Chapter 9
Understanding Auditory Processing Disorder Through the FFR

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Abstract This chapter gives an overview of the importance of auditory processing for successful language learning and describes assessment measures that are not influenced by factors such as alertness and fatigue. The frequency-following response (FFR) to speech is similar to the evoking stimulus both acoustically and visually, that is, it has good accuracy in encoding specific speech features. Thus, FFR can assess sound processing to an extent that is not possible with slower, cortical potentials such as the middle latency response (MLR) and late latency responses. The fidelity of the FFR to the stimulus enables the evaluation of the strength of subcortical encoding of multiple acoustic aspects of complex sounds, including timing, pitch, and harmonics. Taken as a whole, FFR to speech shows patterns in subcomponents of the FFR that are associated with clinical populations. These distinct patterns of neural processing are described and possible mechanisms underlying abnormalities of the FFR associated with auditory processing disorders are discussed.

Keywords Auditory-based learning impairments · Auditory processing disorders · Central auditory function · Electrophysiology · FFR · Objective assessment · Temporal processing

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9.1 Introduction

Auditory processing disorder (APD) has been the subject of much debate and dissension. The controversies surrounding APD are related to its definition, its heterogeneous nature, the lack of a "gold standard" for its assessment and study, and the consequent lack of an appropriate test battery for clinical evaluation. Initially, the study of the underlying physiological mechanisms of auditory processing was based on psychophysical procedures and behavioral responses. However, such measures require the involvement of cognitive processes, attention, intelligence, motivation, fatigue, motor skills, language experience, and language impairments (Jirsa and Clontz 1990; Jerger and Musiek 2000), thus hindering the definition of the sensory deficit as the sole causative factor in APD. By contrast, electrophysiological procedures are independent of the subject's ability to provide behavioral responses (Musiek et al. 2002); thus, electrophysiological procedures have been useful in establishing basic structure-function relationships in the human auditory system. Such relationships have provided researchers and clinicians with valuable information regarding the sequence, timing, and neural location of auditory processes.

Although electrophysiological measures in the form of auditory evoked potentials (AEPs) have important roles in auditory processing studies, the reliability of these responses can be disputed. Some AEPs, such as the N1P2N2 complex, P300, and mismatch negativity (MMN), are widely used but their responses present great variability, and their slow voltage fluctuations, occurring hundreds of milliseconds after the evoking sound, are poor renderings of the acoustics of the stimulus (Kraus and Nicol 2014).

The frequency-following response (FFR) or auditory brainstem response to complex stimuli (cABR), assesses auditory neural functions, especially those believed to be involved in the neural coding of auditory processes. Studies using cABR have provided a more faithful measure of acoustic processing compared with other AEPs because of the physical similarity between the stimulus and response waveforms. Furthermore, cABR also reflects that auditory processing is profoundly affected by external factors, such as communication skills and training (Kraus and Nicol 2014).

The proper identification and quantification of auditory dysfunction is key to providing researchers and clinicians with a clear and irrefutable description of APD. In this regard, this chapter presents research demonstrating the valuable role of electrophysiology in general and of cABR/FFR in the comprehensive study and assessment of APD.

9.2 Auditory Processing Disorder: Definitions and Mechanisms

Although central auditory processing is a relatively recent field of research for audiologists, the first studies of APD date back to the 1950s. These classic studies were performed in subjects with temporal lobe lesions and auditory complaints in

the presence of normal peripheral hearing (Bocca et al. 1954; Sanchez-Longo et al. 1957; Kimura 1961). It was not until the 1970s and 1980s that researchers began to effectively study APD in children with language and learning difficulties despite normal hearing thresholds (Tallal 1976; Sanger et al. 1987). The significant increase in interest in APD provided not only a substantial amount of data but also many controversies and a lack of consensus on the nomenclature, concepts, and diagnostic criteria used in research and the clinic.

Currently, the American Speech-Language-Hearing Association (ASHA), corroborated by the American Academy of Audiology (AAA 2010), defines APD as a deficit in the "perceptual processing of auditory information in the central nervous system (CNS) and the neurobiological activity that underlies that processing and gives rise to the electrophysiological auditory potentials" (p. 2, ASHA 2005). The ASHA definition is based on the concept that APD is a primary dysfunction of the auditory substrate (Musiek et al. 2005) that might be influenced by, but not determined by, cognitive deficits. In contrast, the British Society of Audiology (BSA) places increased weight on cognitive deficits, stating: "the mechanisms underlying APD can include both afferent and efferent pathways in the auditory system, as well as *higher level processing that provides 'top-down' modulation of such pathways*" (p. 3, BSA 2011).

In essence, both ASHA and BSA agree on the underpinnings of APD as the primary consequence of a known lesion to the central auditory nervous system (CANS) or secondary to peripheral hearing impairment. However, when discussing APD as a developmental disorder, these groups disagree to some extent, and this disagreement is the origin of many of the controversies surrounding APD.

In children, APD may be related to auditory deprivation linked to long-term otitis media (Moore 2007), delayed maturation of the auditory central pathway, neurological conditions arising from tumors of the CANS, prematurity and low weight at birth, cerebrovascular and metabolic disorders, epilepsy, and extrinsic damage to the brain caused by bacterial meningitis, head trauma, or heavy metal exposure (Chermak and Musiek 2014; Bellis and Bellis 2015); however, there are no clear etiological factors strongly related to APD diagnosis (Dawes et al. 2008). The prevalence of APD is also unclear, but it is predicted to be 2–5% in school-aged children and approximately 50% in children with learning problems (Chermak and Musiek 1997).

The difficulty in establishing definitions, etiology, and prevalence data is because APD is heterogeneous (Jerger and Musiek 2000; Banai and Kraus 2014), lacks diagnostic "gold standards" (BSA 2011; Moore et al. 2013), and frequently occurs with concurrent difficulties in reading, spelling, and language (Sharma et al. 2009; Witton 2010). APD can be seen as a constellation of different behavioral manifestations from not being able to localize sounds or understand speech in noise to an inability in dealing with competing sounds, following verbal instructions, and, the more radical, central deafness. Such symptoms may overlap with other developmental disorders or cognitive deficits. However, the extent to which these overlaps represent causal relationships (with one primary disorder being responsible for the

other deficits) or are simply different disorders sharing the same underlying deficit is unclear (Bellis 2007).

The central auditory pathway consists of afferent, efferent, and parallel pathways arranged as an intricate circuitry connecting different auditory and nonauditory structures that conduct, analyze, compare, code, and decode acoustic information. Such complex interactions of neuronal fibers are the basis for the perspective that the auditory system is actually a non modular system (Musiek et al. 2005). Based on this perspective, neurons in the auditory areas, which are mainly activated by acoustic signals, might also be activated by other signals (e.g., visual). Thus, a lesion around the auditory areas, even if well-limited within the area, may give rise to nonauditory symptoms. In addition, the auditory cortex also presents a large number of connections with regions related to nonsensory processes that influence how people respond to sounds (e.g., pre-frontal cortex and decision making) (Moore 2012). In summary, with such intricate multisensory and cognitive interactions, it seems natural that lesions and dysfunctions related to the auditory pathway generate such a heterogeneous disorder (for a more detailed description of the interactivity of the auditory system refer to Kraus and White-Schwoch 2015).

If APD is considered a neurobiological alteration, children's deficits could be related to acquired neurological disorders (lesions), neuromaturational delays, or neuroanatomical abnormalities (Chermak and Musiek 2014). Neural maturation follows a caudal-rostral sequence, with peripheral functions reaching maturity around birth and axonal, dendritic, synaptic maturation, and myelination continuing to develop in the brainstem into early childhood and, in the cerebral cortex, into late childhood (Moore and Linthicum 2007; Moore 2012). Auditory development and speech perception are guided by relevant acoustic and linguistic information experienced early in life to ensure cortical maturation (Kuhl 2000). Consequently, children with delayed development, either related to sound deprivation or delayed myelination, might not present with the expected auditory performance of their age, possibly delaying language acquisition and learning (see also Jeng, Chap. 2; Reetzke, Xie, and Chandrasekaran, Chap. 10).

Sometimes, children might have variations in the development of their brain structures, thus presenting both anatomical and functional abnormalities (Chermak and Musiek 2014). For instance, Boscariol et al. (2011) observed that children with language learning problems who had perisylvian polymicrogyria (i.e., an abnormal number of gyri along the Sylvian fissure on the cortex) had poorer performance on auditory processing tests than their peers who also had language problems but normal magnetic resonance imaging (MRI) scans.

It is thought that poor synchrony of neural firing can result in poor representation of sound at all system levels, deficits in conduction velocities of such a signal, abnormalities in inter-hemispheric transmission, desynchronized activation of interneurons affecting the inhibition/activation of specific neurons, etc. Such alterations at the neuronal level could lead to the deficits typically observed in APD, such as the following: difficulties in sound localization, which depend on simultaneous activation of coincidence cells and binaural hearing; pattern recognition, which depends on frequency and duration cues; hearing performance for

competitive and degraded sounds, which depends on interhemispheric analysis and intrinsic redundancies, respectively; and analysis of temporal aspects (Musiek and Chermak 2014).

Electrophysiological measures can provide an objective biological means of investigating the auditory processing of sound and the underlying physiological mechanisms (He et al. 2012; Schochat and Musiek 2006). Integrity of the auditory pathways is a necessary condition for the normal development of auditory abilities, and obtaining direct information on the function of the auditory pathway assists in intervention programming and contributes to monitoring treatment outcomes. Given the frequent comorbidity of APD with language, learning, and attention deficits, the inclusion of electrophysiological measures in clinical assessments is gaining traction in clinical practice.

9.3 Electrophysiological Evaluation of Auditory Processing Disorder

Davis (1939) was the first to report an auditory-evoked response. Knowledge of AEPs has grown as a result of increases in computing power, enhanced signal processing strategies, and the urgent need to develop an objective measure of hearing. Audiologists first focused on the auditory brainstem response (ABR). By contrast, psychologists, psychiatrists, and neurologists focused on late potentials because these evoked response potentials (ERPs) are associated with both perceptual and cognitive processes (McPherson 1996). The AEPs are briefly reviewed to provide a broader perspective on how cABR/FFR contributes to the study, diagnosis, and management of APD.

9.3.1 Click Auditory Brainstem Response (ABR)

Jewett and Williston (1971) explained the clinical advantages of ABR over the already existing late-evoked-potential because of its reliability and independence from the patient´s state of arousal and its value in neurological applications. The conventional ABR is generated by neurobiological activity within the auditory nerve and the central auditory pathways in response to click, tone, or chirp stimuli, and it has a strong track record of being sensitive (able to detect a true positive) and specific (able to detect a true negative) to confirmed lesions of the auditory brainstem (see Starr and Achor 1975; Musiek and Lee 1995; and for a review, Hall 2015). However, click-evoked ABRs are generally normal in children with auditory based learning problems, such as dyslexia and specific language impairment (Billiet and Bellis 2011; Kumar and Singh 2015), and learning disorders (Song et al. 2006; Reetzke, Xie, and Chandrasekaran, Chap. 10).

Since in individuals with APD the proportion of abnormalities in click-evoked ABR is much lower than in middle and long latency potentials (Hall and Johnson 2007), it was suggested that individuals with APD either do not have brainstem lesions/dysfunctions, or do not have difficulties in processing simple acoustic information such as the click (Filippini and Schochat 2009). Recently, there has been an effort to use more complex stimuli (e.g., speech segments) in an attempt to measure subtle processes in the brainstem related to more complex sound processing. This potential will be described in depth in Sect. 9.4.

9.3.2 Auditory Middle Latency Response (MLR)

The MLR is typically evoked by a click or tone burst for neurodiagnosis or audiometry (Hall 2015). The *wave Pa* is the most reliable of the MLR waves (i.e., it is the most visible and robust), but amplitude and latency of the waves are widely variable and, as a consequence, this potential is not yet being used in clinical settings. Furthermore, it is highly affected by sleep as Kraus et al. (1989) found out in their study. Wave Pa was present during wakefulness, stage 1, and REM sleep but poorly detected during sleep stage 4. During sleep stages 2 and 3, Pa detectability was variable. This inconsistency of MLRs in children is another reason that limits its use for a clinical purpose.

Since the early 1980s, the MLR has attracted interest as an electrophysiological measure of central auditory function. There is considerable evidence to suggest that the MLR is especially sensitive to lesions of the auditory cortex and thalamo-cortical connections (Özdamar and Kraus 1983; Schochat et al. 2004). Hit rates in the mid-70% range or better have been reported (Musiek et al. 1999). The amplitudes of the MLR are reduced when the auditory cortex has been damaged; conversely, the MLR amplitude is preserved in the presence of lesions in other areas of the cortex (Shehata-Dieler et al. 1991).

The goal of MLR waveform analysis is to ascertain the symmetry of Pa wave amplitude among the two-electrode or three-electrode arrays used. Although the MLR typically shows considerable inter-subject variability, there is reasonable intra-subject consistency with electrodes located over the auditory cortical regions (e.g., regions C3 and C4) and from a frontal midline electrode site (e.g., Fz or Cz). There is general agreement that latency is less clinically useful than amplitude in the detection of auditory system dysfunction (Hall 2015).

In a study of children with APD, Schochat et al. (2010) observed smaller amplitudes for C3-A1 and C3-A2 waveforms in comparison to the control group. After auditory training, the amplitudes of MLR's waveforms for both electrode positions were increased in the APD group, commensurate with control group values. Figure 9.1 shows an abnormal MLR (electrode effect) from a patient before auditory training and the normal MLR waveform after training.

Weihing et al. (2012) assessed children with normal audiograms and children with APD and observed that the relative difference measurements of the MLR were

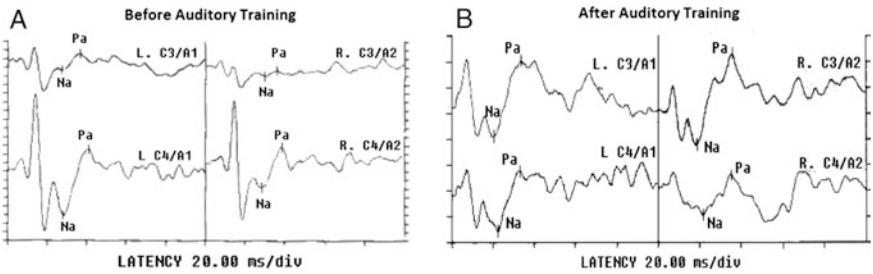


Fig. 9.1 **(A)** Abnormal electrode effect (left hemisphere) of middle latency response (MLR) waveform obtained from C3 and C4 electrode placements for a neurologically involved patient (Pilocytic Astrocytoma) *before* auditory training and **(B)** normal MLR waveform *after* training. *L*, left; *R*, right

less variable than the raw measurements when examined across subjects. The authors concluded that the analysis of the relative differences may provide better utility in the clinical diagnosis of central auditory deficits in children than absolute amplitude measures.

9.3.3 Auditory Late Potentials

Auditory late potentials (ALPs, also known as late-latency responses or LLRs) are determined more by the state of the nervous system when stimuli are presented rather than by the physical properties of the stimuli themselves. In this discussion, the late potentials include the N1P2N2 complex, P3 (P300), and MMN.

9.3.3.1 N1P2N2 Complex

The N1P2N2 complex is believed to originate from the supratemporal plane in or near the primary auditory cortex (Tremblay et al. 2001). This potential is believed to reflect the pre-attentive sensory encoding of the auditory stimulus attributes, including spectral and temporal cues critical to speech perception (McPherson 1996). Temporal cues are crucial to the differential sensitivity of intensity, frequency, and duration, and N1P2N2 components may provide not only a neurophysiological means of identifying dysfunction in this area but also objective monitoring of therapeutic progress in an intervention program (Musiek and Berge 1998). Studies in individuals with neurological lesions have shown latency and or amplitude effects on the N1P2N2 complex related to central auditory involvement in the auditory cortex and associated areas (Knight et al. 1988). In fact, these late potentials are compromised when auditory regions are involved, but this is not the case for nonauditory areas of the brain (e.g., frontal lobe) (Knight et al. 1980).

Studies in young adults with normal hearing have demonstrated that the objective cortical AEPs, in particular the N1 peak latency, can be used as a sensitive measure of temporal changes in sound stimuli at the level of the auditory cortex (Tremblay et al. 2001). However, the N1 component is either inconsistent or undeveloped from 3 to 8 years. The presence of the N1 becomes more reliable at approximately 9–11 years of age (Sharma and Mitchell 2013). In general, the dominant features of the cortical response in young children are the P1, which varies in latency as a function of age, and the N2, a negativity following the P1 at approximately 200 or 250 ms.

9.3.3.2 Acoustic Change Complex (ACC)

The ACC is a large response that can be elicited by changes in an ongoing sound, such as intensity or frequency modulations of a sustained tone, or in response to acoustic changes in more complex ongoing sounds such as speech (Small and Werker 2012). The ACC appears essentially as a second ALR waveform that follows the conventional onset-evoked N1P2N2 complex (Hall 2015). Despite the ACC's potential clinical applications, research on the relationship between the ACC response and auditory discrimination abilities is sparse, and the studies conducted so far have used different measures and procedures, which can affect the interpretation of results (He et al. 2012).

9.3.3.3 P300

The P300 is an endogenous potential that is triggered by the use of the "oddball paradigm" (i.e., an experimental method in which an infrequent or odd stimulus is presented among more frequent standard stimuli), which requires the listener to detect the infrequent stimulus. The P300 is highly dependent on attention as well as sensory processing. Generators of the P300 arise within the temporal lobe, limbic system, thalamus, and frontoparietal cortex. Although nonauditory regions contribute to the P300, there is evidence that lesions in auditory cortical regions compromise the latency and amplitude of the P300.

The P300 complex is affected by central auditory disorders in the auditory areas of the cerebrum. Knight et al. (1988) reported that individuals with lesions of the temporoparietal junction exhibited reduced P300 amplitudes compared with individuals with lesions limited to the parietal lobe. Notably, the P300 successfully identified those with acute and long-standing auditory effects due to traumatic brain injury (Segalowitz et al. 2001; Musiek et al. 2012), which is associated with auditory processing difficulties.

Jirsa and Clontz (1990) observed that the latency of the P300 was later for children with APD compared with a control group. Interestingly, Krishnamurti (2001) showed P300 latencies were delayed for an adult group with APD (diagnosed using behavioral central auditory tests) compared with a control group for

binaural (tone) stimulation and for a competing noise condition. The latencies were later in the noise condition than the binaural condition for the APD group but not for the control group.

9.3.3.4 Mismatch Negativity (MMN)

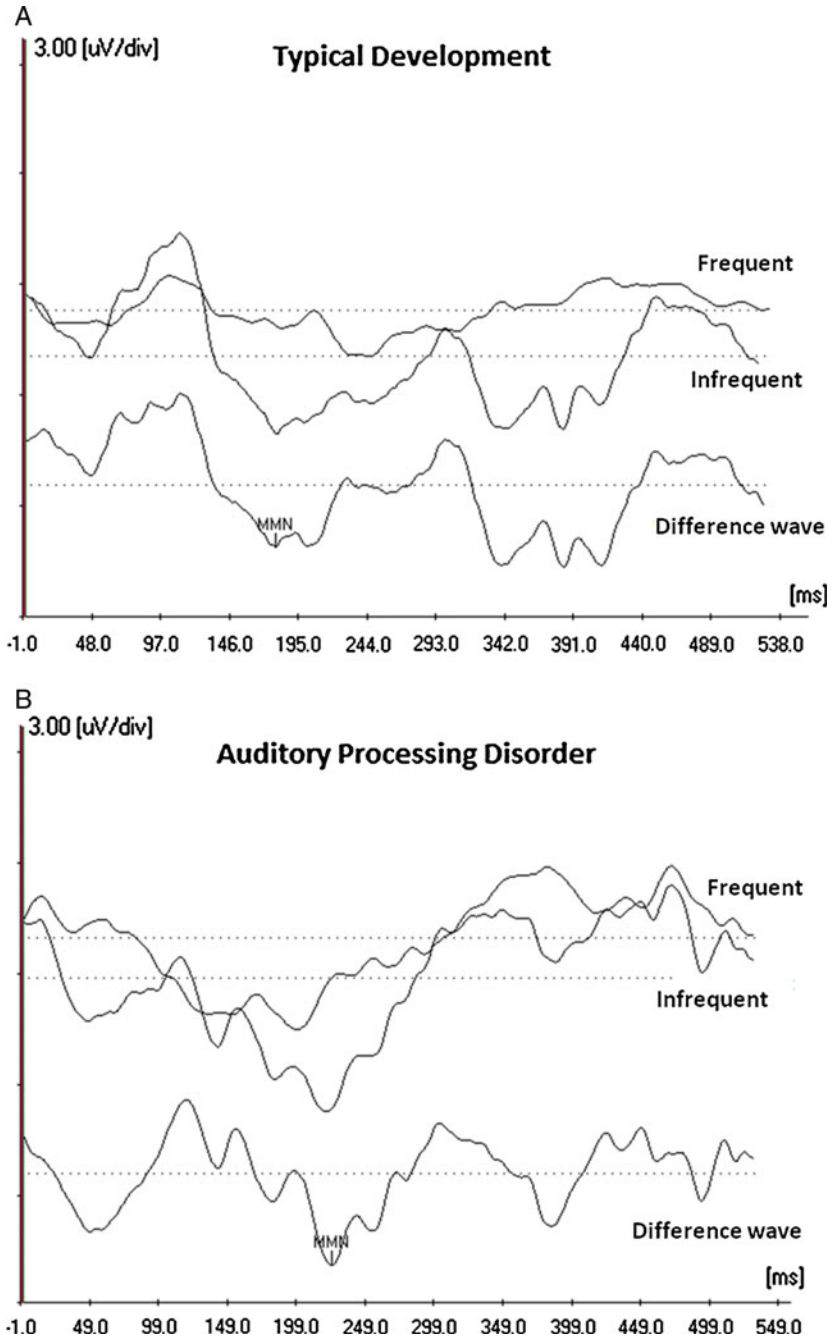
The MMN is an event-related response that reflects the detection of acoustic change. The MMN is elicited using an oddball paradigm, which is based on the premise that a neural trace or template is formed to represent the standard stimulus and is held in short-term memory (Näätänen 1995), and, in contrast to the P300, can be elicited even when subjects ignore the sounds presented to them (Martin et al. 2007).

The advantage of the MMN is that it can be reliably recorded (Escera et al. 2000) even in the absence of a behavioral response or the individual's attention, for example, in sleeping infants (Ruusuvirta et al. 2009), stroke patients, and in comatose (Fischer and Luauté 2005) and persistent-vegetative-state patients (Wijnen et al. 2007). Two major theories have been proposed within the past years: one model that posits the formation of an auditory sensory memory based on the encoding of statistical regularities from the acoustic input (Näätänen et al. 2005), and a complementary view that ascribes deviance detection to a mechanism of release from neural adaptation (May and Tiitinen 2010).

To determine whether MMN is suitable to provide additional information in behavioral auditory central tests, Bauer et al. (2009) assessed 32 children with APD and 13 healthy children. The incidence of MMN was always higher in the healthy children, and they had peak latencies that occurred earlier at frontal, central, and temporal electrode sites.

Another promising use of MMN is the investigation of prosodic abilities of infants as early predictors of specific language impairment (SLI). Weber et al. (2005) based their study on the hypothesis that the prosodic abilities of infants at risk for SLI are less elaborated than those of controls because of the less efficient processing of relevant acoustic cues. In contrast to matched controls, infants with very low word production showed a smaller MMN. This amplitude difference indicates impaired prosodic processing of word stress during early development and thus may be taken as an early marker of risk for SLI.

Rocha-Muniz et al. (2015) investigated speech encoding in the auditory system of children with SLI and compared it with children with APD and children with typical development through the MMN paradigm. The data demonstrated abnormalities in the automatic discrimination of crucial acoustic components of speech sounds in children with SLI and children with APD. This might indicate problems in the physiological processes responsible for ensuring discrimination of acoustic contrasts in pre-attentional and pre-conscious levels, which could contribute to poor perception (also see Kraus et al. 1996). Figure 9.2 shows a normal speech-evoked MMN for a typical-development child and an abnormal speech-evoked MMN for a child with APD.


A
3.00 [uV/div]
Typical Development
Frequent
Infrequent
MMN
Difference wave
[ms]
-1.0 48.0 97.0 146.0 195.0 244.0 293.0 342.0 391.0 440.0 489.0 538.0
B
3.00 [uV/div]
Auditory Processing Disorder
Frequent
Infrequent
MMN
Difference wave
[ms]
-1.0 49.0 99.0 149.0 199.0 249.0 299.0 349.0 399.0 449.0 499.0 549.0

◀ **Fig. 9.2** Speech-evoked mismatch negativity (MMN) responses. The grand average *Difference wave* was obtained by subtracting the response to the *Frequent* stimulus from the response to the *Infrequent* stimulus. **(A)** Speech-evoked MMN responses from a child with typical development. **(B)** Speech-evoked MMN responses from a child diagnosed with auditory processing disorder (APD). (Adapted from Rocha-Muniz et al. 2015)

More studies are necessary to determine whether this potential will be useful in clinical settings regarding time and individual results, although it is well known that MMN has good potential to be used for groups (Hall and Johnson 2007; McGee et al. 1997). It is important to note that the AEPs described above are based on the measurement of latency and amplitude, which usually show a major difference in inter-individual comparison as well as large standard deviations in large samples, making it difficult for them to be a clinically useful tool. Additionally, MMNs (and ALPs in general) only offer measures of latency and amplitude, which are blunt and abstract measures of auditory function.

9.4 New Approach to APD Evaluation: Frequency-Following Response

In speech, timing and harmonic cues are important for distinguishing and discriminating consonants and vowels (Delattre et al. 1955; Blumstein and Stevens 1979), pitch cues are important for understanding prosody and intonation, and pitch and the highest harmonics are important for identifying who is speaking (Bachorowski and Owren 1999; Ladefoged 2006). In the last decade, considerable attention has been given to the representation of speech signals in the brainstem auditory pathway. The FFR, also known as the auditory brainstem response to complex sounds (or cABR), is an important method for studying auditory-neurophysiological processing in humans. More specifically, it can measure neural synchrony in response to the crucial phonemic features of speech.

Speech formants are preserved on the discharge periodicities and interspike rate at the auditory nerve fibers (Young and Sachs 1979; Delgutte 1980). Considering these neural properties, the FFR's electrophysiological responses are the synchronized activity (i.e., phase locked) of a population of neurons in the upper brainstem in response to the individual cycles corresponding to the periodicity of the stimulus frequency (Smith et al. 1975; Krishnan 2007). There is evidence to indicate that the FFR emerges from phase-locked activity at the level of the lateral lemniscus (LL) and/or inferior colliculus (IC) (Krishnan 2007; Chandrasekaran and Kraus 2010). Its phase-locking properties refer to a clear and fixed relationship between some aspect of the response and the phase (or time) of the stimulus. However, the location of the specific generator sites remains controversial (Akhoun et al. 2008).

Phase locking, as reflected in the FFR, has been demonstrated for numerous stimuli, such as complex steady-state stimuli (Greenberg et al. 1987; Krishnan 1999, 2002), two-component tones (Greenberg and Marsh 1979), inharmonic tones

(Chambers et al. 1986), pure tones (Moushegian et al. 1973; Ananthanarayan and Durrant 1992), time-variant stimuli (Krishnan and Parkinson 2000; Plyler and Ananthanarayan 2001), synthesized speech (consonant-vowel) stimuli (Cunningham et al. 2001; Russo et al. 2004), emotional stimuli (Strait et al. 2009), and musical stimuli (Musacchia et al. 2007; Parbery-Clark et al. 2011). Furthermore, the FFR has also been recorded in degraded listening conditions such as reverberation (Bidelman and Krishnan 2010) and noise (Cunningham et al. 2001, Russo et al. 2004). This phase-locking activity has been implicated in the temporal encoding of the spectra of steady-state and time-variant speech sounds (Young and Sachs 1979; Blackburn and Sachs 1990).

Numerous studies have used FFR to assess auditory pathway integrity and auditory processing due to an individual's unique ability for phase locking. Poor phase coherence in individuals with speech perception deficits (a form of an APD) has been demonstrated by Ali and Jerger (1992). Using auditory steady state responses (ASSRs), which are 'phase-locking-dependent' and elicited by periodic signals similar to FFR, the authors observed that phase coherence was significantly poorer in the group with disproportionate speech understanding scores. Another study using ASSRs observed significantly increased thresholds in the APD group and dyslexia group compared with typically developed children (Simões 2009). These data suggest that an underlying temporal processing deficit (as a result of poor phase locking) could be contributing to these results.

The brainstem response to a consonant-vowel (CV) speech syllable (FFR in response to speech sounds) was first used by Kraus and colleagues (Cunningham et al. 2001) in a study of children with learning problems and speech sound-perception deficits. FFR in response to speech sounds consists of two separate portions: the transition, corresponding to the CV formant transition (onset); and the sustained stage, corresponding to the relatively unchanging vowel (Russo et al. 2004; Akhoun et al. 2008).

For consonants, the transient onset response marks the beginning component characterized by a harmonic and broadband frication (onset burst) and is followed by a harmonically rich and spectrally dynamic formant transition. The sustained FFR component is synchronized to the periodicity (repeating aspects) of the sound with each cycle faithfully representing its temporal structure, and it has an upper limit of approximately 1000 Hz for neural phase-locking properties (Chandrasekaran and Kraus 2010).

Taken together, the key elements of the brainstem response to speech represent its features with remarkable fidelity. These elements are recorded from the scalp and are presumed to faithfully reflect activity from an ensemble of neural elements within the central auditory pathway (Kraus and Hornickel 2012). The onset, transition, and sustained FFR components reflect the output of brainstem and midbrain structures and encode stimulus-related information with high temporal and spectral accuracy.

Latency measures and the wave morphology of the FFR are apparent and interpretable in infants (Anderson et al. 2015) and preschoolers (White-Schwoch et al. 2015a, b). However, early childhood is marked by a systematic speeding up of

FFR latencies (Skoe et al. 2013). Around 8 years-of-age, latencies are their earliest, and then they slow down and stabilize to adult-like latencies until senescence (Anderson et al. 2012).

The fidelity of the response to the stimulus enables the evaluation of the strength of subcortical encoding of multiple acoustic aspects of complex sounds, including timing (onsets, offsets), pitch (fundamental frequency, F_0), and timbre (integer harmonics of the F_0) (Skoe and Kraus 2010). The analyses of the FFR include measurement of latency and amplitude in the time domain and magnitude of the individual harmonics in the frequency domain (see Sect. 9.4.1). Because of the FFR's remarkable stimulus fidelity, cross-correlation between the stimulus and the response is also a meaningful measure (Krishnan et al. 2005). In addition, responses obtained from two conditions can be cross-correlated to determine the effects of a specific condition (e.g., noise) on a response (Russo et al. 2004).

Temporal and harmonic cues are important for distinguishing consonants, and the CV transition is perceptually vulnerable, particularly in background noise (Nishi et al. 2007), suggesting that temporal perception is important for understanding the linguistic content of speech in noise. The FFR in background noise has shown markedly worse degradation in the portion correspondent to the consonant transition in comparison to the vowel portion (White-Schwoch et al. 2015a). Based on these findings, the authors suggested that in preschoolers the acoustic processing of dynamic speech components may be more susceptible to noise interference than the processing of static features, at least regarding midbrain coding.

The FFR is similar to the evoking stimulus acoustically and visually (Galbraith et al. 1995) so the accuracy of encoding specific speech features, such as timing, pitch, and harmonics, is reasonable to assess to an extent that is not possible when using slower, cortical potentials like MLR and late latency responses. The following section will describe the applications of the FFR for assessment of APD.

9.4.1 Speech-Evoked FFR: General Interpretation

As mentioned in Sect. 9.4, the evaluation of the neural response to speech components (timing, pitch, and harmonics) has been useful in understanding the biological bases of auditory processing in clinical populations (see also Reetzke, Xie, and Chandrasekaran, Chap. 10; Anderson, Chap. 11). Timing has been defined as the latency of each peak and reflects temporal precision of the synchronous neural activity with respect to the onset, periodicity, and offset of the stimulus. Such measures reflect the amount of activity that contributes to the generation of the peak and the temporal synchronization of the response (Russo et al. 2004). Thus, timing measures provide information on the precision with which the brainstem nuclei respond to the acoustic stimuli, whereas amplitude measures provide information on how robust that response is. Abnormalities in these measures might reflect

differences in the velocity of signal conduction along dendrites and axonal projections, differences in the neurons' kinetic channels, or differences in the generators' synchronization (Johnson et al. 2007). Response timing is directly related to perceptual abilities.

In addition to the latency measures (i.e., measures in the time domain), it is possible, through a Fourier transformation, to represent the waveform obtained for the sustained portion in the frequency domain, allowing measurement of the response magnitude to a specific frequency or a range of frequencies (Aiken and Picton 2008; Banai et al. 2009). The F_0 provides information regarding pitch, allowing identification of a speaker or emotional intonation of the voice. The amplitude of F_1 (first formant) and HF (high frequency) provides phonetic information, making them important in distinguishing the contrasts between the speech sounds (Russo et al. 2004; Kraus et al. 2009).

Pitch is the perceptual correlate of the periodicity, or repetition rate, of an acoustic waveform (Oxenham 2012). The most important determinant of the pitch of a sound is likely its periodicity. Periodicity is most often quantified by the F_0, which has major contributions to the percept (Cruttenden 1997). The F_0 reveals information regarding voicing and manner of speech and also contributes to prosodic features of speech such as stress and intonation.

The F_0 is preserved in the phase-locked neural activity generating the FFR for steady-state complex tones (Greenberg et al. 1987), time-varying pitch contours of lexical tones (Krishnan et al. 2004), and speech stimuli (consonant-vowel) (Cunningham et al. 2001). Thus, electrophysiological FFR measures should provide an important measure of the neural processing of the F_0.

Pitch is encoded in the early stations of the auditory system by the temporal patterns of spikes. Therefore, difficulties in extracting and correctly using prosodic features of speech are symptoms of APD. Due to neural encoding by temporal patterns and synchrony of neuron spikes, prosodic deficits have been attributed to temporal auditory processing disorders (Gelfand 2010).

Further analysis of the spectral content of the response includes the harmonics, which are shaped by the articulators producing the speech formants (i.e., information about the message or verbal meaning of the utterance). Harmonics refer to the spectral characteristics of an auditory object apart from pitch. The harmonics of a sound are expressed by spectrotemporal properties, that is, the changes in the amplitudes of the sound's constituent frequencies over time (Janata 2015). Peaks in the harmonic spectrum are referred to as formants (e.g., F_1, F_2, F_3, etc.), and they are needed to discern the content of speech.

This measurement of FFR in response to speech sounds was defined as the neural activity that arose due to the harmonics of the fundamental frequency (Banai et al. 2009). The formant structure of the signal, determined by the filtering of the harmonics by the articulators, identifies the speech signal independent of pitch (Hornickel et al. 2012a; Skoe and Kraus 2010). Therefore, the first formant (F_1) and HF measures of the FFR appear to be consistent with phonological processing.

9.5 Auditory Processing Disorder in Light of FFR

Some children with language deficits, either dyslexia or SLI, have deficits in auditory ability compared to typically developing children. According to some authors, these clinical communication disorders may lead to difficulty processing rapidly presented auditory stimuli (Tallal 1976; Wright et al. 1997).

Regarding FFR, studies have shown that clinical populations have distinct patterns of response that may offer converging information about speech-sound coding and, potentially, about weaknesses in the neural processes that are important for everyday communication and auditory processing at large (Kraus and Nicol 2014; Kraus and White-Schwoch 2015). In other words, the evoked response for timing (onsets, offsets), pitch (F_0), and timbre (representation of formants above F_0) are shown to be inefficient or reduced in different ways for distinct clinical populations (Reetzke, Xie, and Chandrasekaran, Chap. 10; Anderson, Chap. 11).

A neural signature of FFR findings has been seen in children with reading and language impairments, that is, they have delayed neural responses and reduced representation of higher speech harmonics (Kraus and Anderson 2016). One reason for these results may be a decrease in the synchrony of neural firing, which can lead to abnormal perceptual abilities.

Complex sounds are susceptible to auditory temporal masking, which is a phenomena in which a brief signal might have its perception influenced by an immediately following sound (backward masking) or immediately preceding sound (forward masking). This type of interaction between temporally close sounds happens frequently in natural speech, and difficulties in overcoming such influence have been linked to language impairments and auditory temporal processing deficits (Wright et al. 1997; Montgomery et al. 2005). Johnson et al. (2007) showed that children with learning impairments who had the slowest response timing to the offset of the speech syllable also had the worst behavioral auditory backward-masking thresholds. In contrast, the children with learning impairments who did not have abnormal offset response timing had backward-masking thresholds within normal limits. The authors suggested that it is not the presence of a learning disorder that results in poor backward-masking performance but rather the inability of the nervous system to faithfully represent the final portion of the stimulus that leads to difficulties in distinguishing a tone from a following masking sound.

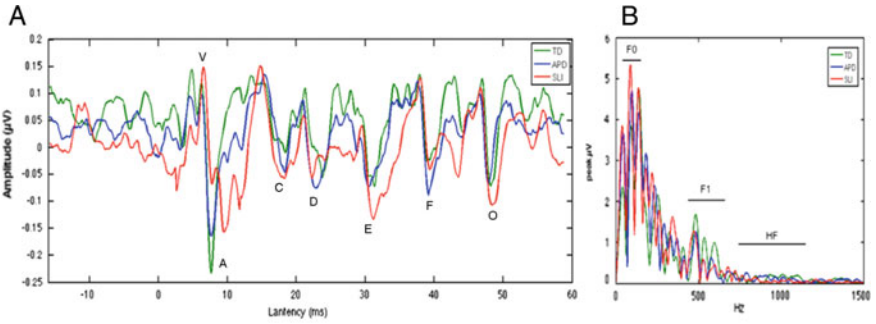
Banai et al. (2005) showed that in addition to cortical processing deficits, brainstem responses to speech are abnormal in approximately one-third of children diagnosed with language-based learning problems. In another study, Banai et al. (2009) found poor timing of subcortical auditory encoding and reduced amplitudes for both middle and higher harmonics in the group with reading impairment compared to the group with normal reading ability.

Many other studies have shown that children with a wide range of learning impairments present delayed responses when compared with their typically developing peers (Cunningham et al. 2001; Wible et al. 2004). The delayed responses observed in children with APD and language-based learning disabilities

are consistent with a possible interruption of timing representation in the brainstem responses (King et al. 2002; Wible et al. 2005). These responses are vulnerable to degradation in background noise (Nishi et al. 2007), but children with reading and language disorders have difficulty differentiating speech even in quiet conditions (Banai et al. 2005; Rocha-Muniz et al. 2012).

Delayed neural timing—but normal spectral content of the neural response—is also found in children who have been diagnosed specifically with APD, despite the fact that only a few studies have used the FFR to speech sounds to investigate neural speech processing in this specific clinical population. Rocha-Muniz et al. (2012) compared FFR to a 40-ms [da] in three groups of children (ages 6–12) who were typically developing (TD), diagnosed with APD, or diagnosed with SLI. The authors reported abnormal neural encoding of timing measures in the APD and SLI groups. Compared with TD children, the auditory and language impairment groups demonstrated prolonged and less synchronized onset responses (Fig. 9.3). These findings suggest that the neural encoding of acoustic characteristics that vary over time, particularly in the case of rapid changes, may be impaired in these children.

While children with APD and SLI appear to have overlapping abnormal neural processes, they also appear to have distinct neural signatures. Both groups had delayed timing compared to the TD group, but the SLI group presented a more pervasive timing delay than the APD group. In addition, these distinctions are more evident in the spectral content of their response. The SLI group had reduced amplitudes for the higher harmonics compared to either the APD or TD groups.



C

	Mean (ms)							Mean (μV)		
	V	A	C	D	E	F	O	F_0	F_1	HF
TD	6.32	7.87	17.57	22.83	30.64	39.37	48.01	5,91	1,32	0,44
APD	6.43	7.93	18.39	22.83	30.64	39.97	48.95	5,46	1,19	0,45
SLI	6.78	8.61	18.76	23.72	31.79	41.14	49.27	6,74	0,96	0,29

Fig. 9.3 **(A)** Grand averages of the time domain response in children with typical development (TD, *solid green lines*), auditory processing disorder (APD, *solid blue lines*), and specific language impairment (SLI, *solid red lines*). Subcortical timing response to speech is delayed in SLI and APD compared with TD. **(B)** Grand-averaged spectra over the formant transition period for three groups. *HF* is the region of the neural responses that differs significantly between children with SLI (lower magnitudes) and the other two groups (TD and APD). **(C)** Mean latency for each peak and mean magnitude of response for each frequency region, according to group. (Reprinted with permission from Rocha-Muniz et al. 2014)

The atypical activity in the high frequencies in the SLI groups (but normal for APD) might reflect group differences in frequency-specific encoding, primarily occurring at higher frequencies that require more precise, rapid activation and recovery mechanisms. This result suggests an underlying weakness in phase locking of the involved neurons and, consequently, poor speech understanding.

Although children with APD or language/reading problems with clinical presentation of APD commonly have temporal auditory processing deficits and abnormal FFR timing, some researchers have demonstrated intact subcortical neural representation of pitch (F_0) using FFR (Hornickel et al. 2012b; Rocha-Muniz et al. 2012). This is in contrast to the more pervasive deficits in children with autism, which include pitch encoding (Russo et al. 2008). Though consistent with behavioral findings (Marshall et al. 2009), this pattern needs to be interpreted with caution, particularly because the pitch trajectory of the stimulus used in these studies was not ecological (i.e., does not occur in natural language). There are some findings showing an FFR advantage in native Mandarin speakers when using an ecological pitch contour (Xu et al. 2006; Chandrasekaran et al. 2007; see Krishnan and Gandour, Chap. 3 for a discussion of how language experience shapes brainstem processing of pitch contours, and Carcagno and Plack, Chap. 4 for a discussion of perceptual learning on pitch tracking).

Abnormalities in FFR have been repeatedly reported in aging populations as well (Anderson et al. 2011, 2012, 2013). Even older adults with normal hearing thresholds report trouble hearing in background noise, echoing one of the primary elements of APD. The FFR in this population is characterized by delayed neural timing (peak latencies) in response to consonant-vowel transition, supporting a deficit in central processing in older adults (Vander Werff and Burns 2011; Anderson et al. 2012). This delay is similar to that seen in children with SLI, dyslexia, APD, and risk for language impairment (White-Schwoch et al. 2015b; Kraus and Anderson 2016).

Despite the influence of peripheral and cognitive factors in both children with language-based learning impairments and older adults, deficits in the FFR are likely to have different etiologies. In older adults, such deficits may arise from peripheral neurodegeneration, cognitive declines, and changes in the balance of neurotransmitters. On the other hand, auditory processing deficits in children are likely to result from a malfunction in making effective sound-to-meaning connections that are necessary for language learning (Hornickel and Kraus 2013). It is important to have in mind that APD may arise from various sources of impairment or delayed development, including auditory nerve, brainstem, auditory cortex, prefrontal cortex, corpus callosum, or other areas (Medwetsky 2011). The FFR may be influenced by impairments in these areas, but the neural patterns may depend upon the specific nature of the impairment.

Although the use of FFR to speech stimuli has exhibited promising results in research settings for more than a decade, its application in clinical practice is still a significant challenge. Rocha-Muniz et al. (2014) aimed to verify the sensitivity, specificity, and efficiency of this AEP. The sensitivity of a clinical test refers to the ability of the test to correctly identify those individuals with the disorder (i.e., true

positives). The specificity of a clinical test refers to the ability of the test to correctly identify those individuals in whom the disorder is absent (i.e., true negatives). Efficiency measures the degree of veracity of a diagnostic test on a condition. The study showed approximately 70% efficiency (analyzing the latency of A-peak) in the identification of auditory-language-based disorders (APD and/or SLI). This study is particularly important given the shortcomings of the behavioral APD test battery. Most of the tests widely used in the APD evaluation have been validated with patients with known brain lesions (Musiek et al. 1991), and it is questionable whether this is an appropriate group to presume the effects of APD, particularly in children.

In contrast, Rocha-Muniz et al. (2014) validated the ability of the FFR to identify individual children with APD and SLI diagnoses. Rocha-Muniz et al. (2016) found that 85% of children with an abnormal FFR performed abnormally on the APD tests. Banai et al. (2005) also observed that approximately 80% of poor readers (children) had abnormal brainstem timing measures. Additionally, White-Schwoch et al. (2015b) developed a composite FFR measure that identifies 70% of children with a learning disability and may predict future auditory processing skills. In conclusion, the data presented in this section could be considered evidence that APD might best be viewed as part of a multicomponent characterization of developmental learning/language disorders and, taken as a whole, studies using FFR to speech stimuli have shown patterns of subcomponents of FFR associated with clinical populations.

9.6 Future Directions

As discussed in this chapter, the FFR may be a useful tool for investigating APD and other disorders as well as the occurrence of comorbidities. Future research could include testing individuals with defined lesion sites. Such studies would provide information about neural origins and insight as to its sensitivity to central auditory disorders with a neurological basis.

Skoe et al. (2013) studied a large dataset of FFRs and found that for each set of FFR measures (latency, frequency encoding, response consistency, nonstimulus activity), developmental changes continue well past the age of two. Their data call into question the conventional wisdom that the auditory brainstem is mature by 2 years of age. The authors suggest that future studies should measure neurophysiological and behavioral development in parallel to assess whether the developmental trajectories of the ABR can be followed by specific perceptual or linguistic skills, which is difficult because the many behavioral tests cannot be easily applied to infant, pediatric, adult, and geriatric populations, whereas ABRs use the same testing protocol for all ages.

Additionally, the FFR has the potential to be used to evaluate the nature of the neural representation of speech sounds processed by different strategies employed in hearing aids and cochlear implants (see Anderson, Chap. 11). Processing

strategies could be modified to provide the optimal FFR neural representation of acoustic features that are important for the identification and discrimination of speech in individual listeners.

9.7 Summary

The importance of auditory processing skills for successful language learning and later academic achievement was discussed. The need for viable objective and biological measures that are less impacted by nonauditory factors, such as alertness/fatigue and comorbidities, to assess these skills, was also covered.

In addition to providing a biological dimension for assessing the mechanisms that underlie listening disorders, auditory evoked potentials add sensitivity to behavioral assessments. Studies on FFR have shown that these potentials provide a more detailed account of acoustic processing in comparison with other AEPs. How pitch, harmonics and timing may be studied in APD through analysis of FFR was also illustrated.

In summary, this chapter reveals how FFR may provide an objective assessment to enhance the monitoring and understanding of APD and provide insight about the mechanisms of neural encoding that underly auditory processing.

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