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Auditory cortical N100 in pre- and post-synaptic auditory neuropathy to frequency or intensity changes of continuous tones

Andrew Dimitrijevic [a,*], Arnold Starr [a], Shrutee Bhatt [a], Henry J. Michalewski [a], Fan-Gang Zeng [b], Hillel Pratt [c]

[a] Department of Neurology, University of California, Irvine, United States
[b] Department of Otolaryngology – Head and Neck Surgery, University of California, Irvine, United States
[c] Evoked Potentials Laboratory, Technion – Israel Institute of Technology, Haifa, Israel

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ABSTRACT

Objectives: Auditory cortical N100s were examined in ten auditory neuropathy (AN) subjects as objective measures of impaired hearing.
Methods: Latencies and amplitudes of N100 in AN to increases of frequency (4–50%) or intensity (4–8 dB) of low (250 Hz) or high (4000 Hz) frequency tones were compared with results from normal-hearing controls. The sites of auditory nerve dysfunction were pre-synaptic ($n = 3$) due to otoferlin mutations causing temperature sensitive deafness, post-synaptic ($n = 4$) affecting other cranial and/or peripheral neuropathies, and undefined ($n = 3$).
Results: AN consistently had N100s only to the largest changes of frequency or intensity whereas controls consistently had N100s to all but the smallest frequency and intensity changes. N100 latency in AN was significantly delayed compared to controls, more so for 250 than for 4000 Hz and more so for changes of intensity compared to frequency. N100 amplitudes to frequency change were significantly reduced in ANs compared to controls, except for pre-synaptic AN in whom amplitudes were greater than controls. N100 latency to frequency change of 250 but not of 4000 Hz was significantly related to speech perception scores.
Conclusions: As a group, AN subjects' N100 potentials were abnormally delayed and smaller, particularly for low frequency. The extent of these abnormalities differed between pre- and post-synaptic forms of the disorder.
Significance: Abnormalities of auditory cortical N100 in AN reflect disorders of both temporal processing (low frequency) and neural adaptation (high frequency). Auditory N100 latency to the low frequency provides an objective measure of the degree of impaired speech perception in AN.

1. Introduction

Auditory neuropathy (AN) is a hearing disorder affecting the encoding and processing of auditory temporal cues that are essential for understanding speech (Rance et al., 2008; Zeng et al., 2005; Zeng and Liu, 2006). The temporal processing deficits can be quantified by abnormal performance on psychoacoustic tasks such as thresholds for detecting brief silent intervals in continuous sounds (gap detection), and thresholds for detecting rapid changes of sound intensity (temporal modulation transfer functions; Zeng et al., 2005). The diagnosis of AN is based on objective physiological tests (Starr et al., 1996) showing normal function of cochlear hair cells (otoacoustic emissions – OAEs; and/or cochlear microphonics – CMs), but abnormal function of auditory nerve and auditory brainstem pathways (auditory brainstem responses – ABRs; Berlin et al., 2003; Rance, 2005; Starr et al., 1996). The physiological bases for auditory perceptual disorders accompanying AN are thought to reflect both altered neural synchrony and reduced magnitude of auditory nerve responses (Starr et al., 2008). Some of the sites of dysfunction causing AN are: (1) pre-synaptic, affecting neurotransmitter release accompanying otoferlin (OTOF) mutations (Marlin et al., 2010; Rodriguez-Ballesteros et al., 2008; Santarelli et al., 2009; Varga et al., 2006; Yasunaga et al., 2000); (2) post-synaptic, affecting initiation of synchronous activity in nerve terminals, accompanying OPA1 mutations due to altered mitochondrial functions (Carelli et al., 2004; Huang et al., 2009); (3) post-synaptic affecting conduction along auditory nerves accompanying mutations causing hereditary motor and sensory neuropathies (e.g., Charcot-Marie-Tooth disease, Butinar et al., 1999; Friedrich's Ataxia, Rance et al., 2008). In all subtypes of AN, the perceptual consequences of AN are similar but may vary

* Corresponding author. Tel.: +949 824 7605; fax: +949 824 2132.
E-mail address: adimitri@uci.edu (A. Dimitrijevic).

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in severity across individuals (Michalewski et al., 2009). Temporal bones from patients with AN show both loss and demyelination of auditory and vestibular nerve fibers and preserved cochlear inner and outer hair cells, findings that correspond to the physiological findings (Bahmad et al., 2007; Hallpike et al., 1980; Spoendlin, 1974; Starr et al., 2003).

Despite the absence of auditory brainstem responses (ABRs), auditory N100 cortical potentials can still be recorded in AN subjects and show promise as an objective measure of auditory perceptual deficits such as threshold for gap detection (Michalewski et al., 2005) and speech perception (Kraus et al., 2000; Kumar and Jayaram, 2005; Michalewski et al., 2009; Narne and Vanaja, 2008; Rance et al., 2002). The study of Michalewski et al. (2009) showed that N100 latency to 1000 Hz brief tone bursts was significantly correlated with both speech perception scores and thresholds for gap detection (Michalewski et al., 2009). In the study to be presented below we test whether N100 measures of auditory cortical potentials to changes of ongoing tones, (“acoustic change potentials” or “C-complexes”; Jones and Perez, 2002; Martin and Boothroyd, 2000) were also related to psychoacoustic deficits in AN since acoustic changes of pitch and or intensity are common during natural speech. We chose changes of frequency or intensity of continuous low (250 Hz) or high (4000 Hz) tones (Dimitrijevic et al., 2009; Dimitrijevic et al., 2008) since AN subjects’ thresholds for detecting frequency change are abnormally elevated for low but are normal for high frequencies (Zeng et al., 2005). Low frequencies are encoded by temporal phase-locked neural auditory nerve and brainstem responses to each period in the stimulus waveforms (Rose et al., 1967) whereas high frequencies are coded primarily by the locus of activation along the basilar membrane. Temporal coding is abnormal in AN (Starr et al., 2008) whereas place coding is normal (Abdala et al., 2000; Vinay and Moore, 2007).

We hypothesized that measures of auditory cortical N100 potentials in AN subjects are: (1) correlated with psychoacoustic measures of auditory temporal processes (e.g., speech comprehension and threshold for gaps); (2) abnormal to changes of 250 Hz but not of 4000 Hz; (3) different in pre- and post-synaptic forms of AN.

2. Methods

2.1. Subjects

Controls: Twenty (8 males, 12 females) subjects (mean age: 21 years, all self-reported right-handed) with normal pure tone thresholds (500 to 8000 Hz) and no history of neurological illnesses participated in the frequency change experiment. A separate group of twelve (6 males, 6 females) subjects (mean age: 24, 11 self-reported “right-handed”) participated as controls in the intensity change study. All subjects gave their informed consent prior to testing. The normative data for controls for frequency and intensity change were previously published (Dimitrijevic et al., 2008; Dimitrijevic et al., 2009).

Auditory Neuropathy: Ten AN subjects were studied (see Table 1). The diagnosis was based on physiological criteria for AN (see Starr et al., 1996) of (1) absent (seven subjects) or abnormal (three subjects) ABRs beyond what is expected for the degree of hearing loss; and (2) preserved activities of outer hair cell function (cochlear microphonics and/or otoacoustic emissions). Table 1 contains details of their demographics: audiological tests (pure tone hearing thresholds, gap detection threshold, speech perception), clinical findings (gene mutations, presence of other cranial or peripheral nerve disorders), used to classify the site of auditory nerve dysfunction as being pre-synaptic (presence of mutation of OTOF), post-synaptic (presence of abnormal cranial and/or peripheral nerve functions, or undefined (absence of relevant gene mutations and normal neurological examinations). We tested the “better” ear except in subjects S4 and S9 who had a unilateral cochlear implant in the untested ear.

The three pre-synaptic subjects (S1–3) had a mutation of OTOF (Varga et al., 2006), expressed as a temperature sensitive transient deafness with loss of both ABR and ability to understand speech (Starr et al., 1998). Two of the three pre-synaptic subjects (S2 and S3) are siblings. The recognition of hearing impairment in pre-synaptic subjects was delayed until speech was developing around 3 years of age when “hearing was lost” during febrile episodes. Other subjects developed hearing complaints as teenagers or adults. The three OTOF subjects were tested when afebrile and showed a delayed Wave V of the ABR without earlier components, normal OAEs, normal or mildly elevated pure tone audiograms, elevated gap detection thresholds, and normal speech perception (88–100%).

The four post-synaptic subjects (S4–7) had absent ABRs, normal OAEs, mild to moderate elevated pure tone audiograms, abnormal gap thresholds, and severely abnormal speech perception (10–50%). All had neuropathies of other cranial and/or peripheral nerves. The three remaining subjects (S8–10) did not have evidence of other cranial or peripheral nerve involvement and were classified as “undefined”. They had absent ABRs, normal OAEs, moderate to severely elevated pure tone audiograms, abnormal gap thresholds, and severely abnormal speech perception (64–80%). The site of the auditory nerve dysfunction in this group is unknown.

2.2. Stimuli

Details of the stimuli have been previously described (Dimitrijevic et al., 2008; Dimitrijevic et al., 2009) for frequency and inten-

Table 1
Summary description of all AN subjects.

–	AN#	Age	Ear tested	ABR	Pure tone thresholds (dB HL)						Speech (%)	Gap detection (ms)	Other clinical	Site of lesion
–	–	–	–	–	250	500	1000	2000	4000	6000	–	–	–	–
S1	30	23	R	7.0	15	15	0	5	-5	5	98	6	OTOF	Pre-synaptic
S2	32	17	L	7.4	30	30	20	25	15	25	100	12	OTOF	Pre-synaptic
S3	33	13	L	7.9	25	15	10	10	0	20	88	11	OTOF	Pre-synaptic
S4*	38	19	L	NR	65	70	25	25	30	35	10	10	Optic NP	Post-synaptic
S5	36	55	R	NR	60	60	20	25	25	35	36	10	Vestibular NP	Post-synaptic
S6	40	13	R	NR	70	70	45	35	35	35	18	11	Optic NP	Post-synaptic
S7*	13	35	L	NR	60	80	40	25	10	10	50	11	Peripheral NP	Post-synaptic
S8	10	28	L	NR	65	60	30	20	10	5	70	5	–	undefined
S9	7	37	R	NR	65	65	50	10	30	25	64	8	–	undefined
S10	27	19	L	NR	10	15	20	80	80	90	80	14	–	undefined
mean	–	–	–	–	47	48	26	26	23	29	61	10	–	–

OTOF = hetereozygous otoferlin mutation; NP = neuropathy; NR = no response; The second column refers to AN subject numbers that were used in previously published manuscripts by our group (see Michalewski et al., 2009).
* =cochlear implant (non-test ear).