Clinical Neurophysiology 125 (2014) 1459–1470

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Inter-trial coherence as a marker of cortical phase synchrony in children with sensorineural hearing loss and auditory neuropathy spectrum disorder fitted with hearing aids and cochlear implants

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ARTICLE INFO

Article history:
Accepted 6 November 2013
Available online 1 December 2013

Keywords:
Auditory neuropathy spectrum disorder (ANSD)
Cortical auditory evoked potentials
P1 CAEP
Inter-trial coherence
Cortical phase synchrony
Sensorineural hearing loss
Development
Cortical maturation
Cochlear implant
Hearing aid

HIGHLIGHTS

- Cortical phase synchrony, as measured by inter-trial coherence (ITC), decreases as sensorineural hearing loss (SNHL) increases.
- Auditory neuropathy spectrum disorder (ANSD) is associated with lower levels of cortical phase synchrony relative to normal hearing and SNHL.
- Cortical phase synchrony increases after cochlear implantation in children with ANSD as a function of experience with the device.

ABSTRACT

Objective: Although brainstem dys-synchrony is a hallmark of children with auditory neuropathy spectrum disorder (ANSD), little is known about how the lack of neural synchrony manifests at more central levels. We used time–frequency single-trial EEG analyses (i.e., inter-trial coherence; ITC), to examine cortical phase synchrony in children with normal hearing (NH), sensorineural hearing loss (SNHL) and ANSD.
Methods: Single trial time–frequency analyses were performed on cortical auditory evoked responses from 41 NH children, 91 children with ANSD and 50 children with SNHL. The latter two groups included children who received intervention via hearing aids and cochlear implants. ITC measures were compared between groups as a function of hearing loss, intervention type, and cortical maturational status.
Results: In children with SNHL, ITC decreased as severity of hearing loss increased. Children with ANSD revealed lower levels of ITC relative to children with NH or SNHL, regardless of intervention. Children with ANSD who received cochlear implants showed significant improvements in ITC with increasing experience with their implants.
Conclusions: Cortical phase coherence is significantly reduced as a result of both severe-to-profound SNHL and ANSD.
Significance: ITC provides a window into the brain oscillations underlying the averaged cortical auditory evoked response. Our results provide a first description of deficits in cortical phase synchrony in children with SNHL and ANSD.

1. Introduction

Auditory neuropathy spectrum disorder (ANSD) is a recently described form of hearing loss. It is estimated that ANSD may be present in 10–15% of infants and children with sensorineural hearing loss (e.g., Uus and Bamford, 2006; Berlin et al., 2010; Roush et al., 2011). While patients with ANSD have essentially normal outer hair cell (OHC) function as measured by otoacoustic emissions (OAE) and the acquisition of a cochlear microphonic, neural synchrony is deficient as evidenced by abnormal or absent auditory brainstem responses (ABR; Starr et al., 1991; Berlin et al., 1998, 2003). The site of lesion in ANSD (i.e., the origin of the dys-synchrony characteristic of ANSD) is thought to be at the level of the inner hair cells (IHC), the synapse between the IHC and the VIII nerve, or the VIII nerve, or any combination of the same (Starr et al., 1996). The degree of hearing loss found in patients with ANSD ranges from mild to profound. Treating ANSD presents a

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1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.11.017

particular challenge to audiologists, as behavioral pure tone thresholds tend to fluctuate, as do speech performance measures (Starr et al., 1996; Sininger and Oba, 2001; Cone-Wesson, 2004; Zeng and Liu, 2006; Wolfe and Clark, 2008; Swanepoel et al., 2013; Doyle et al., 1998). In addition, speech performance measures do not necessarily correspond to the levels of hearing loss noted in ANSD patients (Rance and Aud, 2005; Sharma et al., 2011). Therefore, the severity of dys-synchrony in a given patient with ANSD may not be related to the severity of the hearing loss and cannot be characterized easily with behavioral measures.

It is reasonable to assume that the effects of ANSD on behavioral performance are related to the severity of the underlying neural dys-synchrony (Sharma et al., 2011; Cardon et al., 2012; Cardon and Sharma, 2013). However, traditional physiologic measures such as ABR have limited utility in assessing the severity of ANSD since the short latency ABR recordings require very high levels of precisely synchronous neural firing and are absent or abnormal in all children with ANSD. In contrast, cortical auditory evoked potentials (CAEPs), which occur over much longer latency and are able to absorb greater jitter in the underlying neural synchrony (Michalewski et al., 1986; Kraus et al., 2000), have been more successfully elicited in ANSD patients (see Cardon et al., 2012 for a review). Studies of cortical development using averaged CAEP responses have shown that the obligatory P1 CAEP response latency is a strong predictor of behavioral outcome in children with ANSD (Rance et al., 2002; Campbell et al., 2011; Sharma et al., 2011; Alvarenga et al., 2012; Cardon et al., 2012; Cardon and Sharma, 2013). For example, Sharma et al. (2011) showed that approximately a third of ANSD children in their study had normal P1 latencies. Additionally, they reported a strong correlation between P1 latencies and the IT-MIAS test of auditory skill development for infants and children with ANSD. Furthermore, the children with normal P1 CAEP responses presented with significantly larger P1 peak amplitudes, which may be indirectly indicative of more robust neural synchrony (Starr et al., 2001). Thus far, CAEP studies in ANSD patients have relied on averaged evoked potential recordings; therefore, they were unable to directly examine the underlying cortical synchrony that is assimilated within the aggregate cortical evoked potential response. Given that neural dys-synchrony is a main symptom of ANSD, a direct measure of cortical synchrony could have clinical relevance for the ANSD population.

Time–frequency analyses adopt a different perspective on the evoked response from the traditional time-only analyses where component peaks are averaged, while the remainder of the evoked potential signal is considered to be noise and disregarded. In time–frequency analyses, the focus is on brain oscillations, which can be detected using a time–frequency decomposition of the EEG. When spontaneous EEG is interrupted by a stimulus event (such as a sound), the distribution of EEG phase becomes "phase-locked" to that event (Makeig et al., 2004) and this phase synchronization of brain oscillations can be determined by computing phase relations across single trials. Phase synchronization of brain oscillations within and between cortical areas is a fundamental mechanism involved in information processing and has been found to be critical for feature-binding and other cognitive processes (Tass et al., 1998; Palva et al., 2005). Inter-trial coherence (ITC) is a measure that is computed from single trial EEG, which reflects the temporal and spectral synchronization within EEG, elucidating the extent to which underlying phase-locking occurs. Thus, ITC provides a direct measure of cortical synchrony that is not available in the aggregate evoked response waveform (Makeig et al., 2004).

While time–frequency analyses are relatively new, they have been used in recent studies to examine auditory development and processing. Studies of central auditory maturation have shown that there is an increase in stimulus induced phase synchronization in NH children between childhood and adolescence (Müller et al., 2009; Bishop et al., 2011). An increase in phase synchrony has also been associated with the mismatch negativity event-related potential, which reflects auditory discrimination (Ko et al., 2012). Additionally, changes in cortical phase patterns have been described as an important mechanism that allows for accurate speech discrimination—specifically, the intelligibility of syllabic patterns (Luo and Poeppel, 2007; Howard and Poeppel, 2010). In a recent study from our group (Nash-Kille et al., in preparation), we reported decreased cortical phase synchrony to speech presented in the affected ear of a pediatric patient with unilateral ANSD. In all, these findings suggest that greater phase synchrony seems to underlie better developmental progress and behavioral ability.

In the current study, we examined phase synchrony of cortical oscillations elicited by a speech stimulus in children with ANSD. Our measure of cortical phase synchronization was inter-trial coherence (ITC). Our aim was to examine the extent to which the disruption in neural synchrony, which characterizes children with ANSD, affects cortical phase synchronization, allowing us to better evaluate the severity of the cortical synchrony deficit in children with ANSD. In this report, we examined cortical phase synchrony using ITC in children with ANSD who received intervention with hearing aids and cochlear implants. Children with NH and SNHL (who were also fitted with hearing aids and cochlear implants) were evaluated for comparison with ANSD patients.

2. Methods

2.1. Participants

This study was retrospective in nature, as the cortical auditory evoked potential data used were collected in the Brain and Behavior Laboratory over a period of 15 years. Data were analyzed from a total of 91 children with ANSD. Since the ANSD population is inherently heterogeneous, a large sample size helped to ensure that individual variations would not be missed. Children with ANSD were further divided into those that received no intervention (NI) or received intervention with hearing aids (HA) and cochlear implants (CI). Forty-one children with normal hearing (NH) were included as controls. Fifty children with SNHL were included, who were further divided into children fitted with HAs or CIs. While efforts were made to include children of similar ages in each group, the data were limited by the retrospective nature of the study. Sample sizes and ages for each group are included in Table 1.

Each participant with ANSD was clinically diagnosed through the use of ABR and OAE measures (either through clinician report or access to the tracings). For the children with ANSD with detailed test information ($N = 65$), 100% showed absent or abnormal ABR's with CM reversal (although CM was unclear in one case, OAE results were available), and 44.3% had present OAE's (either DPOAE or TEOAE). 36.9% were clinically diagnosed as having mild to

Table 1
Sample sizes and test ages for participants with normal hearing (NH), sensorineural hearing loss (SNHL), and auditory neuropathy spectrum disorder (ANSD) separated into groups based on types of intervention—either hearing aids (HA) or cochlear implants (CI)—or no intervention (NI). All ages are reported in years.

Group	*N*	Age range	Mean age	Median age
NH	41	0.1–11.1	3.94	2.32
SNHL (HA)	31	0.59–14.81	4.23	2.73
SNHL (CI)	19	2.23–15.29	6.82	6.05
ANSD (NI)	15	0.21–9.95	4.98	5.64
ANSD (HA)	54	0.34–11.55	3.42	2.86
ANSD (CI)	22	1.35–8.39	4.32	3.75