individual neonates from the AGA and FGR groups, respectively. Black lines show the linear trend between the ABR wave V peak latency and each of the FFR parameters. In the upper left corner of each plot, the Person's or Spearman's correlation values are reported together with the corresponding p-value, depending on the normality distribution criteria.

DISCUSSION

This study provides the first documented evidence of functional deficits in the encoding of complex sound features in FGR neonates born at term. Through recordings of the FFR elicited to a complex auditory stimulus, the syllable /da/, we disclose here that being born at term with FGR is associated with impaired neural encoding of the relative magnitude of F_0 energy, as quantified through the SNR estimate. Previous studies on the neural consequences of FGR at birth have

described only hemodynamic, metabolic, microstructural, microanatomic and connectivity abnormalities (Batalle et al., 2012, 2013, 2016; Egaña-Ugrinovic et al., 2013; Egaña-Ugrinovic, Sanz-Cortes, Figueras et al., 2014; Sanz-Cortés, Figueras et al., 2013; Sanz-Cortés et al., 2010, 2014; Sanz-Cortes, Ratta et al., 2013; Simões et al., 2015; Zhu et al., 2016).

From a neurophysiological perspective, the effects of FGR on click-evoked ABRs at birth had been explored, yielding controversial results (Jiang et al., 1991; Mahajan et al., 2003; Saintonge et al., 1986; Sarda et al., 1992; Todorovich et al., 1987). Our findings align with those reporting wave V peak latency delays in FGR neonates compared to their healthy pairs (Jiang et al., 1991; Mahajan et al., 2003; Saintonge et al., 1986). However, no previous study has investigated the potential consequences of FGR on the auditory processing of more complex stimuli at birth. While click ABRs index neural transmission time, a functional property relying on cochlear nerve and brainstem pathway myelination, the FFR provides a neurophysiological window into more sophisticated processing of complex sounds in the auditory neuroaxis (Johnson et al., 2008; Knebel et al., 2018; Skoe & Kraus, 2010; Song et al., 2006): how their periodic fluctuations are tracked by neural assemblies in the auditory hierarchy (Kraus et al., 2017), thus providing a non-invasive tool to investigate neural tracking of relevant speech acoustic cues, such as pitch. Pitch tracking is crucial to allow speaker identification, and to follow continuous speech and its segmentation into word-form units, as a prerequisite for normal speech development (François et al., 2017).

Our results in the AGA group confirm that the encoding of the F_0 of speech, at least for the 100 Hz range tested here, appears to be functional at birth, in line with previous studies (Arenillas-Alcón, 2021; Gardi et al., 1979; Jeng et al., 2011, 2016; Ribas-Prats et al., 2019). Yet, the novelty of the present study relays in the possibility to use the FFR to detect impaired encoding of F_0 at birth in specific clinical groups with a higher risk of language and eventually reading impairments than normal population, such as neonates affected by FGR as observed here. The FFR was quantified through the SNR of its F_0 retrieved by means of spectral analysis (FFT), and the SNR was attenuated in the FGR group, thus indicating that FGR neonates present a less robust pitch encoding than their AGA counterparts. It is important to note that these differences were obtained for similar pre-stimulus RMS in the two groups precluding that differences in phase locking could result from fluctuations in the spontaneous background EEG. Furthermore, the group differences in the neural encoding of the relative magnitude of F_0 as indicated by its SNR were observed for similar wave V amplitudes, neural lag and FFR spectral amplitude at its F_0. This pattern of results highlights the specificity on the neural deficit encountered by FGR neonates to extract the informational contents of the complex sound (its F_0) from the competing auditory background.

Although the different region length (47 ms for the consonant transition and 113 ms for the vowel) did not allow us to conduct a region comparison of the FFT output (i.e., spectral amplitude and SNR values), it is interesting to note that the group differences in phase locking to the F_0 were observed for the vowel region only, whereas they did not emerge for the consonant-transition region of the stimulus. One possible explanation for this dissociation could be that the longer duration and the frequency content stability of the vowel region may have facilitated its processing in the newborns (Benavides-Varela et al., 2012; Kuhl, 2004; Kuhl et al., 2008). Indeed, the lack of effects on the consonant transition suggest that the rapid frequency-fluctuations occurring during the consonant transition section (i.e., its first and second formants) may interfere with phase-locking of the F_0 in the neonates' auditory system, which still is too far from full anatomical and functional maturation (Moore and Guan, 2001; Moore and Linthicum, 2007). Our results are in line with previous studies in which an immature encoding of high frequencies (i.e., formant structure) was observed in neonates compared to adults (Arenillas-Alcón et al., 2021), and with the more pronounced development of phase-locking capabilities from infancy to adulthood described for the consonant transition (Van Dyke et al., 2017), a region of the stimulus where the frequency contents of the formants rapidly change, compared to the vowel region.

On the other hand, the delayed wave V latency values observed in the FGR group compared to the AGA group, together with its significant correlation with the FFR's neural lag, indicates that the clinical group presents a neural transmission slowing. Furthermore, our multiple regression analysis revealed that gestational age at birth and maternal age had a significant partial effect on wave V latency. The resulting model from our regression analysis contrasts with previous literature in which wave V latency was clearly modulated by gestational age at birth but not for maternal age (Cox et al., 1981). This however may be explained by the fact that our model included all neonates, for which their mother differed significantly in age according to the grouping criteria (FGR versus AGA). Regarding the contribution of the gestational age at birth, it should be interpreted with caution, since FGR neonates had a lower GA at birth compared to the AGA group and it has been shown that wave V latency decreases with increasing GA at birth (Cox et al., 1981), we suggest that other factors such as white matter affections in FGR neonates as shown by radiological studies (Eganã-Ugrinovic et al., 2015; Egaña-Ugrinovic, Sanz-Cortés, Couve-Pérez et al., 2014), could have contributed to the neural transmission speed differences observed. This suggestion is in fact supported by animal models of FGR, which have disclosed white mater alterations, including retarded oligodendrocyte maturation (Tolcos et al., 2011), major rate of unmyelinated axons and thinner myelin sheath (Nitsos & Rees, 1990) and signs of inflammation (Olivier et al., 2007) in FGR pups.

One possible explanation for the attenuated FFR in the FGR group obtained in the present study is that the neural transmission affections observed in group could have compromise their phase-

locking capability. A disrupted conduction timing may impoverish the synchronization of the neural firing to the stimulus F_0 and increase the energetic content of its surrounding frequencies. This lower fine-grained codification could explain the results obtained in the SNR of the vowel region: a lower energetic content to the F_0 (i.e., 113 Hz) and a higher amplitude to the non-signal frequencies within the noise windows (i.e., 80-108 Hz and 118-146 Hz). In the case of the consonant-transition region, where rapid frequency fluctuations occur, it is suggested that the functional maturity limitations of the neonate auditory system discussed above (Moore and Guan, 2001; Moore and Linthicum, 2007), which have been shown to turn up into the inability at birth to encode for fine-grained spectral contents (Arenillas-Alcón et al., 2021; Van Dyke et al., 2017) could have masked the neural transmission affections detected in the FGR group at the vowel region. However, it should be bear in mind that the group differences observed in the vowel SNR but not in the consonant SNR were obtained for spectral amplitudes computed with different length of the temporal windows used to retrieve the spectrum. These different time windows influence the spectrum shape, particularly around the F0 as seen also for the stimulus (see Suppl. Fig. 1) and may affect specifically the magnitude of the noise calculation to compute the SNR. This limitation was however, imposed by the different duration of the consonant transition and vowel regions and affected the two groups seemingly.

Language deficits have been reported affecting up to 30% of the FGR population in follow-up studies (Low, 1994). At 2-5 years-of-age both verbal comprehension and expressive language are less advanced when term growth restricted are compared with appropriately grown infants (Gutbrod et al., 2000; Low et al., 1982; Vohr et al., 1988). At 10 years of age, FGR consequences remained visible in the quality and clarity of speech and language abilities, being speech therapy one of the most frequent interventions reported by their parents (Leitner et al., 2007). Strict monitoring is encouraged due to manifestations of early language disorders increasing the risk of poor academic achievement along childhood (Janus et al., 2019; Lewis et al., 2015; Watson et al., 2003; Young et al., 2002), as well as employment outcomes and mental health in the adulthood (Atkinson et al., 2015; Clegg et al., 2015; Law et al., 2009), all risks already associated with FGR (Strauss, 2000).

Previous work conducted in children with neurodevelopmental disorders characterized by impaired communication, such as dyslexia, specific language impairment and autism, revealed typical click-evoked ABR latencies but abnormal FFR to speech stimuli (Banai et al., 2005, 2009; Basu et al., 2010; Cunningham et al., 2001; Font-Alaminos et al., 2020; Hornickel & Kraus, 2013; Otto-Meyer et al., 2018; Russo et al., 2008; White-Schwoch, Woodruff Carr, et al., 2015), reinforcing the potential clinical role of the FFR in anticipating language deficits (Johnson et al., 2008; Knebel et al., 2018; Skoe & Kraus, 2010; Song et al., 2006). Although the possibility to record the FFR in newborns (Arenillas-Alcón et al., 2021; Gardi et al., 1979; Jeng et al., 2011,

2016; Ribas-Prats et al., 2019) and its use to monitor neurofunctional status (Musacchia et al., 2020) in hospital routines have been demonstrated, only few studies have explored clinical populations during the first days of life. The present study contributes to this emerging field of the research focusing on the FFR as a neurocognitive impairment screening tool.

From an otorhinolaryngological point of view, it should be noted that five of our neonates (three AGA, two FGR) did not show a reliable FFR despite they had normal click-evoked ABRs. However, the large number of rejected sweeps and/or the extended time needed to complete the recordings led us to suggest that other factors such as the presence of amniotic fluid in the ear canal (Haghshenas et al., 2014) and muscle artifact (Picton et al., 2005), despite remaining with eyes closed could have interfered. Further research with re-test assessments of the FFR should clarify this issue.

Up to date, FGR neonates with no adverse perinatal outcomes such as prematurity, are discharged with no specific follow-up care guideline, mainly due to the lack of consensus concerning FGR definition and diagnosis (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, 2019; McCowan et al., 2018), and the severity spectrum of their brain injury (Mandy, 2020). However, FGR has a strong impact on public health due to the elevated number of cases, and several international organizations such as the World Health Organization (WHO), promote the implementation of interventions and policies to reduce its incidence (World Health Organization, 2014) and to minimize its short- and long- term associated consequences. In order to extend the continuity of care to FGR cases at risk for neurodevelopmental impairment, a structured program starting with a developmental screening plan implemented as early as possible is needed. We suggest that the possibility to record the FFR during the first days of life in no more than thirty minutes may be part of this screening plan. This electrophysiological recording may allow the early identification of language impairment in neonates affected by FGR in the maternity unit, including those who were not detected as small fetuses before delivery (Bamfo & Odibo, 2011; Chauhan et al., 2014; Figueras et al., 2018; Jahn et al., 1998; Monier et al., 2015; Verlijsdonk et al., 2012). A disrupted FFR could offer clinicians valuable information to decide the derivation of these cases to appropriate experts who could optimize outcomes by individualized interventions. The neural plasticity of the subcortical auditory system during the first years of life (Tzounopoulos & Kraus, 2009), based on the evidenced impact of short- (Song et al., 2012) and long-term (Hornickel et al., 2012) training on speech sound encoding, underlines the importance of offering to FGR neonates strategies and communication training as early as possible. However, the similar group distribution of the FFR's SNR invite for subsequent studies and longitudinal assessments to confirm this potential predictive value of the FFR.

While the results of the present study are novel, there are several limitations that future research should attempt to overcome. First, although the /da/ stimulus is the most common token used in neonates (see Lemos et al., 2021; Richard et al., 2020), to better characterize the neural encoding of the envelope and the temporal fine structure and to reduce the limitations imposed by the immature high frequencies processing at birth, other auditory complex stimuli with better tailored features, such as first formants located at lower frequency ranges than in the consonant-vowel region of the typical /da/ are needed, for example as the proposed by Arenillas-Alcón and colleagues (2021). Regarding our sample size, even though it was comparable to that of previous studies carried out in the same clinical group (Egaña-Ugrinovic, Sanz-Cortes, Figueras et al., 2014; Sanz-Cortés, Figueras et al., 2013), larger cohorts are needed to clarify the neurophysiological alterations –as indexed by the FFR- of the different clinical expressions of FGR. Also, special attention should be put on those AGA cases with similar SNR values to those of FGR neonates. At this stage, neurodevelopment outcome measurements were not yet available, which prevents to explore the existence of the correlation between neurobehavioral examination and the FFR recorded during the first days of life. Previous electrophysiological studies have consistently shown that the FFR has the potential to predict literacy test scores one year later in children aged 3-4 years (White-Schwoch, Woodruff Carr, et al., 2015). It is reasonable to believe that when this assessment will be possible the predictive value of the FFR will be confirmed.

CONCLUSIONS

The present study has shown, using a non-invasive electrophysiological approach termed frequency-following response (FFR), that term neonates affected by FGR present at birth deficits in the encoding of the fundamental frequency of speech sounds. Our results disclosed specific effects in the vowel region only and are compatible with the myelination affections observed in FGR. The clinical potentiality of an FFR recording during the first days of life to detect specific speech encoding impairments at birth is highlighted. Yet, further studies need to be conducted to disclose whether the FFR could become the first step of a screening plan leading to an early intervention guideline in FGR.

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STUDY III:

Perinatal consequences of being born large-for-gestational age: speech-encoding deficits revealed with auditory brainstem responses

Perinatal consequences of being born large-for-gestational age: speech-encoding deficits revealed with auditory brainstem responses[3]

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

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ABSTRACT

Objective: To investigate neural consequences at birth of being born large-for-gestational-age (LGA) using an auditory brain potential termed frequency-following response (FFR).

Material & methods: 27 large-for-gestational-age (LGA) newborns were recruited from SJD Barcelona Children's Hospital. After quality inspection, two recordings were deleted. The remaining 25 LGA neonates were paired by age and sex with 25 born adequate-for-gestational age (AGA) selected from a previous cohort study. FFRs elicited to the /da/ syllable were recorded during sleeping after successful universal hearing screening. Neural encoding of the stimulus fundamental frequency was characterized through the FFR spectral amplitude and its normalization. Descriptive statistics were calculated for sociodemographic characteristics of the mothers and their neonates. Categorical demographic and electrophysiological variables were analyzed by Chi-square test and continuous variables with *t* test or Mann-Whitney *U* test. To explore whether electrophysiological differences related to maternal pre-gestational BMI, maternal gestational weight gain (GWG) and neonatal BMI, a matrix of Pearson's or Spearman's correlations (attending to normality distribution criteria), between each of these variables and the FFR parameters were calculated.

Results: FFR in LGA showed smaller spectral amplitudes (consonant transition: $p = .002$; vowel: $p = .008$) as well as smaller normalized spectral amplitudes (consonant transition: $p = .01$; vowel: $p = .005$) compared to the AGA group. Significant correlations were found between neonatal BMI and the FFR spectral amplitude (consonant transition: $r = -0.54$, $p < .001$; vowel: $r = -0.57$, $p < .001$) and its normalization (vowel region: $\rho = -0.42$, $p = .004$).

Conclusions: Using a novel electrophysiological method, specific deficits in the neural encoding of speech sounds were disclosed in LGA neonates. Based on the observed correlations between BMI and FFR parameters, we suggest that the higher adipose tissue observed in LGA group may impair, via proinflammatory products, the fine-grained central nervous system microstructure required for the neural encoding of speech.

Keywords

auditory brainstem response, auditory evoked potentials, BMI, EEG, FFR, macrosomia, neonatal adiposity, newborn.

Abbreviations

ABR auditory brainstem response

AGA adequate-for-gestational age

BMI body mass index

CNS central nervous system

EEG electroencephalogram

F_0 fundamental frequency

FFR frequency-following response

GA gestational age

LGA large-for-gestational-age

RMS root mean square

SNR signal-to-noise ratio

Key message

Specific central nervous system dysfunctionalities characterized by a deficit in the neural encoding of speech sounds, as revealed by frequency-following responses, were disclosed in large-for gestational-age neonates.

INTRODUCTION

Neonates born large-for-gestational-age (LGA, >90th percentile) are at increased risk of mortality, obesity, type 2 diabetes, cardiovascular diseases, and metabolic syndrome[1-5]. However, evidence regarding neurodevelopmental outcomes is limited and inconsistent. As worldwide obesity ratios are rising[6-11], obstetric research focusing on LGA is increasing. A non-linear association between birth weight and adverse outcomes has been reported[12-15], disclosing a reverse J-shaped/U relationship. Elevated birth weight was associated with impaired cognitive function[14,16,17], poor educational attainments[12,18,19], and with cerebral palsy[20], autism[21], attention difficulties[22], social disorder symptoms[23] and externalizing behaviors[15]. However, other studies found no association[24,25], yet opposite results were described[26,27], with better development and higher educational outcomes for LGA compared to adequate-for-gestational age (AGA).

The lack of consensus on terminology and criteria, with different cutoff values and the use of absolute birth weight or its normalization by gestational age (GA) hampers generalization. A further limitation is the lack of studies focused on infancy –a crucial period for neurodevelopment–. One approach, recently used to disclose functional central nervous system (CNS) dysfunctionalities at birth, is through recordings of the frequency-following response (FFR)[28], a variant of the auditory brainstem response (ABR) elicited to speech sounds.

FFRs provide a snapshot into the neurophysiological encoding of the periodic sound features across the auditory system[29-31]. FFR is disrupted in children affected by dyslexia, reading impairment and autism spectrum disorder (ASD)[32-36] and predicts literacy skills one year ahead[37,] supporting its sensitivity to neurodevelopmental outcomes. Recordings of the neonatal FFR have been successfully carried out in the general population[38-42] and under several pathological conditions such as hyperbilirubinemia[43] and fetal growth restriction[28]. Here we tested in a case-control sample of 50 neonates, whether being born LGA would lead to an altered neural encoding of speech sounds.

MATERIAL AND METHODS

Participants

A sample of 27 LGA mother-neonate pairs were recruited from the SJD Barcelona Children's Hospital (Catalonia, Spain) between April 2019 and January 2020. Two cases were excluded because the FFR signal could not be identified (i.e., the FFR's signal-to-noise ration computed in the consonant transition and/or vowel regions <0; see below). Thus, the final sample included 25 LGA neonates and 25 neonates born AGA, all paired by sex and GA at birth (Table 1). AGA neonates were drawn from a larger cohort assessed in a previous study[28]. In case that a LGA case

could be paired with more than one AGA neonate, the AGA pair was selected randomly using Matlab (R2019b, Mathworks) .

AGA and LGA neonates were defined as those with a birth weight between >10th and ≤90th percentiles and >90th percentile, respectively[44]. Exclusion criteria were multiple gestations, pre-gestational and gestational diabetes mellitus, preterm delivery, preeclampsia, chromosomal or major structural abnormalities or risk factors associated with hearing impairment[45]. To monitor and detect a possible late gestational diabetes debut, in addition to the O'Sullivan test and the subsequent oral glucose tolerance test (OGTT) implemented for positive O'Sullivan cases, a further OGTT was carried out in those pregnant women with a fetus diagnosed of LGA. This further OGTT was implemented after the LGA diagnosis following the hospital LGA care guide, resulting in a negative result in all our cases.

Recording procedure

Brainstem responses to a click stimulus and to the consonant-vowel /da/ were recorded while the neonates were naturally sleeping in their cradle. A vertical montage was used with the active electrode located above nasion at the 10% of the distance from nasion to inion (Fpz according to the International 10-20 EEG system)[46], the ground electrode between Fpz and nasion, and the reference electrodes placed at the mastoids. According to previous studies[28,38,40-42], only the right mastoid (ipsilateral reference) was used. Stimulus presentation, EEG recording and data repository were carried out by the portable SmartEP equipment, including the *cABR* and *Advanced Hearing Research* modules (Intelligent Hearing Systems, Miami, Fl, USA).

Firstly, to confirm auditory pathway integrity, two blocks of 2000 ABRs to a click stimulus (100 μs square; 60 dB SPL) were recorded. Then, four blocks of 1000 artifact-free FFR responses were recorded to the consonant-vowel /da/ following standards procedures[28,42]. The speech stimulus was created using a Klatt-based synthesizer[47] and modified in Praat[48]. The stimulus duration was 170 ms (10 ms onset period, 47 ms for the consonant transition and 113 ms for the vowel region) with a constant fundamental frequency (F_0) of 113 Hz. During the consonant transition, the first and second formants (F_1, F_2) varied from 553 to 688 Hz and 1438 to 1214 Hz, respectively, remaining stable in the vowel region. The speech stimulus was presented at 60 dB SPL every 100.27 ms in alternating polarities though ER3C shielded earphones of 300 Ω (Etymotic Research Inc., Elk Grove Village, IL, USA).

The continuous EEG sampled at 13333 Hz was online bandpass filtered from 30 to 1500 Hz and epoched in sweeps of 270.27 ms (-40.95 ms to 229.32 ms). Any sweep containing activity >±30 μV was rejected during the recording. Less than 3% of sweeps were rejected in click or /da/ stimuli blocks and impedances were kept <8 kΩ throughout the entire recording. Responses were

averaged for each stimulus and neonate and the subsequent evoked potentials were offline bandpass filtered from 80 to 1500 Hz.

Data analyses

To verify auditory pathway integrity, wave V in the click ABR was identified automatically as the major positive peak between 7.70 to 9.90 ms[49] and, subsequently, reviewed by visual inspection for correctness. Wave V peak amplitude and latency were then quantified. Analysis of the FFR was based on recent guidelines[28,38,42]. First, to avoid that group differences in the FFR could be explained by spontaneous neuroelectric fluctuations, the EEG at the pre-stimulus period was analyzed. For that, the root mean square (RMS) of the EEG amplitude of the 40 ms before stimulus onset (i.e., -40 to 0 ms) was computed and defined as the pre-stimulus RMS. Next, to account for the neural transmission delay from stimulus reception at the cochlea until neural phase locking onset in the CNS, the response's lag (i.e., neural lag) was estimated as the time shift with which the correlation between the stimulus and the response waveforms was maximum. All successive FFR parameters computed in the present study were calculated from the FFR onset, which is the stimulus onset plus the individual neural lag.

To investigate the stimulus encoding, the signal was decomposed in its frequency components applying the Fast Fourier Transform (FFT) algorithm. The lowest frequency of a periodic sound such as speech is called fundamental frequency (F_0). Since pitch, as a perceptual correlate of the F_0[50], is a sound attribute essential for language acquisition[51,52], the analysis was centered on the stimulus F_0. The stimulus F_0 spectral amplitude and its normalization were reported as indexes of response strength for the consonant transition and for the vowel regions independently, due to the different complexity in the spectral components of each region[38]. To carry out the spectral amplitude measurement, the mean over a 10 Hz frequency window around the stimulus F_0 (i.e., ±5 Hz to 113 Hz) was retrieved. Its normalization, termed signal-to-noise ratio (SNR), was calculated as SNR = *10*log10(Signal spectral power/Noise spectral power)*[28,38], being the noise spectral power defined as the mean over two 28 Hz frequency windows located at each side of the signal window. All signal analyses were carried out using Matlab scripts (R2019b, Mathworks).

Statistical Analyses

Statistical analyses were conducted by IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY). To assess group differences in demographic and electrophysiological (click ABR and FFR) data, categorical variables were analyzed by Chi-square test (Cramer's V for effect size) and continuous variables with *t* test (Cohen's d for effect size) or Mann-Whitney *U* tests (using the formula $r = z/\sqrt{N}$, where N = number of cases, for effect size) after assessing the normality

distribution by Shapiro–Wilk test. To explore whether maternal pre-gestational BMI, maternal gestational weight gain (GWG) and neonatal BMI could be linked with our FFR results, a two-tailed Pearson's or Spearman's correlations (attending to normality distribution criteria), between each of these variables and the FFR parameters were calculated. A p-value <.05 was considered statistically significant. Multiple comparisons correction with Bonferroni methods was applied where appropriate.

Ethical approval

The specific protocol of this study was approved by the institutional Ethics Committee of Clinical Research (CEIC) of the Sant Joan de Déu Foundation (Approval ID: PIC-53-17) and all parents gave the informed consent in compliance with the Declaration of Helsinki.

RESULTS

Maternal and neonatal clinical characteristics

Maternal and neonatal clinical data were retrieved from SJD Barcelona Children's Hospital and their Health Reference Center. In the event of being unable to find particular data in the mother-child clinical record, information was obtained from the sociodemographic questionnaire filled by the parents (Table 1). From the initial 27 LGA recorded, 25 LGA were compared with 25 AGA paired by sex and GA at birth. Two LGA with unreliable FFR (their SNR was <0) were excluded from the analyses. Significantly higher pre-pregnancy weight (p = .03) and pre-pregnancy body mass index (BMI) (p = .04), but not height (p = .47), were found in LGA mothers compared to AGA mothers, as well as higher incidence of maternal obesity (pre-pregnancy BMI ≥30 kg/m^2) amongst LGA mothers than in AGA mothers (p = .04). No group differences were found in any other of the maternal characteristics assessed.

Table 1. Maternal characteristics.

Measures	AGA (n = 25)	LGA (n = 25)	Statistic	*df*	*P* value	Effect size
Age, y	35.65 (4.96)	34.27 (4.87)	1.00[1]	48	.32	0.29[2]
Smoker, %	8.0	12.0	0.22[3]	1	.64	0.07[4]
Maternal pre-pregnancy weight, g	57.00 (15.25)[5]	66.00 (26.55)[5]	203.00[6]	-	**.03***	-0.30[7]
Maternal length, cm	162.20 (6.25)	163.52 (6.53)	-0.73	48	.47	-0.21
Maternal pre-pregnancy BMI, kg/m^2	23.24 (7.44)[5]	25.1 (8.26)[5]	207.00[6]	-	**.04***	-0.29[7]
Obesity (pre-pregnancy BMI ≥30), %	4.0	24.0	4.15[3]	1	**.04***	0.29[4]
Gestational weight gain (GWG)[8], kg	11.17 (3.48)	10.34 (4.24)	0.56[1]	27	0.58	0.21[2]
Primiparity, %	40.0	44.0	0.08[3]	1	.77	0.04[4]
White ethnicity, %	84.0	64.0	2.60[3]	1	.11	0.23[4]
Maternal education[9,10], %	8.0	27.8	3.00[3]	1	.08	0.26[4]

Results are expressed as mean (SD) or percentage as appropriate. [1]*t* test. [2]Cohen *d*. [3]Pearson's χ^2. [4]Cramer's V. [5]Median (IQR, interquartile range). [6]Mann-Whitney U test. [7]Effect size calculated by $r = z/\sqrt{N}$. [8]13 AGA versus 16 LGA [9]Sixteen years of education or less. [10]25 AGA versus 18 LGA. **P* value <.05. y, years; BMI, Body mass index; kg, kilograms; m^2, square meter.

Regarding the neonatal clinical characteristics (Table 2), LGA neonates presented, as expected, a significantly higher birth weight and centile (p = <.001), length (p = .001), BMI and head circumference (p = <.001) compared to AGA neonates. In the remaining variables, no significant differences were observed.

Table 2. Neonatal clinical characteristics.

Measures	AGA (n = 25)	LGA (n = 25)	Statistic	*df*	*P* value	Effect size
GA at birth, w	39.77 (1.14)	39.74 (1.15)	0.07[1]	48	.94	0.02[2]
Time birth to EEG recording, d	1.72 (0.69)	1.54 (0.70)	0.91[1]	48	.37	0.26[2]
GA at EEG recording, w	40.01 (1.12)	39.97 (1.17)	0.14[1]	48	.89	0.04[2]
Birth weight, g	3323.20 (366.23)	4037.20 (238.2)	-8.17[1]	41.22	**<.001*****	-2.54[2]
Birth length[3], cm	50.00 (2.00)[4]	52.50 (3.00)[4]	109.50[5]	-	**.001****	-0.49[6]
Birth BMI[3], kg/m^2	13.00 (1.31)[4]	14.88 (0.75)[4]	49.00[5]	-	**<.001*****	-0.69[6]
Birth Head circumference[3], cm	35.00 (1.13)[4]	36.00 (2.00)[4]	80.50[5]	-	**<.001*****	-0.59[6]
Birth centile	43.00 (46.00)[4]	97.00 (2.00)[4]	0.00[5]	-	**<.001*****	-0.86[6]
Male gender, %	56.0	56.0	0.00[7]	1	1.00	0.00[8]
Labor induction, %	40.0	60.0	2.00[7]	1	.16	0.16[8]
Emergency cesarean section, %	8.0	4.0	0.36[7]	1	.55	0.08[8]
Neonatal acidosis[9,10], %	12.5	0	2.55[7]	1	.11	0.24[8]
Apgar score <7 at 5 min[11], %	0	0	-	-	-	-

Results are expressed as mean (SD) or percentage as appropriate. [1]*t* test. [2]Cohen *d*. [3]22 AGA versus 24 LGA. [4]Median (IQR, interquartile range). [5]Mann-Whitney U test. [6]Effect size calculated by $r = z/\sqrt{N}$. [7]Pearson χ^2. [8]Cramer's V. [9]Neonatal acidosis: umbilical artery pH<7.15. [10]24 AGA versus 19 LGA. [11]25 AGA versus 24 LGA. **P* value <.05. ***P* value <.01. ****P* value <.001. GA; gestational age; w, weeks; d, days; g, grams; BMI, Body mass index; kg, kilograms; m^2, square meter; cm, centimeters; min, minutes.

Neurophysiology

ABR. Typical ABRs were observed in all neonates. Grand-average waveforms, and wave V amplitude and latency distributions are illustrated in Figure 1. Statistical analyses (Table 3) revealed that wave V amplitude was smaller in LGA compared to AGA neonates (p = .01). However, after normalization by the pre-stimulus neural activity, these differences washed out (p = .23). No group differences were observed in wave V peak latency (p = .07).

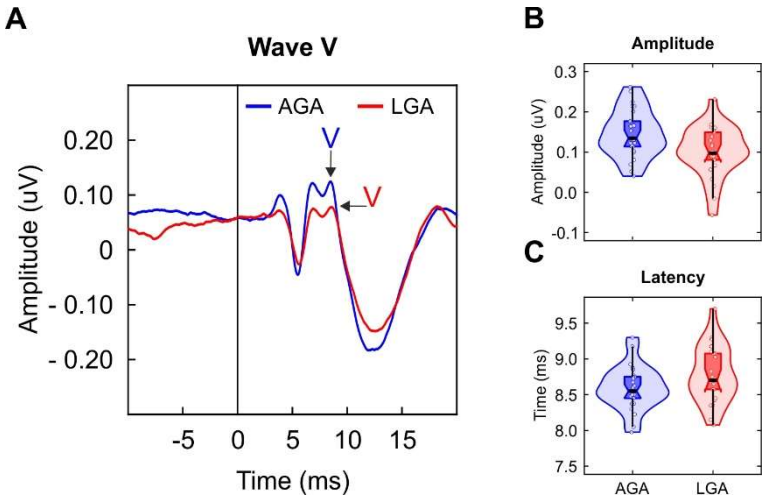

Figure 1 (**A**) Grand-averaged click ABRs for AGA (blue) and LGA (red) groups, with wave V peak pointed out. Data distribution (violin plots) for (**B**) wave V amplitude and (**C**) its latency. The black horizontal line indicates the median, the dark colored box (blue and red for the AGA and the LGA group, respectively) shows the interquartile range (IQR) and the black vertical lines stretched from the box illustrate 1.5 times the IQR. White filled circles indicate data corresponding to the individual neonates and the violin plot outlines illustrate kernel probability density, i.e., the proportion of the data located

Table 3. Descriptive statistics and comparisons between AGA and LGA groups for wave V and FFR parameters.

Measures	AGA (n = 25)	LGA (n = 25)	Statistic	*df*	*P* value	Effect size	Adjusted *P* value[1]
Wave V							
Baseline amplitude, µV	0.06 (0.04)[2]	0.04 (0.04)[2]	189.00[c]	-	**.02***	0.34[d]	
Amplitude, µV	0.15 (0.06)	0.10 (0.06)	2.61[e]	48	**.01***	0.75[f]	
Amplitude baseline corrected, µV	0.08 (0.06)	0.06 (0.06)	1.21[e]	48	.23	0.35[f]	
Latency, ms	8.59 (0.31)	8.78 (0.39)	-1.86[e]	48	.07	-0.54[f]	
FFR							
Pre-stimulus RMS, µV	0.02 (0.01)[2]	0.02 (0.01)[2]	296.00[3]	-	.75	-0.05[4]	
Neural lag, ms	5.85 (0.86)	6.37 (1.3)	-1.67[5]	48	.10	-0.48[6]	
Spectral amplitude, nV							
Consonant transition (10 to 57 ms)	36.18 (10.56)	25.55 (12.29)	3.28[5]	48	**.002****	0.95[6]	**.004****
Vowel (57 to 170 ms)	24.69 (8.82)	17.96 (8.38)	2.76[5]	48	**.008****	0.80[6]	**.02****
SNR, dB							
Consonant transition (10 to 57 ms)	3.36 (0.75)[2]	2.93 (1.07)[2]	182.00[3]	-	**.01***	-0.36[4]	**.02***
Vowel (57 to 170 ms)	8.77 (1.64)[2]	6.36 (4.05)[2]	168.00[3]	-	**.005****	-0.40[4]	**.01***

Results are expressed as mean (SD). [1]Adjusted *P* value after correcting for the number of comparisons conducted within the same parameter. [2]Median (IQR, interquartile range). [3]Mann-Whitney U test. [4]Effect size calculated by $r = z/\sqrt{N}$ V. [5]*t* test. [6]Cohen *d*. **P* value <.05. ***P* value <.01. ****P* value <.001. µV,microvolts; ms, milliseconds; nV; nanovolts; dB, decibels.

FFR. Clear FFR waveforms were recorded in both groups, LGA and AGA, although in the LGA group a notably smaller amplitude through the entire FFR duration was observed compared to the AGA group (Figure 2B). Notice, however, that the background EEG was similar in the two groups (no group differences in pre-stimulus RMS: p = .75; Figure 3A; Table 3). Neural lag was also comparable across groups (p = .10; Figure 3B; Table 3).

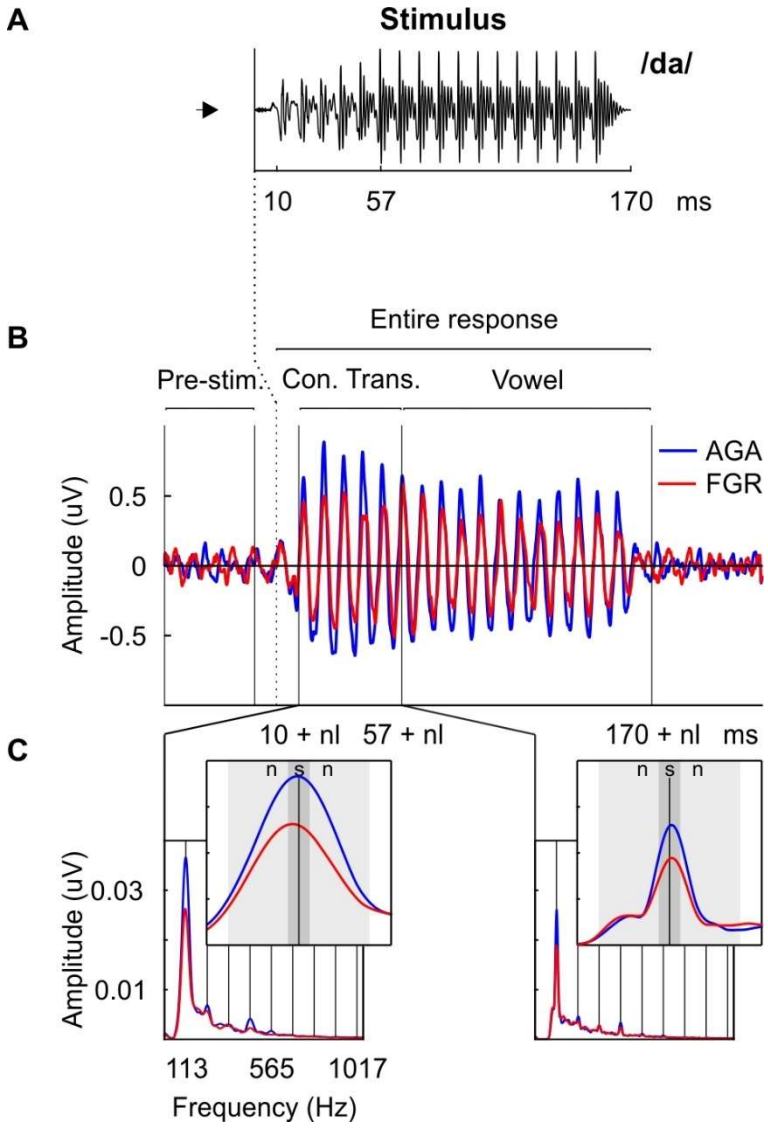

Figure 2 Temporal and spectral neural representation of the consonant-vowel /da/ in the neonate's auditory brain. (**A**) Stimulus waveform (/da/); (**B**) grand-averaged FFR waveforms; and (**C**) amplitude FFR spectra extracted from the consonant transition and from the vowel regions for AGA (blue) and LGA (red) groups. The signal (s) and noise (n) spectral windows used for FFR quantification are marked with dark and light gray rectangles, respectively.

To quantify the FFR, the F_0 spectral amplitude and its normalization (SNR) were retrieved by means of the FFT for the responses to both the stimulus consonant transition and the vowel

regions in each group (Figure 2C; Figure 3C to F). Smaller spectral amplitudes were found in LGA compared to the AGA group for the consonant transition (p = .002) and the vowel regions (p = .008). Similar results were obtained after normalization (i.e., after retrieving the FFR's SNR), showing that the LGA group had a smaller SNR than the AGA group in both regions (consonant transition region: p = .01; vowel region: p = .005).

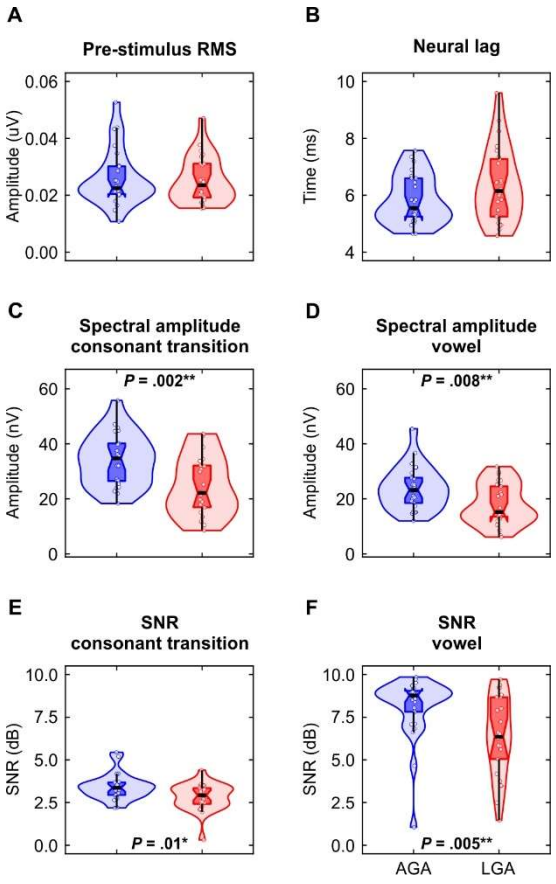

Figure 3 Data distribution (violin plots) of the (**A**) Pre-stimulus RMS; (**B**) Neural lag; (**C, D**) spectral amplitude; and (**E, F**) its normalization (SNR) extracted from the consonant transition and from the vowel. The layout is the same to that used in **Fig. 1** (**C**) and (**D**).

To explore if our results could be explained by maternal pre-gestational BMI and/or GWG based on previous studies in which an association with the offspring cognitive outcomes was observed[53,54], we carried out two matrices of correlations, one for each maternal variable (maternal pre-gestational BMI and GWG) and all the FFR parameters. These analyses yielded no significant correlations. Since an increased pro-inflammatory response has been linked to an elevated neonatal adiposity[55], we also explored the relation between neonatal BMI and the FFR parameters with the same statistical approach. In this analysis, strong significant correlations between neonatal BMI and spectral amplitude for the consonant transition (r = -0.54, P <.001) and for the vowel region (r = -0.57, P <.001) were found, as well as with the normalized spectral amplitude (SNR) for the vowel region (ρ = -0.42, p = .004) (Figure 4).

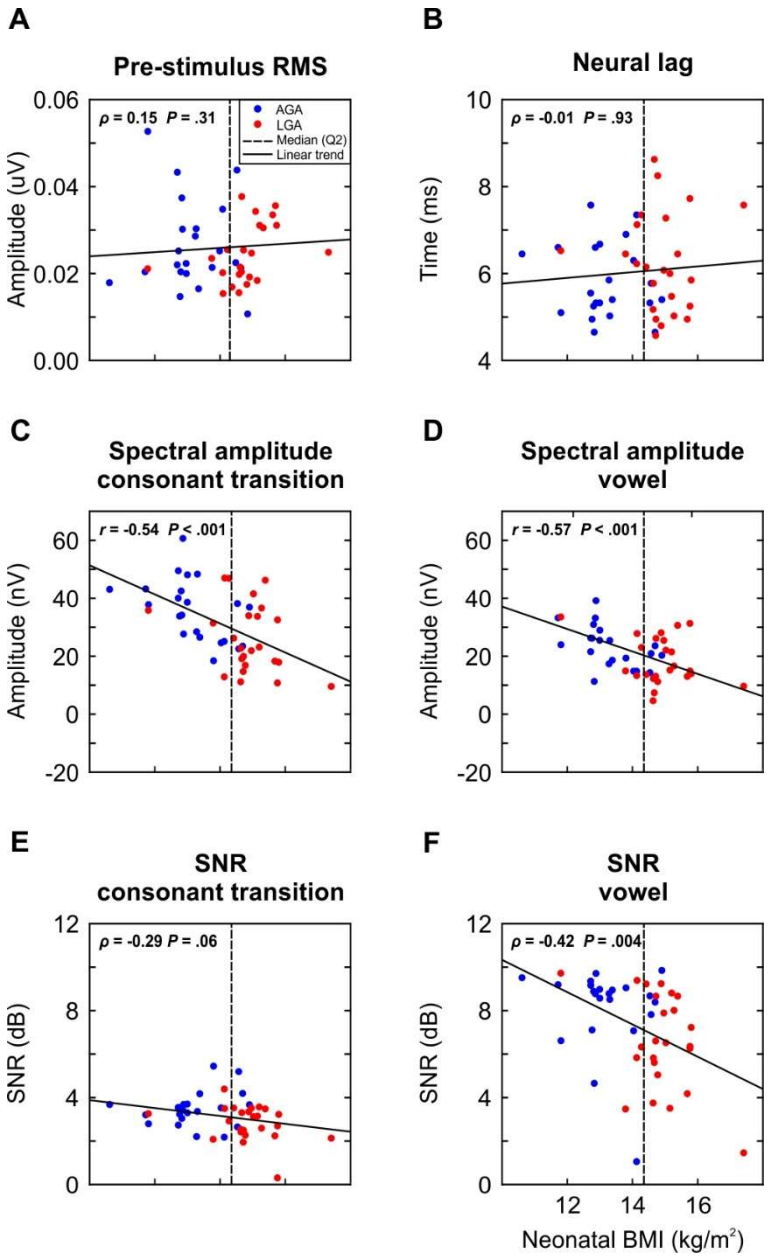

Figure 4 Correlation between Neonatal BMI and FFR parameters. Blue and red dots illustrate individual neonates from the AGA and LGA groups, respectively. Neonatal BMI lower or higher than Q2 is indicated by light and dark colors. Dashed lines illustrated the Neonatal BMI Q2 point. Black lines show the linear trend between the Neonatal BMI and the FFR parameter. In the upper left corner of each plot, the Person's or Spearman's correlation is reported together with the corresponding p-value, depending on the normality distribution criteria.

DISCUSSION

This study revealed a CNS functional alteration in the encoding of speech sounds in LGA neonates born at term. Using the FFR, an electrophysiological probe revealing the neural encoding of speech stimuli, we showed for the first time a weaker pitch encoding in LGA neonates compared with a control group of AGA neonates, as quantified through the FFR spectral

amplitude and its normalization (SNR estimation). Group differences in pitch encoding were present in the absence of any differences in neural transmission timing as indicated by ABR's wave V latency, and equivalent spontaneous EEG activity (i.e., pre-stimulus RMS). Moreover, these effects were related to the neonates' adipose tissue but not to that of their mothers or their gestational weight gain.

Previous studies on LGA populations have described impaired cognitive function from children to adulthood[14,16,17], as well as low academic scores[12,18,19] and associations with other neurological disorders[15,20-23]. Although all these studies investigated a large period of life, according to our knowledge no one addressed perinatal CNS consequences of being born LGA. The findings disclosed here may help shedding light on the existent disparity in neurodevelopmental studies conducted with LGA populations. We suggest that mixed LGA cases with normal and altered neural encoding of speech sounds may have obscure results in previous work, yielding the incongruities observed.

Pathophysiological mechanisms leading to this neurofunctional alteration at birth in LGA neonates remain unexplored. LGA neonates have greater adipose tissue compared to their AGA pairs[56], displaying a higher neonatal BMI index (see Table 2 and Figure 4) . Higher neonatal adiposity has been associated with higher pro-inflammatory cytokines such as IL-1β, IL-6, and IFN-γ and IL-1Rα and IL-4[57] which, in turn, may unleash a sustaining neuroinflammatory state after overcoming the blood-brain barrier[58], with adverse consequences on structural and functional neural networks involved in cognitive skills[59-62]. One of these main brain affections is on white matter. During pregnancy, between 24 and 40 weeks of GA, pre-oligodendrocytes actively develop to their mature form of myelinating glial cells (i.e., oligodendrocytes)[63]. During this period, preoligodendrocytes are susceptible to many risk factors, including inflammation, which can compromise the myelinization process[64]. The vast mounting evidence linking child and adult high body mass with low white matter integrity[65], together with the possible disruption of myelinization processes due to neuroinflammation, suggests white matter affections in LGA neonates at birth. Since a significant relation between FFR–F_0 strength and white matter mean diffusivity underlying primary auditory cortex has been found[66], we suggest that the neural effects caused from neonatal adiposity via proinflammatory products could impair the fine-grained CNS microstructure required for fast processing of speech sounds, hence leading to a weaker neural encoding of the stimulus fundamental frequency observed here in LGA neonates. Further studies should clarify the potential different contributions of subcutaneous versus visceral fat to the observed effects on FFR.

On the other hand, since high maternal pre-pregnancy BMI[67] and GWG[68] have been associated with an inflammatory in utero environment, which is linked with offspring's neurodevelopmental

impairment, an association between each of these maternal characteristics and our electrophysiological data was expected, which could not be confirmed though. The small sample size and the few pregnant women with a high pre-pregnancy body mass index may be behind these negative results. Yet, the fact that a significant correlation between electrophysiological data was found with the neonatal BMI index but not with the maternal BMI or GWG indices indicates a neonatal proinflammatory state as a result of an immune response from the neonate's own adipose tissue which may not have been exclusively mother-induced[55].

One of the strengths of the present study is the use of a novel technique –recordings of the so-called frequency-following response– to assess non-invasively the CNS functionality in LGA neonates during the first days of life. In addition, the selection of a neonatal sample from non-diabetic mothers, a well-known risk factor for poor infant neurodevelopment[69,70], makes it possible to assess specifically the effect of neonatal high birth weight on CNS functionality. Yet, the present results should be interpreted with caution, as key limitations include sample size, potential confounds, single-center origin, and the lack of postnatal follow-up. Our sample was indeed small but yet similar to that of previous electrophysiological studies on others clinical conditions[32-36]. Also, we acknowledge that our results were obtained on a sample recruited from one single maternity unit. Future multi-centric studies should increase external validity. Furthermore, the inclusion of a much larger number of cases would allow us conduct multiple regression analysis to control for potential confounds, such as maternal smoking. Follow-up studies should aim at determining whether the CNS alterations observed at birth are only transient to normalize with development or, otherwise have a potential predictive value. In the next stage of our project, we pursue assessing neurodevelopment at the age of 2 years. The existence of previous studies demonstrating that the FFR can predict literacy scores one year ahead[37] makes us confident that it will be possible to corroborate a relation between the neonatal FFR and neurodevelopmental test scores.

From a clinical point of view, the association between being born LGA and the risk to develop metabolic and cardiovascular diseases and obesity, both linked to behavioral problems and poor academic achievement[15,71], demand further studies focusing on babies and infants born with high birth weight. The promotion of effective early detection and intervention plans to maximize an appropriate development and to reduce the negative consequences of obesity in the public health is required. Thus, given that language is crucial to acquire knowledge and that poor reading ability leads to academic failure, greater incidence of social and emotional problems, and lower economic outcomes[72], a disrupted FFR could provide crucial information to pediatricians to determine follow-up monitoring with an interdisciplinary group to promote appropriate neurocognitive development and minimize the negative consequences.

CONCLUSION

This study has shown a CNS dysfunctionality in term LGA neonates. Using a non-invasive, cheap, and novel electrophysiological technique –the so-called FFR–, specific deficits in the encoding of voice pitch, were disclosed. The possibility to record the FFR in the maternity ward during the first days of life, with a routine EEG/ABR system, allows the early identification of CNS dysfunctionalities in LGA neonates. The FFR could become part of a screening plan leading to an early intervention program. The detection of a disrupted FFR could trigger the derivation to a multidisciplinary expert group who could individualize a stimulation program and to monitor the progress. Follow-up studies are needed to determine the extent of these dysfunctionalities and their predictive value on the infant's neurodevelopment.

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Author contributions

CE and MDGR conceived the idea for the study. CE and TRP designed the experiment. TRP and SAA carried out the implementation. TRP, SAA and JCF analyzed the data. TRP, MPC, JCF and CE interpreted the results. TRP wrote the initial draft of the manuscript in consultation with MPC and CE. MDGR and CE supervised the project. All authors provided critical feedback and approved the final manuscript.

Tweetable Abstract

Overweight no good: A neural deficit in encoding speech sounds revealed at birth in large-for-gestational neonates. (@aogs_tweets; @Brainlab_UB).

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SUMMARY OF RESULTS

Impact factor director report

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A QUI CORRESPONGUI

El sotasignant, Dr. Carles Escera, Catedràtic del Departament de Psicologia Clínica i Psicobiologia i director de la tesi doctoral titulada "*Detection of abnormal neural encoding of speech sounds at birth using the frequency-following response*", presentada per Teresa Ribas-Prats, fa constar que les següents publicacions –el factor d'impacte de les quals es fa constar- no s'han utilitzat ni de forma implícita o explícita per cap dels coautors en cap altra tesi doctoral:

Ribas-Prats, T., Almeida, L., Costa-Faidella, J., Plana, M., Corral, M. J., Gómez-Roig, M. D., & Escera, C. (2019). The frequency-following response (FFR) to speech stimuli: A normative dataset in healthy newborns. ***Hearing research***, 371, 28–39. https://doi.org/10.1016/j.heares.2018.11.001.
IF: 3.693 [Q1 Audiology & Speech-Language Pathology, Q1 Otorhinolaryngology, Q2 Neurosciences, JCR-SCI].

Ribas-Prats T., Arenillas-Alcón, S., Lip-Sosa, D.L., Costa-Faidella, J., Mazarico, E., Gómez-Roig, L., Escera, C. (2021). Deficient neural encoding of speech sounds in term neonates born after fetal growth restriction. ***Developmental Science***, accepted.
IF: 5.131 [Q1 Psychology, Developmental, Q1 Psychology, Experimental, JCR-SCI].

La tesi consta, a més, d'un tercer manuscrit:

Ribas-Prats, T., Arenillas-Alcón, S., Pérez Cruz, M., Costa-Faidella, J., Gómez-Roig, MD., Escera, C. Perinatal consequences of being born large-for-gestational age: speech-encoding deficits revealed with auditory brainstem responses. ***Hearing research***, submitted.

que està enviat a revista.

Així mateix, es fa constar que la doctoranda ha tingut un paper destacat en la concepció dels estudis, en la seva realització (implementació en els sistemes del laboratori, recollida de dades), en l'anàlisi de les dades, la interpretació dels resultats i la redacció dels manuscrits corresponents per a la seva publicació.

Carles Escera
Director de la tesi

Barcelona, 30 de setembre del 2021

Results

In the first study, the FFR was recorded in an original sample of 50 neonates; however, four of them were excluded because the presence of the wave V in the ABR to the click stimulus could not be confirmed. From the final sample of 46 neonates, the FFR grand-average waveforms and spectra for the consonant transition and for the vowel were clearly visualized to the two speech tokens presented: /da/ and /ga/ (see Figure 3 of the corresponding publication). To characterize the neonatal FFR, seven parameters were computed in either the temporal or spectral domains, and descriptive statistics and distribution values for each FFR parameter were reported (see Table 1 and 2 and Figures 5 and 8 of the corresponding publication). To highlight the variability within neonates, two individual cases who represented both ends of the SNR parameter distribution were plotted and marked in each figure. In general, the same pattern of results was found across all the FFR measurements. No differences were found between syllables, and in those which the consonant transition region and the vowel were calculated separately, higher values were obtained in the consonant transition. Finally, in the spectral amplitude parameter which was calculated for the F_0 and for the harmonics located under the FFR phase-locking limits (i.e., 1500 Hz), a higher amplitude for the F_0 was observed compared to the harmonics.

Regarding the second study, eight neonates were discharged from the final sample because in spite passing the hearing screening test and their wave V peak could be identified, their FFR was not detectable. Since the second and third study of this thesis evaluated a clinical group, to better characterize the neonates included in both groups (the control and the clinical group), a compound of sociodemographic factors in line of previous studies conducted in FGR and LGA were reported. In the second study, sociodemographic results were in line of previous studies focused on FGR fetuses. FGR mothers were younger and presented a higher rate of smoking than AGA mothers, and FGR neonates, as expected, presented a lower birth weight and a lower birth centile compared to their healthy pears. Also, they showed a lower GA at birth and higher index of labor induction than AGA group. These two last differences were explained by the hospital FGR care guide. Since the mortality index associated with FGR increases with GA, neonates affected by FGR are induced to be born between the 37 and 40 GA.

Regarding the electrophysiological results, FGR group present a delayed values of wave V latency compared to the AGA group. However, once the sociodemographic factors were included in the statistical analysis, group differences evanished and GA at birth explained in major proportion the wave V latency results. Related to FFR recordings, a delayed onset and weaker neural response for the vowel region by means of relative F_0 spectral amplitude values was observed

in the clinical group compared to the control group. It has to be highlighted that the neural activity between groups was similar in resting state and the results did not change after the inclusion of sociodemographic factors to the statistical analysis. In addition, to investigate if differences in wave V latency could explain the FFR results, a matrix of correlations with wave V latency and all FFR parameters was calculated, yielding only an association between wave V latency and neural lag.

In the third study, 27 LGA neonates were recorded but in two cases, their FFR could not be identified and were therefore disregarded from the final sample. Thus, the 25 LGA neonates were paired by sex and GA at birth with 25 AGA neonates. Sociodemographic analysis disclosed that LGA mothers had a higher pre-pregnancy weight, pre-pregnancy BMI and a higher rate of obesity compared to the AGA mothers. Regarding to the neonates, LGA group disclosed a higher birth weight and birth centile, length, BMI and heard circumference than AGA group.

Regarding to electrophysiological data, LGA group had a smaller wave V amplitude than the control group. However, when corrected by the baseline the wave V amplitude did not differ between groups. The analysis of the FFR showed that LGA group had a smaller spectral amplitude than the AGA group for the consonant and for the vowel, and the same pattern of results was observed after normalization (i.e., SNR). To explore the origin of these differences, three matrices of correlations were calculated between the FFR parameters and each of the following variables: maternal pre-pregnancy BMI, GWG and neonatal BMI. Although no associations were disclosed for the maternal variables, regarding the neonatal BMI, significant findings were found with spectral amplitude for both regions (i.e., consonant transition and vowel) and SNR at the vowel region.

DISCUSSION

The present doctoral thesis was set to validate the frequency-following response as a clinical tool to identify neural encoding of speech deficits in neonates born after some form of altered fetal growth. From a clinical perspective, the terms small-for-gestational age (SGA) or fetal growth restriction (FGR) and large-for-gestational age (LGA) are used to describe an abnormal fetal growth and represent both extremes of the birthweight spectrum. SGA/FGR and LGA have a major risk to health along lifetime however small or large fetal size does not directly mean pathology (Damhuis et al., 2021). At present, several international health organizations such as WHO claim the need to design and implement biometrical and functional indicators that contribute to detect those cases at the highest risk as early as possible and implement strategies to minimize the negative consequences derived from an altered fetal growth. To contribute to this aim, the present series of studies were conducted with the major goal of exploring by means of the electrophysiological response called FFR the existence of an association between a disrupted neural encoding of complex sounds at birth and an aberrant fetal growth. Although our contribution is limited to compare differences in group means, we hope that our work will motivate further electrophysiological studies on the altered fetal growth research field. Follow-up studies are needed assessing neurodevelopmental outcomes periodically to deeper explore the childhood period in SGA/FGR and LGA neonates, and to generate regression analysis such as ROC curve to deeper exploring the predictor value of the FFR and to identify those neonates at higher risk of communication disorders.

The first step of this endeavor was to establish a references values of the neonatal FFR after the possibility to record the FFR in newborns was confirmed. This aim was accomplished in the first study in which by using a portable equipment, we could record the neural response to the syllables /da/ and /ga/ in 50 newborns and a set of parameters to characterize the neonatal FFR was reported. Mean or median, depending on the score's distribution, were described with their respective measurement of statistical dispersion (standard deviation (SD) or interquartile range (IQR)). The results of the first study showed that neonates are able to encode the F_0 and phase-lock to voice-pitch from the first hours of life, in line with previous studies (Arenillas-Alcón et al., 2021; Jeng et al., 2011, Jeng, Lin, & Wang, 2016; Madrid et al., 2021). Although similar pith strength values to those reported by Jeng and colleagues (2011) or Arenillas-Alcón et al. (2021) were reported, and spectral amplitude values were similar to those of Madrid et al. (2021), the use of different stimuli, intensities and analysis parameters limits the possibility to extrapolate far reaching conclusions between different neonatal FFR studies.

In the first study, two speech tokens widely used in previous literature (/da/ and /ga/; Kraus et al., 1996; Tallal & Stark, 1981; Turner et al., 1992) were presented to elicit the FFR, and 2000 neural responses were recorded to each of them. In all the parameters retrieved from the FFR, no differences were observed between syllables. However, several limitations in the stimuli's frequency structure and in the analysis approach prevent us from concluding that newborns cannot discriminate sounds that differ only in their format components (i.e., fine structure). Among the study's limitations, we highlight the short duration and the dynamic frequency content of the consonant transition, the region where the stimuli differences were placed. Also, the F_2 -formant in which both speech tokens differed- were located at the highest frequency range of the spectrum (/da/: 1438-1214 Hz; /ga/: 1801-1214 Hz) to which the FFR is sensitive (Aiken & Picton, 2008). In addition, the continuous myelinization of the auditory pathway, which is speculated to be frequency-dependent (Lahav & Skoe, 2014), suggests that high frequency encoding at birth could have yet not developed. Finally, the use of averaged polarities emphasizes the envelope representation and reduce dramatically the fine temporal structure of the signal (Aiken & Picton, 2008). To deal with all the limitations discussed above, a recent study from our laboratory was carried out with a novel stimulus, and an integrative FFR analysis approach combining averaged and subtracted polarities was proposed to overcome these limitations (Arenillas-Alcón et al., 2021; see Figure 3).

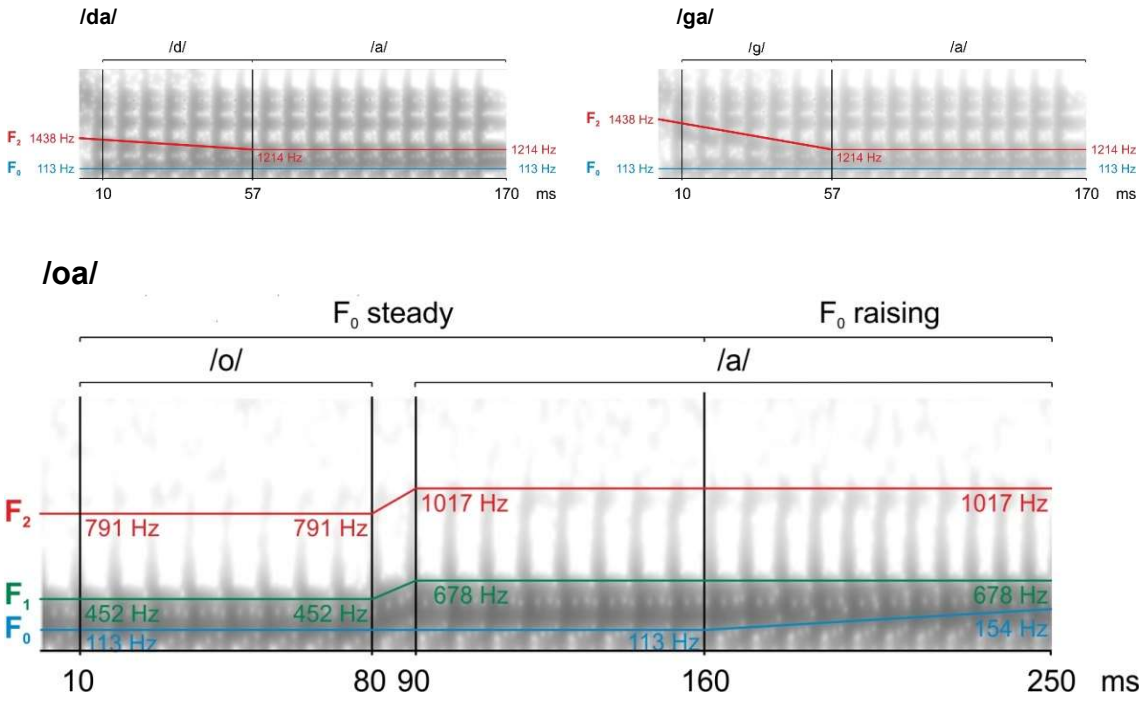

Figure 3. Espectrogram of the stimuli used in Ribas-Prats et al., 2019 (/da/ and /ga/) and in Arenillas-Alcón et al., 2021 (/oa/).

In addition to the syllables comparison, the stimulus region --with the levels consonant transition and vowel, and the harmonic factor --with the F_0 and the averaged of the existent harmonics within the first 1500 Hz of the spectrum (as the limit of the FFR phase locking capability) as levels, were also analyzed. Regarding the region factor, higher values were disclosed for the consonant transition than for the vowel. Previous studies reported a similar pattern of results in the spectral amplitude, but not for the SNR, in which higher values were found in the vowel region (White-Schwoch, Davies, et al., 2015). The lower amplitude at the vowel region found in our study was interpreted as neural adaptation (i.e., repetition suppression). Regarding the frequency component factor, higher spectral amplitudes were found for the F_0 compared to the harmonic frequencies as expected, since the F_0 is the frequency component with the highest amplitude in the stimulus spectrum.

The results obtained in the first study, confirm the possibility to use the FFR as a snapshot of complex sounds representation in the neonatal subcortico-cortical network, and contribute to make real the idealized scenario in which the implementation of an automatic FFR recording after passed the UNHS was suggested. However, before the neonatal FFR recording as part of the standard clinical practice could be possible several aspects need to be debated and agreed, such as the stimulus parameters, the number of sweeps need to verify the presence of a neural response, procedures and analysis routines (Lemos et al., 2021; Richard et al., 2020). Also, longitudinal studies including predicting models are essential to confirm the relationship between the neonatal FFR with the communication skills thought the lifetime.

Based on the experience of our first FFR study conducted in AGA newborns, some changes regarding the stimulus presentation and the FFR analysis were introduced in subsequent studies, with the aim of improving the fidelity with which the neonatal FFR can be captured. Firstly, to ensure that the low intensity chosen does not interfere in the quality of the neural response, we decided to deliver the stimulus at 60 dB SPL in line with previous studies (Jeng, Lin, & Wang, 2016; Jeng, Lin, Chou, et al., 2016). Also, as no differences were found in the voice-pitch representation between stimuli, we decided to use only the /da/ syllable as it is the speech token most used in FFR neonatal research (Lemos et al., 2021; Richard et al., 2020). Regarding the neural response, based on a recent study in which it was suggested to record more than 2000 sweeps in the neonatal FFR studies (Jeng et al., 2018) and to obtain a more robust FFR for each neonate, we averaged 4000 neural responses instead of 2000. Finally, to facilitate results interpretation from a clinical point of view, in the second and third study we focused a reduced

and planned set of measurements based on the neurophysiological information provided by each of them (Arenillas-Alcón et al., 2021; Ribas-Prats et al., 2019).

Once the normative database was published, the next phase was to record the FFR in a group affected by abnormal fetal growth, specifically those affected by fetal growth restriction (FGR), and to investigate whether their FFR response would differ from healthy newborns, given that FGR have been associated with high risk of language and communication disorders. To that end, we compared the FFR to the syllable /da/ recorded in 48 neonates born with adequate birth weight for their gestational age (AGA) and 53 neonates affected by FGR. After assessing in each individual the presence of the FFR by means of finding a higher spectral amplitude at the F_0 than in the surrounding frequency bins (i.e., a SNR > 0), five neonates were excluded. Thus, the final sample was 96 neonates: 45 AGA and 51 FGR neonates.

The results showed that FGR was associated with a weaker voice-pitch encoding in FGR compared to their healthy peers, and this was interpreted as the first evidence of functional deficits in the encoding of complex sounds during the first hours of life in FGR neonates. This finding supports the existence of neural damage as reported by previous radiological studies and contributes to characterize the neuropathological consequences derived from FGR.

This second study add to the previous findings the possibility to observe disrupted speech neural encoding at birth, at least altered pitch encoding at the 100 Hz range, in a group of neonates with a higher probability to present communication disorders than healthy pears. In this study, we observed that although similar spectral amplitude at the F_0 was disclosed between the clinical and the control group, when this spectral amplitude value was divided by the surrounding F_0 frequencies amplitudes, group differences were observed at the vowel region. Also, it has to be clarified that FGR and AGA groups did not differ in neural activity at the baseline.

The significant results located at the vowel region could be explained by the differences in duration and spectral content between the consonant transition and the vowel region and the immaturity of the auditory system at birth. Based on previous studies which suggested that the duration and the stability of the frequency components of the vowels could facilitate its encoding (Benavides-Varela et al., 2012; Kuhl, 2004; Kuhl et al., 2008), we hypothesized that the rapid spectro-temporal fluctuations and the short duration of the consonant transition compared to the vowel could compromise the immature FFR's brain underpinnings to encode the F_0 at birth in both groups. Recent studies disclosed evidence of the immature auditory

system at birth such as significant differences in the high frequency encoding between adults and newborns (Arenillas-Alcón et al., 2021) and a phase-locking improvement at the consonant transition with age (Van Dyke et al., 2017). Thus, we suggest that the functional immaturity of the auditory system could have masked the neural affections in the FGR group at the consonant transition.

The delayed electrophysiological response to click stimulus observed in the FGR group (indexed by the wave V latency) and the significant correlation with the onset time of the FFR (i.e., neural lag) suggested an impoverished neural transmission timing. The vanishing of group effects after the inclusion of the GA at birth to the statical model of the wave V latency parameter should be accurately interpreted. These results are expected since FGR has typically a lower GA at birth compared to the control group and wave V latency decreases with GA at birth but, we hypothesize that the white matter affections described by several radiological (Batalle et al., 2012, 2013, 2016; Eganã-Ugrinovic et al., 2015; Egaña-Ugrinovic, Sanz-Cortés, Couve-Pérez et al., 2014; Sanz-Cortes et al., 2014; Sanz-Cortés, Figueras et al., 2013; Sanz-Cortes, Ratta et al., 2013) and animal (Nitsos & Rees, 1990; Olivier et al., 2007; Tolcos et al., 2011) studies could also contribute to the delayed electrophysiological responses in the FGR group. At the same time, the neural transmission affection could explain indirectly the SNR results observed in the vowel region. The accuracy with which FGR neonates track the F_0 along the stimulus duration could be compromised and the low fine-grained F_0 codification could explain the presence of high energetic content at the surrounding frequencies.

Taking into account the high prevalence of FGR cases, the elevated rate of communication disorder associated with FGR and the positive effects widely demonstrated by the implementation of early intervention programs, we suggest that the neonatal FFR as a part of a screening plan during the first days of life could have a decisive role to maximize the correct development of the neonates affected by FGR.

In the third study of this thesis we aimed to test whether the neonatal FFR would be also altered in those neonates located at the opposite end of the birth weight continuum, usually called large-for-gestational age (LGA). This study describes that LGA neonates showed an altered neural representation of complex sounds, specifically a diminished F_0 encoding compared to the control group as notified by means of FFR spectral amplitude and its normalization. It has to be highlighted that these spectral amplitude differences were observed with similar baseline neural activity and neural transmission timing between groups. Thus, the high risk of disrupted F_0 encoding -a language skill needed for a correct language development- associated with being

born LGA discovered in the present work support previous studies which reported neurodevelopmental impairments in this group (Cesur & Kelly, 2010; Kirkegaard et al., 2006; Richards et al., 2001; Sørensen et al., 1997).

Although the pathophysiological underpinnings of our findings remain unexplored, several studies suggested that maternal factors such as high maternal pre-pregnancy BMI and GWG could condition the offspring neurodevelopment (Hrolfsdottir e al., 2016; Van der Burg et al., 2016). Recently, maternal and fetal inflammation derived from maternal obesity have been proposed as possible causes of the neurofunctional alteration in LGA babies at birth (Van der Burg et al., 2016). To explore the existence of any association with the FFR parameters, a matrix of correlations was conducted between each of these maternal variables (i.e., maternal pre-pregnancy BMI and GWG) and the FFR measurements, and no significant results were observed. However, since a recent study suggest that a possible neonatal neuroinflammation response could derived from the baby's own fat tissue (Hernandez-Trejo et al., 2020) we also computed a matrix of correlation between neonatal BMI and FFR parameters. This time, significant findings were observed for spectral amplitude in both regions analyzed (i.e., consonant transition and vowel region) and for normalized spectral amplitude (i.e., SNR) at the vowel region. Hernandez-Trejo et al. (2020) suggested that an accumulation of neonatal adipose tissue could activate a neuroinflammatory response which in turn could trigger negative structural and functional brain consequences, being white matter affections one of the most prevalent (Carlini et al., 2008; Li et al., 2018; Miller et al., 2015; Pannacciulli et al., 2007). Since a relationship has been disclosed between the degree of white matter diffusion and the strength with which the F_0 is encoding -by means of FFR- (Coffey et al., 2017) and the possible damage of white matter caused by proinflammatory agents, we hypothesized that an accumulation of neonatal adipose tissue (indexed by neonatal BMI) could limit the neural transmission timing.

The findings disclosed in the third study of this thesis highlight the importance to deeper explore the neonatal cognitive consequences of being born LGA and shed light in the disparities reported by previous studies. Also, since neonatal BMI was linked to the FFR results, we highlight, in line with Damhuis et al. (2021), the need to a more accurate definition of large neonates including other biometric variables such as body length. We expect that more studies using behavioral, electrophysiological, and imaging techniques will carry out in LGA neonates with a longitudinal perspective to confirm our present findings and, in the event they are corroborated, promoting the establishment of early screening plans to minimize the impact of negative neonatal outcomes.

Despite the present thesis contribute to better characterize the neonatal FFR and explore its clinical use in neonates with an aberrant fetal growth, we acknowledge several limitations altogether. First, our studies were carried out in a single hospital center which limits results generalization (i.e., a low external validity). Future multi-centric studies are needed to investigate the feasibility of the FFR recording as a universal screening tool. Second, although the sample size was similar to previous electrophysiological studies, to obtain more robust results from a clinical point of view and to make possible more complex and informative statistical analysis we claim future research assessing hundreds or, even, thousands of neonates. Also, to comprehend the extend of the results found during the first days of life, a follow-up exploration is needed. We also would like to address to those neonates eliminated from the sample because their FFR could not be identifiable. We acknowledge the need to deeper explore these cases and the longitudinal studies are specially interesting and crucial in these neonates. Further testing should be done before the family discharged the hospital or, if it was not possible, rescheduled them during the first weeks of life to explore whether factors such as muscle artifact, fluid or vernix inside the neonate’s ear could be affecting the FFR's results.

CONCLUSIONS

The present doctoral thesis was set to investigate the potential clinical utility of the frequency-following response to detect alterations in the neural encoding of complex sounds in neonates born after compromised fetal growth.

In the first study of this thesis, the feasibility to record the FFR in neonates at the maternity unit as part of the clinical routine was corroborated. An extensive normative database of the neonatal FFR to the syllable /da/ and /ga/ was provided to characterize the neural representation of speech sounds during the first days of life.

In the second study, functional deficits in the encoding of complex sound features in neonates born at term was shown. Through recordings of the frequency-following response elicited to the syllable /da/, it was found that being born at term with fetal growth restriction is associated with an impaired encoding of the F_0 of speech sounds. Significant results were observed at the vowel region only, which are compatible with the white matter affections disclosed in radiological and animal studies.

In the third study of this thesis, perinatal auditory system consequences of being born large-for-gestational age were disclosed for the first time. By means of the neonatal frequency-following response, specific deficits in the encoding of voice-pitch were observed. We suggested that the high adipose tissue observed in the large-for-gestational age group could impair, via proinflammatory products, the fine-grained auditory system microstructure required for fast processing of speech sounds.

We suggest that if future studies confirm these results and disclose association between the frequency-following response at birth and neurodevelopmental outcomes, this brain response associated to the neural encoding of speech could become an early biomarker of language impairments that would allow the implementation of early interventions programs to maximize normal neurodevelopment.

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