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Thesis for the degree of Philosophiae Doctor

Trondheim, June 2019

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Barn med auditive prosesseringsvansker - en studie av underliggende nevrofysiologiske mekanismer og standardisering av et testbatteri.

Auditive prosesseringsvansker (APD) er en fellesbetegnelse på hørselsvansker som skyldes en dysfunksjon i de sentrale hørselsbanenes bearbeiding av lyd. Typiske vansker er lytting i bakgrunnsstøy, redusert auditiv oppmerksomhet, vansker med å følge muntlige instruksjoner og forståelse av rask eller utydelig tale. Forekomsten varierer fra 0.5 -7 %, med en overvekt blant gutter. Der er i dag mangel på en universelt akseptert definisjon og diagnostiske kriterier for APD.

Denne avhandlingen inneholder tre artikler som fokuserer på normeringen av et norsk testbatteri for diagnostikk av APD og funksjonen av de sentrale hørselsbanene hos barn med lyttevansker. Otoakustiske emisjoner og elektrofysiologiske EEG-målinger gir et innblikk i mekanismene som ligger bak auditiv prosessering, fra cochlea til auditiv korteks og tilbake til hjernestamme og indre øre.

Målsettingen med den første artikkelen var å utvikle et standardisert APD testbatteri til bruk på norske barn. Normalt hørende barn i alderen 7-12 år gjennomgikk lyttetester for auditiv prosessering utarbeidet på norsk. Basert på resultatene ble normal data beregnet og tester for diagnostikk av APD i Norge ble anbefalt.

Artikkel to og tre omhandler resultater fra elektroakustiske og elektrofysiologiske EEG målinger hos barn med lyttevansker, med og uten diagnostisert APD, og normalt hørende barn.

De ytre hårcellene i det indre øre er sentrale i overføringen av lydbølger til nervesignal. Otoakustiske emisjoner (OAE) er målbare lyder som produseres av de ytre hårcellene i det indre øret, cochlea, når øret stimuleres med lyd. Ved bakgrunns støy vil aktivering av nedad stigende sentrale hørselsbaner fra hjernestammen (MOC refleks) redusere aktiviteten til hårcellene og bedre talediskriminasjonen. Redusert MOC refleks er ansett som en mulig årsak til hørselsvansker i bakgrunnsstøy hos barn med APD. I artikkel 2 ble MOC refleksen vurdert ved OAE målinger med lydstimuli presentert i et øre, med og uten støy i det motsatte øret. Forskjellen i OAE med og uten støy (OAE suppresjon) gir et mål på MOC refleksens styrke. Vi fant ingen forskjell i OAE suppresjon mellom de tre gruppene, noe som indikerer at funksjonen i de nedad stigende hørselsbanene er intakt hos dette utvalget barn med lyttevansker, med og uten APD.

Lyd stimuli utløser en reaksjon i de sentrale hørselsbanene i hjernen i form av elektriske impulser (EEG-bølger) kalt auditive evoked potentials (AEP). Ved hjelp av AEP målinger kan man få objektive mål på timing, styrke og anatomisk lokalisasjon av prosesser som ligger bak auditiv

oppfatningsevne. I artikkel 3 undersøkte vi elektrofysiologiske AEP responser i hjernestamme, mellomhjerne og hørselsbark for å se om redusert funksjon i de sentrale hørselsbanene var årsak til lyttevanskene hos barn med APD. Vi fant senere auditiv prosessering og mindre synkroniserte nerveimpulser i banene fra mellomhjernen til hørselsbark hos barn med lyttevansker, både med og uten APD. I tillegg hadde disse to gruppene barn nevrokognitiv dysfunksjon tilsvarende vansker med allokering av oppmerksomhet og arbeidshukommelse.

Funnene indikerer at redusert nevral dysfunksjon kan ha bidratt til vansker med å diskriminere tale- og ikke-tale lyder. Kognitive prosesser som gjenkjennelse, oppmerksomhet og diskriminasjon av auditive stimuli kan ha bidratt til lyttevansker generelt, og APD spesielt. Resultater på APD tester alene bør ikke være styrende for en diagnostisk beslutning. Tverrfaglig utredning med audiologiske tester i tillegg til vurdering av kognitiv og språklig funksjon vil identifisere barnets vansker i et helhetlig perspektiv.

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SUMMARY

Auditory processing disorder in children.

A study of underlying neurophysiological mechanisms, and the standardization of a behavioural test battery.

Individuals with auditory processing disorder (APD) typically report listening difficulties in challenging auditory environments, despite a normal audiogram. APD has been regarded as a disorder in the bottom-up perceptual processing of auditory information in the central auditory nervous system (CANS), and the neurobiological activity that underlies that processing (American Speech-Language Hearing Assosiation, 2005). APD is separate from, but can co-exist with disorders in top-down processes related to cognition and/or language. Recently, this view has been challenged by the notion that APD may include both auditory and cognitive elements, thus advocating the need for a multi-disciplinary approach to diagnosis of APD.

As APD covers several aspects of audition, one test alone cannot address all dimensions of APD, and a battery approach with several behavioural tests for auditory processing (AP) is needed. A number of existing behavioural tests developed for English-speaking populations were considered, and based on the work of Brandt (2010), the Norwegian AP test battery was developed.

Processing of the auditory signal in the CANS is complex and the mechanisms leading to listening difficulties are still poorly understood. Otoacoustic emissions and electrophysiological methods may complement each other by providing a window into the mechanisms underlying auditory processing, from the cochlea to the auditory cortex and back down to the brainstem and ear. The medial olivocochlear reflex (MOCR) is thought to aid speech discrimination (particularly in noise) by selectively inhibiting cochlear amplification. Deficits in the central auditory efferent system, as reflected by reduced suppression of transient evoked otoacoustic emission (TEOAE) with contralateral noise, may be the cause of listening difficulties in background noise found in children with APD.

The auditory middle latency response (AMLR) and the auditory late latency response (ALLR) have been used to assess neural function in the thalamo-cortical pathways essential for processing speech and non-speech signals, and elementary levels of auditory sensory coding and automatic processing, respectively. The P300 has been used to assess discriminative responses thought to represent cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli.

This thesis includes three papers focusing on the underlying neurophysiological mechanisms and diagnostics of auditory processing in children. The aim of paper 1 was to standardise the Norwegian AP test battery for children aged 7-12 years. Normative data were obtained from 268 children with normal hearing, the test-retest reliability was examined and a final AP test battery was presented.

For papers 2 and 3 the study population included 46 children aged 8-14 years with normal peripheral hearing, divided into three groups based on AP assessment: i) children with listening difficulties and APD, ii) children with listening difficulties without APD, and iii) children with normal hearing and no listening difficulties. Some of the children with listening difficulties had comorbid disorders, such as attention disorders, autism or language disorders.

The aim of paper 2 was to investigate the suppression of otoacoustic emissions in children with listening difficulties. No significant group difference was observed for contralateral TEOAE suppression in children with APD, children with listening difficulties (without APD) and children with normal hearing, indicating normal medial olivocochlear (MOC) function. The results did not support the hypothesized link between reduced contralateral suppression of TEOAE and listening difficulties in the presence of background noise in this sample of children with APD.

The third paper aimed at investigating neurobiological aspects of early and late auditory processing and their relationships with AP performance and cognitive function. Three auditory

evoked electrophysiological tests that have been widely used to investigate both auditory and non-auditory systems were used; the auditory middle latency response (AMLR), the auditory late latency response (ALLR) and the auditory P300, and the Integrated Visual and Auditory Continuous Performance Test plus (IVA+). Abnormal AMLR and P300 results were found in children with listening difficulties, with or without APD, compared to normal hearing children. However, no difference was observed between the two groups of children with listening difficulties. This indicate that impaired thalamo-cortical (bottom up) and neurocognitive function (top down) may contribute to difficulties discriminating speech and non-speech sounds. Cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli could contribute to listening difficulties in general and to APD in particular.

This thesis provides a standardised AP test battery for use in Norwegian children. New knowledge in the field of neuroscience is provided, elucidating mechanisms regarding the level of neurobiological problems in the CANS. Similar neural deficits in children with listening difficulties, regardless of APD diagnosis or not, have been identified. The impact of higher cortical regions influencing cognitive processes involved in attention, discrimination and working memory of the acoustic stimuli was identified. Listening difficulties in children may be part of a developmental disorder, with symptoms of impaired working memory capacity or reduced ability to allocate attentional resources in demanding listening situations.

The need for a multidisciplinary approach was recognized, with the evaluation of electrophysiological measures, cognition and AP abilities, not merely the results of AP tests, in order to address the specific needs of the patient.

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As always, I must thank my dear parents Evy Ann and Olav, for your everlasting support and for teaching me that as long as you work hard, dreams do come true. Last, but most of all, I want to thank my beloved husband Torbjørn and our three children Håkan, Louise and Aksel for being the best part of my life. You are a constant reminder that even though a job is important, a family is everything. I love you to the moon and back.

LIST OF PAPERS

Paper 1

MATTSSON, T. S., FOLLESTAD, T., ANDERSSON, S., LIND, O., OYGARDEN, J. & NORDGARD, S. 2018. Normative data for diagnosing auditory processing disorder in Norwegian children aged 7-12 years. *Int J Audiol,* 57**,** 10-20.

Paper 2

MATTSSON, T. S., LIND, O., FOLLESTAD, T., GROENDAHL, K., WILSON, W. & NORDGAARD, S. 2019. Contralateral suppression of otoacoustic emissions in a clinical sample of children with auditory processing disorder. *Int J Audiol,* 1-10.

Paper 3

MATTSSON, T. S., WILSON, W., FOLLESTAD, T., GROENDAHL, K., LIND, O., NICHOLAS, J., NORDGAARD, S. & ANDERSSON, S. 2018. Electrophysiological characteristics in children with listening difficulties, with and without auditory processing disorder. *Int J Audiol,* In review.

ABBREVIATIONS

AAA = American Academy of Audiology;

ABR = auditory brainstem response

AD = attention disorder

ADHD = attention deficit hyperactivity disorder

AEP = auditory evoked potentials

ALLR = auditory late latency response

AMLR = auditory middle latency response

ANOVA = analysis of variance

AP = auditory processing

APD = auditory processing disorder

APDQ = Auditory processing domains questionnaire

ASD = autism spectrum disorder

ASHA = American Speech-Language-Hearing Association

Asust = auditory sustained attention

BMLD = binaural masking level difference

BSA = British Society of Audiology

CAS = contralateral acoustic stimulus

CAEP = cortical auditory evoked potentials

CANS = central auditory nervous system

CBBN = contralateral broadband noise

CD = compact disc

CHAPS = Children's Auditory Performance Scale

CW = competing words

CN = cochlear nucleus

CSC = cognitive spare capacity

daPa = decapascal

dB = decibel

DD = dichotic digits

DP = duration pattern

DPOAE = distortion product otoacoustic emission

ECLiPS = Evaluation of Children's Listening and Processing Skills

EEG = electroencephalogram

ELU model = Ease of language understanding model

ERP = event related potential

ff = fundamental frequency

FP = frequency pattern

FW = filtered words

GIN = gaps in noise

HIST SIN = Høyskolen i Sør-Trøndelag speech in noise

HL = hearing level

Hz = hertz

ICC = intra-class correlation coefficient

ISI = inter stimulus interval

ITI = inter trial interval

ITPA = Illinois test of psycholinguistic abilities

IVA+ = Integrated Visual & Auditory Continuous Performance test +

IQ = intelligent quotient

kHz = kilohertz

kΩ. = kilo ohm

LiSN-S = Listening-in-Spatialized Noise-Sentence test

LOC = lateral olivocochlear

LMM = linear mixed models

MEMR = middle ear muscle reflex

MOC = medial olivocochlear

MOCR = medial olivocochlear reflex

ms = millisecond

NH = normal hearing

OAE = otoacoustic emissions

OHC = outer hair cells

OME = otitis media with effusion

μPa = micro pascal

μsec = microsecond

peSPL = peak equivalent sound pressure level

PP = percentage points

PT = planum temporale

PVCN = posteroventral cochlear nucleus

REA= right-ear-advantage

sec = second

SD = standard deviation

SIFTER = Screening Instrument for Targeting Educational Risk

SOC = superior olivary complex

SLI = specific language impairment

SPL = sound pressure level

SNR = signal-to-noise ratio

SPSS = statistical package for the social sciences

TEOAE = transient evoked otoacoustic emission

ΔTEOAE = absolute suppression

ΔTEOAEn = normalized index.

Vsust = visual sustained attention

WM = working memory

WMC = working memory capacity

Q-Q plots = quantile-quantile plot

BACKGROUND

We live in a world imbued with a rich mixture of complex sounds. Successful acoustic communication requires the ability to extract meaning from those sounds, even when degraded. In everyday communication, we can often hear the words that are being said, even though external factors such as background noise make listening effortful. It has often been stated that we hear with our ears, but we listen with our brains.

During my years as a physician and specialist in oto-rhino-laryngology, I have met many children with listening difficulties. When testing peripheral hearing with pure-tone and speech audiometry, results were often normal despite reports of difficulties hearing in background noise and degraded listening conditions. With no indication of a cochlear hearing impairment, there was no intervention to offer. As a result, children struggled with listening difficulties and problems coping with their daily living. Being a mother, I know that having a child struggling with hearing implies the social as much as the educational aspects of life, adding an extra piece to the puzzle of daily living. Not being able to help these children, was unsatisfactory for me.

When attending the American Academy of Audiology conference in mid-2000, I first learned about auditory processing disorder (APD). This encounter showed me that there was more to hearing than the hair-cells in the inner ear. This initiated my commitment to spread knowledge of APD and the important role the central auditory system plays in hearing. As a professional, I wish to provide the best possible care to children with hearing impairment, including APD, and to improve knowledge of aetiology, diagnostics and rehabilitation. This thesis is the result of this commitment, providing a standardised auditory processing (AP) test battery to the Norwegian population and new knowledge of the underlying neurobiological mechanisms of auditory processing.

1. INTRODUCTION

Anatomy and physiology of the central auditory nervous system

Sounds originate as vibrations in the air around us. The auditory system converts these vibrations into electrophysiological signals for the brain to interpret. To understand the processes behind auditory processing and listening, we need to know the anatomy and physiology of the central auditory nervous system (CANS) with which it is intimately intertwined. Therefore, this section aims to provide a brief overview of some of the main aspects of anatomy and physiology of the CANS. The central auditory nervous system extends from the cochlear nucleus (CN), through the superior olivary complex (SOC), via the lateral lemniscus fibre tract, to the inferior colliculus in the midbrain, on to the medial geniculate body, and finally to the auditory cortex, as illustrated in Figure 1. Parallel processing continues throughout the ascending pathway.

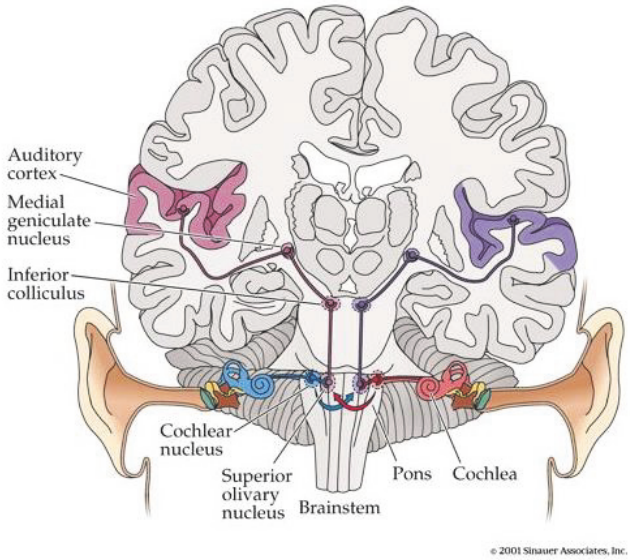

Figure 1. The central auditory nervous system, from the cochlear nucleus to the auditory cortex.

The cochlear nucleus

As the auditory nerve reaches the brainstem, it terminates in the ipsilateral cochlear nucleus, located between the medulla and the pons. The CN is the first obligatory synaptic station from which all ascending pathways have their origin. It consists of three divisions, all of which are connected to the auditory nerve: the anterior ventral, the posterior ventral and the dorsal cochlear nucleus. This is the first step in the parallel processing, which continues throughout the ascending pathway, with connections allowing stimuli presented monaurally to activate both sides of the auditory cortices (Stebbings et al., 2014). Leaving the CN, fibres project mostly to the contralateral inferior colliculus through the stria of Monaco (dorsal), the stria of Held (intermediate) and the trapezoid body (ventral), although some fibres project to the superior olivary nuclei (Cant and Benson, 2003). The three fibre tracts cross the brainstem and form the lateral lemniscus fibre tract, as they reach the opposite side, together with some fibres from the superior olivary complex on that side (Pannese et al., 2015).

The lateral lemniscus then projects to the central nucleus of the inferior colliculus. However, not all fibres cross over the brainstem. Fibres from the ventral cochlear nucleus also reach the ipsilateral inferior colliculus. This is the first point of connection between the two sides of the auditory pathway. In addition, some fibres connect the ventral cochlear nucleus to the facial and trigeminal motor nuclei (Cant and Benson, 2003).

Superior olivary complex

The superior olivary complex receives information from the ipsilateral and contralateral cochlear nucleus, and plays a part in directional hearing by comparing timing and intensity inputs from the two ears (Stebbings et al., 2014). The complex contains three main nuclei: the medial and superior olivary nucleus and the trapezoid body nucleus.

Lateral lemniscus

While the ventral nuclei of the lateral lemniscus mainly receive contralateral input, the dorsal nuclei integrate input from both ears, and is thus involved in binaural hearing. The lateral lemniscus projects axons to the inferior colliculus on both sides (Ono and Ito, 2015).

Inferior colliculus

Located in the midbrain, the inferior colliculus is the largest nucleus in the CANS. It acts as a relay station for both afferent and efferent neurons in addition to comparison of intensity between the two ears. Three groups of nuclei form this structure, the central and external nuclei and the dorsal cortex of the inferior colliculus (Ono and Ito, 2015).

Medial geniculate body

Fibres from the inferior colliculus terminate in a relay nucleus called the medial geniculate body, located in the thalamus (Ono and Ito, 2015). The ventral, medial and dorsal divisions form this structure. The ventral division receives projections from the central nucleus of the inferior colliculus. This projection, called the brachium, has ten times the number of fibres seen in the auditory nerve, implying an important role in signal processing (Winer, 1984).

Auditory cortical areas

From an anatomical perspective, the auditory cortex can be defined as the regions of the cerebral cortex that receive information from one or more divisions of the medial geniculate body (Hackett, 2011). The auditory cortex occupies the posterior portion of the superior temporal cortex, including Heschl's gyrus, the planum temporale, and some portion of the posterior superior temporal gyrus.

The primary auditory cortex lies in the transverse Heschl's gyrus. Concentric belts formed by the secondary and higher order auditory areas surround the primary auditory cortex (Da Costa et al., 2011). Projections from the medial geniculate body provide input to the primary auditory cortex and

the posterior auditory field, while the anterior auditory field is in contact with the ipsilateral posterior thalamus complex. Fibre tracts from the primary auditory cortex reach other regions, both within the auditory cortex and associated cortices. Thus, auditory information is integrated with information originating in other sensory modalities and various regions of the central nervous system. The two auditory cortices are connected by the corpus callosum, through which a considerable amount of information is passed (Henkin et al., 2015). The connections of the auditory cortex differ across its six layers.

The descending pathways

The ascending pathway has a parallel descending pathway, reaching all auditory nuclei of the brainstem. The descending pathway emerges from the fifth and sixth layers of the primary auditory cortex, and is involved in modulation of ascending information with loops allowing circulation of information (Schofield and Cant, 1999).

The olivocochlear system

The olivocochlear system provides efferent innervation thought to modulate cochlear activity (Kemp, 1978, Kemp and Chum, 1980). Its fibres travel from the region of the superior olivary complex in the brainstem through the vestibulocochlear nerve (VIIIth nerve) to the organ of Corti along two pathways; the MOC fibres that originate on the medial side of the SOC and terminate mainly at the base of the outer hair cells (OHC), and the lateral olivocochlear (LOC) fibres that originate on the lateral side of the SOC and terminate on the auditory neurons at the base of the inner hair cells (Rasmussen, 1946, Warr and Guinan, 1979, Warr et al., 1997). The MOC pathways have both crossed (crossing to the other side of the brainstem) and uncrossed fibres, whereas the contralateral pathway involves mainly uncrossed fibres in what are thought to be similar numbers in humans based on estimates drawn from animal studies (Guinan et al., 1983, Ryan et al., 1990).

Following an acoustic stimulus, the MOC fibres act to suppress OHC function both ipsilaterally and contralaterally, providing the neural substrate for the MOC reflex (Guinan, 2006). For the ipsilateral MOCR, the stimulated cochlea excites auditory nerve fibres that innervate reflex interneurons in the posterior ventral cochlear nucleus. These interneurons cross the brainstem to innervate MOC neurons on the contralateral side that cross back to complete the ipsilateral MOCR in the originally stimulated cochlea (Liberman, 1988a, Liberman, 1988b). The contralateral MOCR crosses in the trapezoid body and involves mainly uncrossed MOC fibres. Both the ipsilateral and contralateral MOCR act to hyperpolarize OHC in their target cochlea, which reduces OHC and basilar membrane motility and attenuates the cochlear amplifier effect.

Maturation of the CANS

The human auditory system is fully developed at birth; however, different elements mature subsequently at different rates (McGee and Kraus, 1996, Ponton et al., 1996, Johnson et al., 2008, Sussman et al., 2008, Muller et al., 2009). The cochlea is mature at the age of 6 months (Abdala and Keefe, 2012), the auditory brainstem matures around the age of 4 years (Ponton et al., 1996, Johnson et al., 2008), and the corpus callosum becomes fully myelinated at around 11 years of age (Obrzut and Pirozzolo, 1981). Although evidence of myelination is present through the cortical layers by six years of age, increased myelination of the neural pathways continues into adolescence (Hallett and Proctor, 1996). This myelination allows for more rapid transmission within and between cortical structures.

The maturation of auditory processing (AP) skills follows the normal development of the CANS (Eggermont and Ponton, 2003). Some auditory processing skills develop relatively early in life, while others continue into adolescence or even adulthood. The left hemispheric dominance for speech is established at the age of four, but as children mature and language abilities develop, the

dichotic processing abilities improve in both ears, leading to decreasing ear differences with increasing age (Katz, 1962, Kimura, 1963, Keith, 2000, Moncrieff, 2011).

Temporal resolution matures during childhood (Davis and McCroskey, 1980, Irwin et al., 1985, Wightman et al., 1989, Hall and Grose, 1994a, Trehub et al., 1995). However, there are some controversies regarding the developmental time course, with reports of temporal resolution reaching adult levels by the age of six years (Wightman et al., 1989, Hall and Grose, 1994a), or eleven years (Irwin et al., 1985). Others have shown that temporal resolution approaches adult levels by age 6 at high frequency regions, while maturation continues beyond 10 years of age at low frequencies (Grose et al., 1993).

Previous work has suggested that development in frequency discrimination may not be fully mature until 10 years of age (Maxon and Hochberg, 1982, Sinnott and Aslin, 1985, Olsho et al., 1987, Moore et al., 2011) . Duration discrimination varies with age, young children having poor performance in discriminating short stimulus durations, with maturation continuing into adulthood (Elfenbein et al., 1993, Jensen and Neff, 1993, Moore et al., 2011).

Binaural interaction is dependent on accurate temporal resolution and coding of inter-aural time and amplitude cues. The neural connections underlying binaural processing are present at birth, but mature during childhood (Moore, 1985, Kapfer et al., 2002). Some studies have found an age effect on children aged 6 to 12 years, suggesting a developmental improvement in binaural interaction (Hall and Grose, 1990, Hall et al., 2004), while others have not shown improvement by age (Roush and Tait, 1984, Moore et al., 2011).

Speech perception and the temporal lobe

The first cortical region to be activated during speech perception, is the primary auditory cortex. The ascending auditory signal will at this level serve as the principal input to the secondary areas, which communicate the information to higher-order areas. The left hemisphere's crucial role in speech processing and production has been established since the 19th century. The classic models of speech production and comprehension, such as the Wernicke-Lichtheim-Geschwind model, suggested a cortical network in the left hemisphere consisting of Wernicke's area, Broca's area and the angular gyrus, and their interconnections through the arcuate fasciculus pathway (Geschwind, 1970).

However, the simplicity of these classic models now seems obsolete considering the advancements of cognitive neuroscience and neurophysiological research, leaving questions regarding localization of speech perception in the brain to be readdressed (Hickok and Poeppel, 2007, Tremblay and Dick, 2016) . The classical view of a pure left-lateralized network is challenged by results from functional neuroimaging studies demonstrating that both hemispheres are activated by sound, depending on the speech processing task (Hickok et al., 2008).

In this thesis, we use the term speech processing to refer to any task involving aurally presented speech. Further, speech perception and speech comprehension are two distinct functions. The speech perception process is mainly an automated processing of auditory signals and is used when referring to sub lexical tasks (such as syllable discrimination). Auditory perception, that is the perceptual processing of auditory information in the CANS (e.g. auditory processing, AP), is considered to be a part of speech perception. While speech comprehension is a complex, multifunctional task that not only requires processing of auditory information; it requires attention, working memory, and integrative processes in order to understand not only single words but also sentences and narratives. AP is the link between sound detection and the extraction of meaning

from the signal, and inefficient AP may result in compromised listening ability (Bamiou et al., 2006).

Hemispheric asymmetry in speech processing

Speech processing engages a clearly defined cortical network involving the classical language areas in the left inferior frontal cortex and superior temporal gyrus. Functional imaging studies and animal studies have revealed different spectro-temporal resolutions and processing properties of the left and right auditory cortex. It is widely accepted that the left hemisphere is dominant for processing fast temporal information, and the right hemisphere is dominant for processing tonal information such as pitch processing (Zatorre et al., 2002, Schonwiesner et al., 2005, Boemio et al., 2005). The planum temporale (PT) is an important structure in the secondary auditory cortex, also involved in early auditory processing of non-verbal stimuli, spatial hearing as well as auditory imagery (Specht and Reul, 2003, Isenberg et al., 2012).

Adequate perception of speech requires the ability to discriminate between rapidly changing stimuli, as the listener must be able to differentiate between consonants and between places of articulation. Consonants are acoustically more complex than vowels, hence the left auditory cortex is expected to have a higher processing ability of consonants then the right auditory cortex (Zatorre et al., 2002, Boemio et al., 2005, Isenberg et al., 2012, Specht, 2014). This has been investigated by using various dichotic listening paradigms, where stimuli are simultaneously presented to the two ears. Results have shown preference for consonant-vowel syllables presented to the right ear. Since the ipsilateral auditory pathways are assumed to be suppressed under dichotic listening, the presence of a right ear advantage (REA) is accepted as reflecting the language dominant left hemisphere (Hugdahl and Westerhausen, 2016).

On the other side, some dichotic listening studies have suggested a right hemispheric dominance when speech is processed in the presence of noise (Specht and Reul, 2003, Sequeria et al., 2008).

This could be related to the preference for long time scales of the right hemisphere. An increased ability to analyse the input signal over a longer timescale could possibly allow for more efficient averaging out of noise, thus isolating the speech signal.

Other dichotic neuroimaging studies using speech and non-speech sounds that hold the same temporal and spectral modulations found in natural speech, reported that left hemispheric domination for language requires the presence of linguistic information. The authors concluded that the left hemispheric dominance in speech processing cannot rely solely upon low-level acoustic features of the speech signals, but necessarily involves higher-order lexical systems (Rosen et al., 2011).

Based on recent neuroimaging studies, a new model of speech and language processing is emerging. Effective processing of speech seems to take place in hierarchical network structures, with different regions in both hemispheres constantly interacting. However, listening to words activates the middle and superior temporal gyri bilaterally, while listening to sentences engages regions in the left prefrontal cortex involved in processing semantics and syntax (Peelle, 2012). The pathways linking these regions represent different functional streams. The ventral route, also called the "what" stream, is involved in mapping sound to meaning, and runs along the posterior-anterior axes of the temporal lobe. The dorsal route, also called the "how" stream, is related to articulatory processing, originating in the posterior temporal lobe running through the parietal and premotor areas to reach the inferior frontal areas (Hickok and Poeppel, 2004, Hickok and Poeppel, 2007, Rauschecker and Scott, 2009, Hickok, 2012). While the dorsal stream is assumed to be strongly left lateralized in adults, the ventral stream is assumed to be bilateral, at least in its posterior part. This would explain why brain lesions of the temporal lobe often affects speech production more than speech perception (Hickok and Poeppel, 2007, Rauschecker and Scott, 2009).

The dynamic distribution of work flow between and across the hemispheres seems to be essential for an effective speech comprehension in various listening scenarios, with a key

component being the right hemisphere's ability to discriminate speech in noise (Specht and Reul, 2003, Sequeria et al., 2008). The left hemisphere's superiority for speech comprehension could still hold true under more optimal listening conditions and when the speech is intelligible, thus involving linguistic information. Results from dichotic listening studies demonstrating that the REA is modulated by the stimuli used and presentation methods, further show that speech comprehension is a dynamic process involving neuronal networks spread across both hemispheres.

However, the simplified understanding of auditory processing disorders being defined as "difficulties in the perceptual processing of auditory information in the central auditory nervous system and the neurobiological activity that underlies that processing" (American Speech-Language Hearing Assosiation, 2005), now seems obsolete considering new knowledge of the dual streams underlying speech and language processing. This is reflected in the recent British position statement on APD (British Society of Audiology, 2018).

The audiogram

The pure-tone audiogram serves as a critical tool in the diagnosis of many audiological and otology disorders, and is important in providing information regarding type, degree and configuration of hearing loss. Audiometric related events date back to 377 BC, when Hippocrates reported clinical findings of hearing loss (Feldman, 1970). In 1879 Hughs created a manual audiometer, with Hartman creating the first auditory chart in 1885 (Vogel et al., 2007). The first electronic audiometers were manufactured in the 1930s, and technological advances have occurred since, with computer based platforms.

For more than 70 years, the pure-tone audiogram has been considered the gold standard for normal hearing (Johnson, 1970). However, even detailed pure-tone threshold audiometric measures are insufficient to characterise hearing ability, and additional auditory measures (e.g.

psychoacoustic or temporal processing) will be able to explain individual differences (Humes et al., 2013). Cognitive ability plays an important role in speech understanding, arguably the most important function of human hearing. The cochlea, in addition to providing exquisitely sensitive transduction of sounds, also contributes to spectral, temporal and supra-threshold aspects of sound coding (Oxenham and Bacon, 2003). All these aspects of hearing critically underpin speech perception. The accumulating evidence of the pure-tone audiogram's limitations has penetrated all aspects of audiology. In addition, advances in neuroscience have begun to emphasise the considerably larger role of the CANS in hearing and related disorders. As a result, attention has turned from almost exclusive focus on the auditory periphery to include more central mechanisms.

The history of APD

The foundation for the first neurobiology of language models can be traced back to Broca's pioneering clinical work in 1861 (Broca, 1861). Based on observations of brain lesions in patients with aphasia, he described the left posterior part of the inferior frontal gyrus as site for language articulation. The inferior frontal area is referred to as Broca's area.

Some years later, Wernicke reported lesions in the superior temporal gyrus in patients who had difficulties understanding spoken language, despite fluent articulation. He concluded that this region, referred to as Wernicke's area, was crucial to language comprehension, and provided the first description of a language model based on brain anatomy (Wernicke, 1874/1969). The model argued for functional specialisation of brain regions, with neuroanatomical pathways communicating among brain regions, and was revolutionary in its approach to brain-behaviour relationships. He was the first to ascribe to a brain region a role in auditory perception, and proposed that acquired lesions to the left temporo-parietal cortex, called Wernicke's aphasia, affect areas involved in semantic, phonological and auditory processing (Wernicke and Friedlander,

1883). Wernicke's aphasia is characterized by severely impaired single-word comprehension with reduced temporal processing and repetition with fluent but disordered speech (Blumstein et al., 1977, Baker et al., 1981, Ogar et al., 2011, Robson et al., 2013). Based on the symptoms, Wernicke's aphasia could be described as APD. However, the dominance of linguistic processing may overshadow what may be an important and independent auditory processing impairment.

Freud introduced the term auditory agnosia in his monograph of 1891, where the impaired recognition of non-verbal sounds and noises was defined in his discussion of aphasia and related disorders (Freud, 1891). In 1926, the neurologist Henry Head were the first to separate auditory processing from language deficits. Based on his work on neurologically war-injured soldiers, he described difficulties understanding speech in noise despite normal pure tone hearing. In his monograph, he concluded that speech perception defects were located at a lower level than aphasia (Head, 1926).

While acknowledging researchers such as Broca, Wernicke, Head and Freud as the first to link brain injury and disturbances of receptive and expressive language, the first conceptualisation of APD is attributed Myklebust. In 1954 he described a group of children with delayed language development having difficulties recognising speech in noise despite normal pure tone thresholds. (Myklebust, 1954). Myklebust considered two conditions which could underlie such a presentation. The first was an auditory agnosia caused by extensive damage or lesion to the auditory cortex, including receptive areas for hearing, resulting in the "incapacity to understand the meaning of environmental sounds in general." The second was a disturbance in primary function of auditory perception, resulting in difficulties structuring auditory stimuli for possible selection for attention and behaviour.

Following Myklebust, a number of reports demonstrated auditory deficits in people with central nervous system disorders. However, these deficits were manifested only on tests more complex than pure-tone audiometry. In 1954 Bocca reported that patients with temporal lobe lesions had normal

auditory thresholds, but difficulties understanding filtered speech (Bocca et al., 1954). Later, Kimura described problems repeating dichotic digits in epilepsy patients after surgical removal of one temporal lobe (Kimura, 1961b). Jerger reported that lesions of the central auditory nervous system (CANS) had apparent effect on auditory behaviour only in tasks placing heavy demands on the auditory system (Jerger, 1960). Katz used staggered spondaic words to assess the integrity of the CANS in patients with brain anomalies (Katz, 1962). The work of these researchers drew attention to the need for evaluating patients with CANS lesions with audiological tests sensitized to central auditory dysfunction, and the futility of pure tone thresholds to assess CANS function.

Approaches to APD

When tracing the history of auditory processing as a construct and topic of research, it becomes clear that there are distinct strands of research that have developed largely independently of each other. Different groups of researchers with different goals, assumptions and methods, have most often been involved in theories about three disorders: APD, specific language impairment (SLI) and dyslexia. This has led to multiple definitions and the lack of a gold standard test for the determination of the presence of APD.

With this in mind, we can better understand points of convergence and controversy within and among the different branches of the literature and how research has influenced clinical practice. Jerger identified three such strands: the audiological approach, the psychoeducational approach, and the language processing approach (Jerger, 2009). Since Jerger, further conceptualisations of APD have gained prominence, and will be discussed briefly.

Audiological

It was not until the mid-1980s that the distinct audiological approach to APD gained momentum. This approach grew out of the earlier observations of brain-lesions and perceptual

problems. Over the next decades, considerable amounts of research amassed in the area of central auditory dysfunction, mainly based on studies with well-defined lesions in the CANS in adults (Musiek et al., 1980, Musiek, 1983b, Musiek, 1983a, Keith, 1986, Musiek and Pinheiro, 1987, Musiek et al., 1990, Griffiths et al., 1999, Wilson et al., 2003).

The audiological approach emphasises APD as being a site-of-lesion, or at least a dysfunction, in the CANS thought to affect how sound is processed, and potentially affecting auditory behaviour. The lesions potential downstream effects on processes performed by other sites in the brain depending on auditory input, are acknowledged.

Tests and test batteries are developed to assess central auditory processing abilities. The most popular tests are the SCAN: Screening test for Auditory Processing Disorders (Keith, 1986), SCAN-C for children (Keith, 2000), the Staggered Spondaic Words test (Arnst and Katz, 1982) and the Pediatric Speech Intelligibility test (Jerger et al., 1983). Musiek and colleagues have shown a battery of tests of dichotic digits, frequency patterns, filtered speech and competing sentences being sensitive to the superior temporal gyrus and surrounding areas in adults (Musiek et al., 2011). Less research on tests of this type has been performed on children (Galaburda and Kemper, 1979, Musiek et al., 1985, Boscariol et al., 2009, Boscariol et al., 2010).

According to Musiek, there is no true gold standard auditory test to which one can compare test results (Musiek, 1999). The closest standard is a group of individuals with well-defined lesions of the CANS. Thus, the tests' diagnostic accuracy (sensitivity and specificity) for a lesion of the CANS is presumed valid for individuals with APD. The above tests still represent the core assessment battery used to diagnose APD.

Psychoeducational

It took more than ten years for Myklebust's ideas to become formalized in the widely popular Illinois Test of Psycholinguistic Abilities (ITPA) (Kirk et al., 1968). In the perceptual-

motor domain, the ITPA had five auditory subtests: auditory reception, auditory association, auditory sequential memory, auditory closure and sound blending. Poor performance on one of these subtests was taken as evidence that the child had an auditory perceptual problem. These perceptual problems formed the foundation of the discrete-skill, psychoeducational view of language development that influenced the assessment and treatment of children with APD and language impairments in the 1960s and 1970s.

The psychoeducational approach to APD focuses on abilities believed to be necessary for learning and language, with tests and test batteries developed to assess these specific auditory skills. Researchers, often speech-language pathologists and psychologists, ask whether an APD could be the cause underlying dyslexia and SLI through psycho-physical tasks, (discrimination of tones and syllables). The Cattell-Horn-Carrol theory of cognitive abilities is a comprehensive example of psychoeducational approach that encompasses auditory processing (Flanagan and Dixon, 2014). Most new and revised intelligent batteries are based on Cattell-Horn-Carrol theory.

This approach emphasises APD as being a deficit in independent, measurable set of auditory abilities likely to affect auditory behaviour, and does not emphasize the neuroanatomical origin of these disabilities.

Language processing

Based on studies on patients with acquired language disorders and aphasia, Efron (1963) claimed that a language disorder could arise from deficits in central auditory processing, more specifically temporal processing (Efron, 1963). The idea that the temporal aspect of central auditory processing could underlie language disorders, was taken up and adapted to SLI and dyslexia.

In a series of papers, Tallal and colleagues presented the *rate processing constraints hypothesis*. Research on children with SLI showed that a primary temporal processing deficit could restrict higher auditory processes and reduce the perception of rapid and sequential transients within speech

(Tallal and Piercy, 1973, Tallal and Piercy, 1974, Tallal, 1976, Tallal, 1980, Tallal et al., 1993, Tallal, 2004). From this association of auditory deficits sprang the claim that the auditory problem *caused* the language problem.

In the 1990s, a sudden growth of interest in this theme emerged, for at least three reasons. First, an increased awareness of the high incidence of language impairments was coupled with an emphasis on academic performance in children. As many as 5-10% of children were reported as having SLI or dyslexia, with much overlap of the groups (Bishop et al., 1999, McArthur et al., 2000). Second, the development of a computer based rehabilitation program, Fast for Words, which reported remarkably results in ameliorating SLI through improving AP (Merzenich et al., 1996, Tallal et al., 1996). Finally was the demonstration of a dramatic auditory deficit in SLI children with the psychoacoustic task backward masking, showing 40dB difference in median threshold compared to normally developing children (Wright et al., 1997).

The language processing approach to APD focuses on abilities believed to be important for the comprehension and production of spoken language and/or literacy. Tests and test batteries are developed to assess specific auditory abilities thought to be important for language acquisition and learning. Researchers appreciate the top-down influence of language knowledge, and tend to emphasise the unique properties for speech and how speech may be processed differently from other auditory stimuli. This approach emphasises APD as being a deficit in the AP abilities related to language and learning.

Modality specificity

In the 1990s, the general lack of agreement on various topics in the area of APD, due in large part to reliance on expert opinion rather than controlled experiments, led Cacace and McFarland to advocate a new way of thinking. The concept of modality specificity as a criterion for diagnosing APD, and the need to differentiate APD from other disorders was launched (McFarland and Cacace, 1995).

This approach argues that APD is a deficit in processing of auditory stimuli only, that is not due to peripheral hearing loss, and as such is modality specific (Cacace and McFarland, 2005). Based on this idea, deficits should not be apparent, or at least manifested to a lesser degree, when similar types of information are presented to other sensory modalities. APD should therefore be distinguishable from cognitive, language related and/or attentional problems.

According to the signal detection theory, even a simple detection experiment could be viewed as reflecting multiple factors (Green and Swets, 1974). Tests could often be confounded by non-auditory abilities, such as attention, memory and linguistic problems (Cacace and McFarland, 1998). Therefore, test batteries, including matched tasks to assess specific skills in multiple sensory modalities, were developed to evaluate specific skills in both auditory and non-auditory modalities (Cacace et al., 1992, McFarland and Cacace, 1997, Bellis and Ross, 2011). By systematically varying the nature of the stimulus while holding all other factors constant, interpretations of deficient performance in terms of supra-modal, cognitive and/or linguistic process could be ruled out.

The modality specificity approach seeks to determine if an individual who fails tests of APD has (Cacace and McFarland, 2005):

1. specific perceptual problems processing auditory information, a “pure APD”.
2. auditory perceptual problems that coexist with perceptual problems in other modalities
3. no auditory perceptual problems, but problems in other modalities, such as motivation, memory, attention or motor skills

Auditory attention

The approach to APD based on auditory attention emphasises APD as being primarily a deficit in auditory attention (Moore et al., 2010). Top-down processes typically associated with cognition,

in particular auditory attention, are emphasised as more frequently associated with APD than bottom-up processes.

Moore and colleagues argue that APD should be defined by the dominant findings of the listening problems, which are most often reduced general cognitive ability and auditory attention (Moore, 2012). This notion stems from reports showing that listening performance in the classroom was poorly predicted by a composite measure of AP and demographic factors. The best predictors were cognitive test scores and variable individual performance on the AP tests (Moore et al., 2018). The influence of cognition and attention on listening difficulties has gained support from subsequent studies (Dhamani et al., 2013, Ahmmed et al., 2014, Sharma et al., 2014a, Tomlin et al., 2015).

Hierarchical assessment of listening difficulties

This approach acknowledges the lack of a unified definition of APD, and argue that efforts should focus on the diagnosis and management of real-life listening difficulties, and less on defining APD (Dillon et al., 2012). A hierarchical test battery, which begins with an overall test of listening to identify impaired ability to understand speech in difficult listening conditions, is advocated. If an impairment is identified, a different set of detailed tests will be performed, focusing on the failed test(s) from the master test battery.

This approach attempts to minimise the number of tests used to identify the primary source of listening difficulties. Disorder-specific remediation can then be given. The Listening-in-Spatialized Noise-Sentence test (LiSN-S) can be interpreted in a hierarchical manner, and is recommended (Cameron and Dillon, 2008). The Australian APD position statement favours the hierarchical approach to APD assessment (Dillon and Cameron, 2015).

Clinical entities

This approach focuses on the ambiguity of APD definitions, and the need for identification of legitimate disorders, or clinical entities, in the field of speech and hearing (Cowan et al., 2009, Vermiglio, 2014). Vermiglio argues for the use of nosography, the systematic description of diseases, when assessing APD (Vermiglio, 2018). In order to be defined as a clinical entity, APD should be considered within the four Sydenham-Guttentag criteria: 1. possess an unambiguous definition, 2. represent a homogenous patient group, 3. represent a perceived limitation, 4. facilitate diagnosis and intervention.

The diagnostic accuracy for most tests used to diagnose APD are referenced to patients with well-defined lesions of the CANS. Vermiglio argues that a behavioural test with known diagnostic efficiency for a CANS lesion has unknown diagnostic efficiency for APD, due to the non-existence of a reference standard. As the construct of APD fails to meet these four criteria, it should be abandoned in favour of identifying specific auditory disorders that meet these criteria. Candidates in this regard include a speech recognition-in-noise disorder (Vermiglio, 2014) and spatial processing disorder (Cameron and Dillon, 2008, Cameron et al., 2014).

CNS networks

Traditional inside-out models characterise the auditory system as series of rely stations along an assembly line, each with distinct functions (Winer and Schreiner, 2005). However, an emerging trend in neuroscience considers the interplay of multiple processing stations and the give and take between cortical and subcortical systems underlying human behaviour (Bajo and King, 2012, Atiani et al., 2014). Kraus and colleagues proposed a complementary outside-in approach that views the auditory system as a distributed, but integrated circuit. AP should be seen as a reflection of this integrated network. Cognitive, sensorimotor and reward systems optimise the AP and auditory learning that underlie language and communication. Both expertise and disorder should be considered from a common standpoint of neuroplasticity (Kraus and White-Schwoch, 2015).

In recent decades, a new field of interdisciplinary research concerning the interaction between human hearing and cognition has evolved; cognitive hearing science. The core research question is the nature of the interaction between bottom-up and top-down processes that promote understanding in various communication conditions, in any modality (Arlinger et al., 2009). The main topics of research are language processing in challenging listening conditions, the use of auditory communication technologies or the visual modality to boost performance, and changes in performance with development, aging and rehabilitative training. New models concerning the interactions between auditory and cognitive processing during speech processing and language comprehension have evolved (Baddeley and Patterson, 1971, Ronnberg, 2003).

Evolving concept of auditory processing

Children with auditory processing disorders encounter listening difficulties despite having normal or near-normal hearing acuity. While not diagnostic of APD, frequently reported symptoms are difficulties understanding speech in noisy environments, problems locating the source of a signal, failure to respond correctly to verbal information, frequently asking for repetition of information, reduced attention to auditory information, distractibility and problems with oral and written language (American Academy of Audiology, 2010).

Over the past two decades, the dominant conceptualisation of APD has been as a disorder in the bottom-up processing of sound inside the central auditory system (CANS) that is separate from but can co-exist with disorders in top-down processes related to cognition and/or language (American Speech-Language Hearing Assosiation, 2005, American Academy of Audiology, 2010). In this conceptualisation, bottom-up AP is deemed relevant because it affects the human experience of sound. The American Speech-Language-Hearing Association (ASHA) defines APD as being "difficulties in the perceptual processing of auditory information in the CNS and the

neurobiological activity that underlies that processing and gives rise to electrophysiological auditory potentials". In this context, AP includes the auditory mechanisms that underlie abilities or skills including sound localisation and discrimination, recognition of auditory patterns, temporal processing or auditory performance in competing acoustic signals or degraded signals (American Speech-Language Hearing Assosiation, 2005). The working groups of ASHA 2005 and American Academy of Audiology (AAA) 2010 do not make any distinction between speech and non-speech information.

Recently, the British Society of Audiology (BSA) updated its definition of APD as being "characterised by poor perception of speech and non-speech sounds" that "has its origins in impaired neural function, which may include both the afferent and efferent pathways of the central auditory nervous system (CANS), as well as other neural processing systems that provide 'top-down' modulation of the CANS" (British Society of Audiology, 2018). The BSA (2018) approach to APD challenges the dominant conceptualisation of APD (American Speech-Language Hearing Assosiation, 2005, American Academy of Audiology, 2010), arguing that APD may include both auditory and cognitive elements, thus advocating the need for a multi-disciplinary approach in diagnosing APD. This argument is based on research suggesting bottom-up AP could be of limited relevance to listening, learning and language; and that APD specifically, and listening difficulties generally, are the consequence of (top-down) cognitive, particularly attention and language disorders outside the traditional auditory system (Moore et al., 2010, de Wit et al., 2016).

The second challenge to the dominant conceptualisation of APD, is the hierarchical approach to APD, which deems bottom-up AP to be relevant to listening and learning at the same degree as cognitive and language abilities (Dillon and Cameron, 2015). While favouring the dominant conceptualisation of APD, this approach de-emphasises the importance of diagnosing APD in favour of identifying the primary sources of the person's listening difficulties and responding appropriately.

In addition, multiple professional societies and groups around the world have published guidelines, position statements and/or recommendations to standardise approaches to APD (Speech-Language & Audiology Canada, 2012, Esplin and Wright, 2014, Dillon and Cameron, 2015, de Wit et al., 2017, Iliadou et al., 2018). These will not be covered in this thesis.

Diagnostic criteria

The dominant diagnostic criteria are poor performance (at least 2SD below the mean) on two or more tests of the APD test battery. If poor performance is observed on only one test (at least 3SD below the mean), a diagnosis of APD should be withheld until the sole test is re-administered and the difficulty confirmed by a second test assessing the same AP ability (American Speech-Language Hearing Assosiation, 2005). The American Academy of Audiology did specify ear performance in their diagnostic criteria, with poor performance (at least 2SD below the mean) on at least one ear on two or more tests of the APD test battery (American Academy of Audiology, 2010). The British Society of Audiology did not specify specific diagnostic criteria, but argued for the use of standardized questionnaires and tests of auditory perception (British Society of Audiology, 2018). Opinions of which tests should be in the AP test battery vary from country to country, clinic to clinic and time to time. As the number of tests increases, so does the likelihood of failing at least one test, due to both accumulation of statistical probability and fatigue related to test time.

The variety of diagnostic criteria reflects the heterogeneous nature of APD, the lack of a gold standard test, the advantages and disadvantages of various pass-fail criteria, and different purposes of the APD diagnosis. Although it is documented that different diagnostic criteria will result in different rates of APD (Wilson and Arnott, 2013, Jutras et al., 2007), a unified approach to diagnostics is still not agreed upon.

Prevalence and categories of APD

Depending on the definition used, the prevalence of APD among children and adults varies between 0.5% and 7.0% (Chermak and Musiek, 1997, Bamiou et al., 2001, Hind et al., 2011), with a 2:1 ratio between boys and girls (Ferguson et al., 2011, Chermak and Musiek, 1997).

The British Society of Audiology (2018) defines three categories of APD:

- *developmental APD.* Children with listening difficulties, even though their audiogram shows they have normal peripheral hearing. There is usually no known aetiology or potential risk factors other than family history of developmental communication and related disorders. These children may retain APD into adulthood.
- *acquired APD* associated with a post-natal event, such as aging or known medical or environmental event. This category includes neurological lesions or compromise of the CANS (e.g. neoplasms, degenerative processes like multiple sclerosis, seizure disorders, head trauma or stroke) and infections (Landau and Kleffner, 1957, Jerger, 1987, Musiek et al., 1994, Klein et al., 1995, Hugosson et al., 1997, Bloom et al., 1998, Bamiou et al., 2001, Davis et al., 2001, Robinson et al., 2001)
- *secondary APD* occurring in the presence of, or as a result of, either short term (otitis media with effusion) or permanent peripheral hearing impairment. Previous bouts of otitis media in childhood are associated with APD (Davis et al., 2001).

This thesis will focus on children with APD with normal peripheral hearing, including children with previous bouts of otitis media.

Auditory processing and otitis media

During development, extended periods of sound deprivation can alter neural processing in the CANS, with long-lasting effects on auditory perception (Han et al., 2007, Rosen et al., 2012, Buran et al., 2014).

Otitis media with effusion (OME) is the most commonly diagnosed childhood illness, with accompanying conductive hearing loss (Lanphear et al., 1997). 80% of children will experience one or more bouts of otitis media before 3 years of age, in one or both ears, with effusion in the middle ears persisting for six or ten weeks, respectively (Hogan et al., 1997). 15% of these children will have hearing thresholds >25dB (Gravel and Wallace, 2000).

Early conductive hearing loss induces deficits in the perception of rapidly changing sounds, including speech, and is associated with auditory processing and speech perception deficits. (Roberts et al., 2004, Jung et al., 2005, Whitton and Polley, 2011). Despite normal pure-tone audiograms and effusion free ears, children with a history of chronic OME may have impaired temporal processing (Hall and Grose, 1994b), poor sound localisation (Besing and Koehnke, 1995), and disrupted binaural processing (Pillsbury et al., 1991, Moore et al., 1991). In addition, elevation of the brainstem mediated contralateral acoustic stapedial reflex threshold is observed, suggesting persistent dysfunction of the neuronal circuitry within the auditory brainstem (Gravel et al., 2006). Years after resolution of the OME, disrupted binaural processing and abnormally delayed latencies of the auditory brainstem response (ABR) have been observed, suggesting immaturity in neural conduction (Folsom et al., 1983, Anteby et al., 1986, Gunnarson and Finitzo, 1991, Hall and Grose, 1993, Hall et al., 1995, Hall et al., 1998, Hogan and Moore, 2003, Gravel et al., 2006).

Auditory processing and cognition

Everyday listening frequently occurs in the acoustically challenging conditions that degrade the auditory signal. In such adverse conditions, cognitive functions and executive functions have been proposed to play a critical role in communication.

Speech processing

Hearing is often regarded as a passive function providing access to audition via perception of sound. Listening is viewed as a higher order function requiring intention and attention, processes loading on cognitive resources, thus putting demands on mental effort (Pichora-Fuller and Singh, 2006). When listeners hear speech, they must match the rapid acoustic stream to stored representations of words and phonemes to successfully extract the intended meaning. This process is made more difficult when speech is acoustically degraded: less information is available, which reduces the quality of speech cues and thus increases the chance for error (Mattys et al., 2012). Listening effort refers to the allocation of mental resources to overcome challenging listening situations, and is influenced by cognition, motivation, fatigue and psychosocial considerations (Pichora-Fuller et al., 2016).

Speech comprehension requires the auditory ability to hear the signal and the cognitive ability to relate this information to existing knowledge stored in semantic long term memory (Kiessling et al., 2003, Pichora-Fuller and Singh, 2006), and relies on the ability to pull on cognitive function such as working memory and attention (Shinn-Cunningham, 2008, Ronnberg et al., 2008, Anderson et al., 2013). Engagement of these systems strengthens the neural circuits that facilitate listening (Kraus et al., 2012). A network of prefrontal and parietal cortical areas is involved in the selection required for top-down attention, and other high level cognitive functions, such as working memory and inhibitory control (Corbetta and Shulman, 2002, Fedorenko et al., 2013, Bichot et al., 2015). In favourable listening conditions, the speech signal is intact and speech comprehension is implicit and automatic. However, as acoustic challenge increases, more cognitive processing is needed to understand speech, requiring increased listening effort to retain behavioural performance.

Cognitive processes implicated in speech comprehension

Evidence supporting a role for cognitive resources in understanding acoustically degraded speech is wide-ranging. However, less knowledge exists about the specific cognitive processes engaged.

- *Working memory*

Acoustically degraded speech requires the listener to rely to a greater extent on verbal working memory (Ronnberg et al., 2008, Ronnberg et al., 2013). Working memory (WM) is a limited capacity system for temporarily storing and processing information required to carry out complex cognitive tasks such as comprehension, learning and reasoning (Baddeley, 2000). An individual's working memory capacity (WMC) is the ability to temporarily store and process information. During speech comprehension, executive functions are required to update WM with new information and remove old information (Miyake et al., 2000). Based on studies with hearing impaired listeners, it seems that both WM and updating processes compensate for speech understanding difficulties in adverse listening conditions (Rudner et al., 2011b). Memory performance is reduced in the presence of background noise, but the effect is dependent on the difficulty of the task and the individual's WMC (Ronnberg et al., 2014). However, WMC can be increased by training, with effect both on WM specifically, or cognitive abilities in general (Klingberg et al., 2005, Dahlin et al., 2008, Owen et al., 2010).

The ease of language understanding (ELU) model describes the role of working memory in speech understanding. In favourable listening conditions, the speech signal is intact and understanding is implicit and automatic. However, when listening takes place in adverse conditions, such as background noise or having impaired hearing, a mismatch between the input from the speech signal and the phonological representations stored in long term memory may occur (Ronnberg, 2003, Ronnberg et al., 2008, Ronnberg et al., 2013). Thus, high-level cognitive functions like working memory and executive functions are needed for successful speech

recognition (Larsby et al., 2005, Rudner et al., 2012). The processing generated by this mismatch can often lead to the establishment of new or altered neural representations, which is proportionate to learning (Rudner and Holmer, 2016, Holmer et al., 2016). Executive functions refer to higher order cognitive functions relating to control of thought, action and emotion (Zelazo and Cunningham, 2007).

- *Cognitive spare capacity*

In the act of listening, cognitive resources are consumed, leaving fewer resources available for processing the auditory information at a higher level (Rudner and Lunner, 2013). This is particularly evident in adverse listening conditions. The remaining cognitive resources are referred to as cognitive spare capacity (CSC) (Rudner et al., 2011a) It has been shown that CSC is sensitive to processing load related to both requirements of memory storage and background noise (Mishra et al., 2013b, Mishra et al., 2013a). CSC is closely related to WM in its concern with short-term maintenance and processing of information. Cognitive resources are gradually consumed by increasing processing demands when listening takes place in adverse conditions, thus resulting in fewer resources left to process and store auditory information. In other words, the CSC is reduced (Rudner and Lunner, 2014). As a consequence, individuals with higher cognitive function are likely to cope better with adverse listening conditions than individuals with lower cognitive function (Lunner, 2003, Larsby et al., 2005, Rudner et al., 2009).

- *Attention*

Attention is defined as an individual's selection from a multitude of available sensory information, while these selected stimuli are perceived and processed (Broadbent, 1954). Attention is critical to higher level cognition, allowing for the voluntary processing of relevant over irrelevant inputs; that is, it is a filter mechanism (Desimone and Duncan, 1995). This selection is driven by currently active behavioural goals held in working memory, so the two processes are interactive.

The similarities between visual and auditory perception in complex scenes suggest that common neural mechanisms control attention across modalities (Serences et al., 2004).

Sustained attention is the vigilant focus on specific stimuli, considered a basic function that determines selective and divided attention (Sarter et al., 2001). Selective attention is the process of allocating resources on specific input, while divided attention is the process of resource allocation between different stimuli by rapidly shifting or splitting focus (Hahn et al., 2008). Sustained attention can be modulated by top-down influence such as motivation, by reallocation of resources to alleviate attentional strain, and by bottom-up stimulus-driven influence (Arnott and Alain, 2002). Sustained attention is often measured as the ability to respond accurately under low demand conditions, and to sustain attention under high demand conditions in various continuous performance tests.

Active listening requires mental effort to direct attention towards the target sound, and to separate the target sound from noise (Arbogast and Kidd, 2000, Woods et al., 2001). Several studies have reported deficits in auditory timing in children with ADHD, and there is growing evidence for an association between perceptual timing deficits and behavioural measures of impulsiveness and inattention (Barkley et al., 2001, Smith et al., 2002, Noreika et al., 2013). APD assessments involve active, sustained participation because completion of most AP tasks requires 5-10 minutes of listening and attention per task. The AP batteries consist of several such tasks, requiring a certain degree of sustained attention to successfully complete the tasks. Previous studies on children with suspected APD showed associations between auditory sustained attention and AP tests (Sharma et al., 2009, Gyldenkaerne et al., 2014, Tomlin et al., 2015, Cameron et al., 2016).

High WMC is associated with neural interactions that facilitate attention, which are important for further speech signal processing (Freunberger et al., 2011, Peelle, 2012, Sorqvist et al., 2012). This cognitive tuning of the brain does not seem to involve any explicit processing component. WMC is related to the ability to inhibit processing of irrelevant information, and overrule undesired

responses (Kane et al., 2001, Engle, 2018). Individuals with high WMC thus have a superior ability to modulate attention span (i.e. regulate how much information is given access to cognitive processing).

Provision of semantic context can facilitate speech understanding under adverse listening conditions, engaging language networks in the temporal and frontal lobes. Text cues can facilitate speech understanding in noise when the semantic content matches the auditory signal, and inhibit it when it is misleading (Zekveld et al., 2008, Zekveld et al., 2012, Zekveld et al., 2013).

Neuroimaging and cognitive hearing science have shed new light on the understanding of models of speech perception. There seems to be an increasing consensus on the important role of cognition in hearing, particularly in adverse listening conditions (Pichora-Fuller et al., 2016).

Auditory processing and comorbid disorders

Although the existence of APD has been discussed in the clinical and research literature for more than 50 years, poor agreement remains on when an APD diagnosis should be made and what it means. There is also concern as to whether the condition is separate from other comorbid disorders (i.e. the presence of one or more additional disorders occurring with the primary disorder).

Several researchers have reported that the characteristics of children diagnosed with APD correspond to the behaviours and symptoms of children diagnosed with other developmental disorders. Difficulties in comprehending and complying with verbal information are commonly observed in children diagnosed with-learning disorders (Dawes and Bishop, 2009, Ferguson et al., 2011, Miller and Wagstaff, 2011), specific language impairment (SLI) (Sharma et al., 2009, Ferguson et al., 2011) or dyslexia (Dawes et al., 2009, Dawes and Bishop, 2010). The attention and concentration complaints reported in children diagnosed with APD correspond to the difficulties of children diagnosed with ADHD (Riccio et al., 1994, Dawes et al., 2008, Dawes and Bishop, 2009). Atypical processing of auditory information (e.g. difficulties listening in noise, hyperacusis,

hypersensitivity to pitch) can be seen in children diagnosed with APD, also an inherent component in autism spectrum disorders (ASD) (Dawes et al., 2008, Jones et al., 2009).

The difficulty hearing in noise may lead to auditory fatigue in children with APD, requiring more effort for them to hear and thus reducing processing capacity to perform school work. The mechanism behind is probably reduced CSC and WMC, as shown in hearing impaired individuals (Rudner et al., 2011a, Classon et al., 2013, Ronnberg et al., 2014). Developmental APD can contribute to learning difficulties, but its status as a distinct learning disability is controversial.

There is an ongoing discussion about how symptoms of listening difficulties relate to other developmental disorders. Some reports conclude that cognitive disorders and APD exist independently (Tillery et al., 2000, Sharma et al., 2009, Rosen et al., 2010, Gyldenkaerne et al., 2014), while others conclude that APD is itself a cognitive disorder (Cook et al., 1993, Moore et al., 2010, Ferguson et al., 2011). The question of the degree to which cognitive abilities influence AP ability and AP test performance has not been definitively answered.

Behavioural auditory processing tests

As APD covers several aspects of audition, one test alone cannot address all dimensions of APD and a battery approach is needed. There is at present no agreed “gold standard” diagnostic test battery that differentiates APD from other disorders (Moore et al., 2013). The diagnosis of APD is currently achieved by using a variety of criteria such as the presence of listening difficulties in background noise and/or poor performance on a set on behavioural tests (Cacace and McFarland, 2009, Ahmmed et al., 2014). The American Speech-Language-Hearing Association (2005) suggests that a test-battery for APD should have high sensitivity and specificity for lesions in the CANS, contain both verbal and non-verbal stimuli, and be able to test auditory discrimination, auditory temporal processing and patterning, dichotic speech, monaural low redundancy speech and binaural

interaction. The existing AP tests are influenced by cognition and language in various aspects, in loading on WM, putting demands on attention, speech comprehension or speech production. This underscores the importance of a multidisciplinary approach.

Behavioural AP test batteries have been developed in various languages, for example, in US English (Domitz and Schow, 2000, Keith, 2000), Dutch (Neijenhuis et al., 2001), French (Demanez et al., 2003), Spanish (Fuente and McPherson, 2006) and Danish (Pedersen et al., 2017). For many languages, no APD test battery is available.

Monaural low-redundancy speech

This category assesses the ability to understand degraded speech stimuli; the auditory closure ability. It was among the first tests used to detect central auditory dysfunction in the 1950s by removal of spectral information. The degradation can be achieved in several ways, for example, by filtering (Bocca et al., 1954), compressing the original speech signal (Wilson, 1994), or by presenting the signal in competition with speech or noise (Olsen et al., 1975). Despite limited sensitivity and specificity data, the tests are frequently used due to high ecological validity to functional deficits in the CANS. Additionally, together with a dichotic listening test, they can give directions for deficit-focused interventions.

Degradation achieved by filtering and compressing the speech signal are generally less vulnerable to influence from higher-level confounding, but language and cognition can nonetheless influence the results of such tests (Pichora-Fuller, 2003). When parts of the information of the speech stimuli are removed, clearly this puts demand on linguistic experience and working memory.

The filtered words test (FW) from SCAN (Keith, 2000), the filtered speech test (Willeford, 1976) and the time compressed speech test (Beasley et al., 1972) are examples of monaural low redundancy tests in clinical use.

Binaural integration of speech signals

Dichotic listening refers to the listeners ability to separate and integrate different auditory signals from the two ears, presented at the same time (Broadbent, 1954). For decades, dichotic tests have been used to investigate hemispheric dominance for language and binaural integration skills in children with listening, learning and reading disabilities thought to stem from APD. Various dichotic tests using speech materials (e.g., words or sentences) are available.

For binaural separation tasks, competing signals are presented to the two ears. One of the signals are target signals. The listeners are instructed to repeat the target signal and ignore the other, such as Competing Sentence test (Keith, 2000). For binaural integration tasks, the listeners are instructed to combine and repeat the information from both ears, such as the Dichotic Words test (Keith, 2000) or Dichotic digits test (Musiek, 1983a). The dichotic digits test (DD*)* is illustrated in Figure 2.

The advantages for clinical application of dichotic listening tests are established sensitivity and specificity to cortical and brainstem lesions, high test-retest reliability, relative insensitivity to mild hearing loss (Musiek, 1983a, Musiek et al., 1991), and clinical feasibility. However, the speech stimuli used render the tests dependent on cognition and language (Penner et al., 2009).

The tendency to report speech-material presented to the right ear preferentially (right ear advantage, REA) in dichotic listening is a normal phenomenon in children, with larger REA accompanying higher linguistic load (Broadbent, 1954, Kimura, 1961b, Kimura, 1961a, Hugdahl et al., 1990). The REA is thought to reflect the slower maturation of inter-hemispheric connections via the corpus callosum (Obrzut and Pirozzolo, 1981) and the dominance of the left hemisphere in processing language (Rosenzweig, 1951, Katz, 1962, Kimura, 1963, Keith, 2000, Moncrieff, 2011). Studies have shown that test scores increase and REA diminishes with age and language development (Keith, 2000, Moncrieff, 2011).

It is noteworthy that reports of results in children with language or reading difficulties, or APD, have been varied, from lower scores in both ears when tested with consonant-vowels, digits, words, and sentences (Hynd et al., 1979, Roush and Tait, 1984, Vanniasegaram et al., 2004, Pinheiro et al., 2010), to poor performance in the right ear (smaller REA) (Obrzut et al., 1985, Helland and Asbjornsen, 2001) or poor performance in the left ear (larger REA) (Moncrieff and Musiek, 2002, Vanniasegaram et al., 2004, Moncrieff and Black, 2008). This heterogeneity of results across different studies has made it impossible to achieve consensus on a model related to hemispheric dominance for language in children with disabilities.

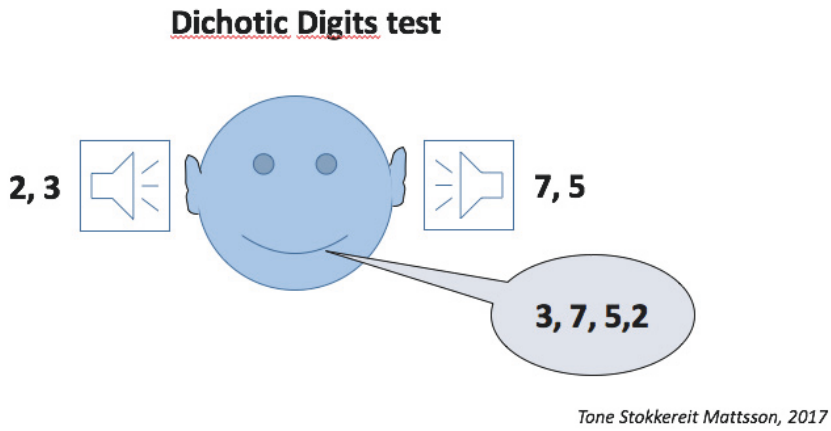

Figure 2. Illustration of the dichotic digits test. Two different digit pairs were presented to each ear simultaneously, the children were instructed to repeat the digits in free-recall mode.

Temporal processing

Tests of temporal processing refer to the listener's ability to perceive temporal auditory characteristics. There are multiple tests evaluating different sub-processes of temporal processing;

temporal ordering, temporal resolution or discrimination, temporal integration and temporal masking.

One test on ***temporal resolution*** is the gaps in noise test (GIN), which is a within-channel gap detection measure (Musiek et al., 2005). The GIN assesses the temporal resolution ability of the listener (the listener's ability to detect short duration silences between two auditory signals), and is based on extensive psychoacoustic literature for gap detection. The advantages for clinical application include low cognitive demand, relative insensitivity to hearing loss at specific frequencies, ease of administration, evidence of early maturation of the AP skills assessed rendering it suitable for children aged 7 and older (Shinn et al., 2009), in addition to established sensitivity and specificity to cortical and brainstem lesions (Musiek et al., 2005). Another gap detection test being used clinically, is the random gap detection test (Keith, 2000).

Temporal sequencing tests are also an important component of the AP test battery in current use, and assess the temporal ordering abilities. Two temporal sequencing measures, with documented sensitivity and specificity in children, commonly used in AP assessment are *the frequency pattern test (FP)* (Musiek and Pinheiro, 1987) and *the duration pattern test (DP)* (Musiek et al., 1990). In addition, the Newcastle auditory test battery (NAB) includes tests of temporal processing, primarily threshold measures of various frequency and amplitude modulation rates (Griffiths et al., 2001).

Processing of pitch and duration stimuli involves interaction between both hemispheres in decoding the auditory pattern before reporting it verbally: contour recognition in the right hemisphere before the signals are passed via the corpus callosum to the left hemisphere for verbal labelling (Kimura, 1967, Musiek et al., 1980, Musiek and Pinheiro, 1987). However, the tests are subject to influence from memory and linguistic experience (Cacace et al., 1992, Talcott et al., 2000, Bellis et al., 2011). For instance, the FP test consists of three-element binary patterns of high

and low frequencies, and the subject is required to encode these, store them in working memory, attach linguistic labels to the individual frequencies and reproduce the sequence verbally.

Binaural Interaction

Tests of binaural interaction refers to the listener's ability to integrate information from the two ears, process inter-aural phase differences of acoustic stimuli, and provide a measure of the ability to segregate sounds on the basis of their location in space.

A traditional, but frequently used measure of binaural integration is the binaural masking level difference (BMLD), which is determined by presenting a broadband noise containing either tones or speech stimuli. For some trials, the stimuli and noise are presented in-phase to the ears, whereas for others either the stimuli or noise is presented in the anti-phase. The difference in thresholds between the two trial types represents the masking level difference, as illustrated in Figure 3 (Wilson et al., 2003). Subjects having normal brainstem function, present a lower (i.e. better) threshold for the anti-phase condition than the in-phase condition. The better threshold for the anti-phase condition is due to greater release of masking for this condition, yielding higher masking level difference. The advantage of the BMLD is that it is sensitive to lower level brainstem dysfunction (Lynn et al., 1981).

Another clinical measure to evaluate spatial aspects of audition, is the listening in spatialized noise-sentence test (LiSN-S) (Cameron et al., 2006). The LiSN-S is an adaptive, virtual-reality test that measures speech perception ability for simple sentences presented in competing speech.

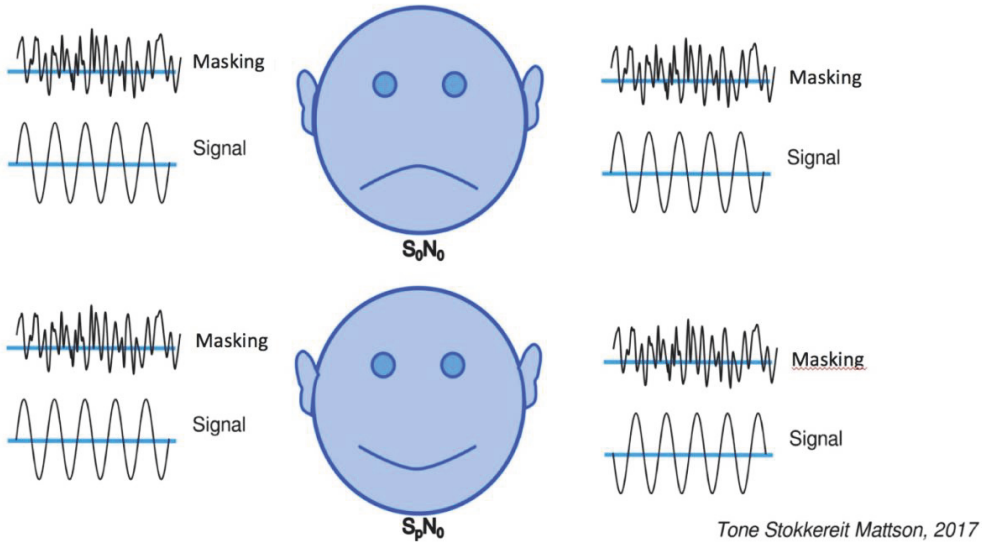

Figure 3. Illustration of the binaural masking level difference (BMLD). When the signal is in phase between the ears, masking effect is greatest (top). When the signal is out of phase between the ears, masking effect is reduced (bottom). BMLD = S_0N_0 -S_pN_0

Diagnosis of APD

Despite more than 40 years of research, the body of knowledge for establishing the best set of tests for assessing real word listening difficulties does not yet exist (Dillon et al., 2012). Many clinically available AP tests are sensitised by manipulating the speech quality or the task demands to stress language or memory systems. Such strategies can undermine test validity by complicating interpretation regarding the latent trait being probed. Once stresses to supra-modal abilities are removed, most AP tests become relatively insensitive to the listening problems (Moore et al., 2010). All auditory tests can be influenced by a number of factors, such as age, auditory experience, or the cognitive skills used on the task; such as attention (Riccio et al., 1994, Riccio et al., 1996, Tillery et

al., 2000, Gyldenkaerne et al., 2014), cognitive abilities (Tomlin et al., 2015), motivation (Silman et al., 2000), and linguistic factors (Richard, 2007).

Clinical evaluation

As previously stated, the definitions of developmental APD has shifted from delineating what makes the disorder unique, to acknowledging that it can occur in the context of other developmental disorders (British Society of Audiology, 2018). While there is an auditory component to the difficulties these children experience, it might not be specifically auditory in nature because of frequent coexisting problems with working memory, attention, literacy, language or social skills.

For an adequate evaluation of children with listening difficulties, a multidisciplinary assessment is recommended (American Speech-Language Hearing Assosiation, 2005, American Academy of Audiology, 2010, British Society of Audiology, 2018). While APD is an audiological diagnosis, the assessment typically involves physicians, audiologists, speech-language therapists, psychologists and educators. The choice of tests should be guided by the children's difficulties. Broader assessment of psychometric tests of cognitive functions and language abilities is most often needed prior to AP assessment. Such assessment could include Clinical Evaluation of Language Fundaments (Semel et al., 2006), Wechsler Intelligence Scale for Children (Wechsler, 1991), Integrated Visual and Auditory Continuous Performance Test plus (Sandford and Turner, 2004).

A clinical examination with a thorough anamnestic report is important to provide information regarding underlying factors, likelihood of CANS compromise, and functional auditory and related complaints. This information may be of help in designing specific behavioural auditory tests and/or electrophysiological procedures for an optimal evaluation. The existence of comorbid conditions may necessitate the use of a modified test battery, and the need for taking possible influence from these conditions into consideration when interpreting the test results (American Speech-Language Hearing Assosiation, 2005, American Academy of Audiology, 2010).

Pure tone and speech audiometry in addition to tympanometry and otoacoustic emissions, should be performed. Peripheral hearing loss has potential negative impact on AP test performance, and must be evaluated. Children with lesser degrees of hearing loss and good speech recognition can be candidates for AP assessment using tests which are less affected by cochlear hearing loss (e.g., dichotic digit tests, frequency pattern tests). However, assessing children with a significant degree of hearing loss and reduced speech recognition abilities is not recommended.

A battery of behavioural tests that assess multiple auditory processes, including both speech and non-speech tests, should be selected according to the nature of the listening difficulties, and to minimise the influence of language and cognition (Moore, 2006). Electrophysiological evaluations may be of use when AP problems are suspected or verified. Finally, a cross-disciplinary evaluation of the test results is recommended to ensure that the child receives the appropriate diagnosis.

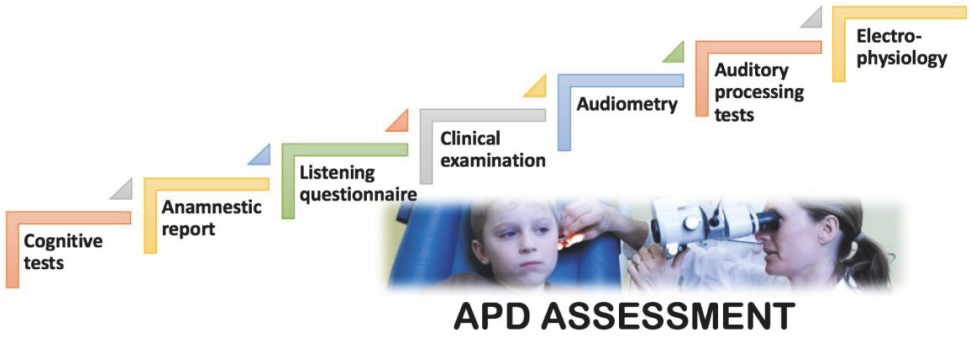

Figure 4. Illustration of the diagnostic process towards a diagnosis of APD.

The diagnosis of APD can be dependent on the referral route (Moore, 2006, Dawes and Bishop, 2009). The challenge is to find appropriate multidisciplinary referral pathways to ensure that each patient receives the correct diagnoses, to permit the most appropriate set of interventions to be administered.

Behavioural questionnaires

The potential relationship between APD, language, cognitive and related factors has led to an increase in referrals for APD assessments. To reduce inappropriate referrals, and to expedite the correct diagnosis and treatment, the use of screening questionnaires is promoted prior to referral (Jerger and Musiek, 2000, Bellis, 2003, Schow and Seikel, 2007, Chermak et al., 2007). Questionnaires can be used to highlight concerns about a child, identify additional areas that require assessment or supplement the diagnostic process, but not to determine whether an AP assessment is warranted or to differentially diagnose disorders (Iliadou and Bamiou, 2012).

The advantages of behavioural questionnaires include their ease of administration and cost effectiveness, as well as their being powerful tools for supporting clinical assessment (Brown et al., 2001). Because the same measures can be administered to multiple respondents, clinicians can develop a broader insight into the range and severity of a child's real word listening problems in different contexts. However, the above advantages presuppose that the measure has the requisite properties of psychometric reliability and validity. This requires that the questionnaires include items to which all respondents are sensitive, and that all items are readily understandable and minimally ambiguous regarding interpretation. Despite their potential strengths, the disadvantages of report-based measures are that they are liable to problems of subjectivity and response bias (Schow and Seikel, 2007, Wilson et al., 2011). These problems cannot be excluded, but can be minimised by careful design.

In the search for effective screening tools for APD, various behavioural questionnaires have emerged as a means of summarising symptoms observed by clinicians; Children's auditory

performance scale (CHAPS) (Smoski et al., 1998), the Screening instrument for targeting educational risk (SIFTER) (Anderson, 1989), and Fisher's auditory problems checklist (Fisher, 1976). Reliable relationships have yet to be demonstrated between these questionnaires, AP test results and APD diagnosis (Lam and Sanchez, 2007, Wilson et al., 2011, Barry et al., 2015). As such, the questionnaires do not approach the required level of psychometric robustness for reliably assessing the severity or nature of a child's listening difficulties.

To address the lack of a well-designed and validated measure of symptoms associated with APD, newer questionnaires which fulfil the following are developed: 1) specification of the psychological construct, 2) development of a sufficiently, broad-ranging worded item-pool, 3) assessment of the construct validity and reliability of the final scale. Examples are the Evaluation of children's listening and processing skills (ECLiPS) (Barry and Moore, 2014) and the Auditory processing domain questionnaire (APDQ) (O'Hara, 2006). Both questionnaires are sensitive to the presence of listening difficulties, and offer more information about potential underlying cognitive or language difficulties that might manifest as listening difficulty (Barry et al., 2015, O'Hara and Mealings, 2018).

To conclude, behavioural questionnaires can be used to highlight concerns about a child's listening difficulties, and to supplement the assessment of children referred for APD. More research is needed involving large-scale clinical studies, with exploration of the role of questionnaires in supporting clinical decisions regarding APD referral or designing of management plans subsequent to assessment. For use in Norway, the CHAPS and the APDQ are translated and standardised (Ukvitne and Nicholas, 2017). In this study, the APDQ was used, with the parents providing the responses.

Intervention

Following APD diagnosis, intervention should be implemented to exploit the plasticity of the CANS, an inherent ability to adapt to experience. Neuronal plasticity is the functional and structural reorganisation of the brain in response to a given event or sets of events. Training and perceptual learning has been shown to involve alterations in neural connections and activity at multiple levels of the auditory pathway (Merzenich et al., 1996, Hayes et al., 2003, Russo et al., 2005, Anderson and Kraus, 2013, Tierney et al., 2015).

Given the potential impact of APD on listening, communication and academic outcome, and the frequent comorbidities with related language and learning disorders, intervention tailored to each individual should be offered. Comprehensive intervention, incorporating both bottom-up (e.g., acoustic signal enhancement, auditory training) and top-down (i.e., cognitive, metacognitive and language strategies) approaches are considered effective (Chermak and Musiek, 1997, Sharma et al., 2014b, Weihing et al., 2015a).

Modifying the listening environment is important to improve access to the acoustic signal and reduce competing auditory signals. Accommodations can include preferential seating, use of visual aids in teaching, modification of the speaker's language or use of classroom amplification (Bamiou et al., 2006). Improving the quality of the acoustic signal by providing personal amplification devices is reported to enhance hearing and learning, improve psychosocial adjustment and can lead to lasting improvement in hearing skills (Johnston et al., 2009, Sharma et al., 2012, Keith and Purdy, 2014)

Auditory training addresses the AP deficit by attempting to improve the affected auditory processes, by repeating tasks several times a week over a given time period. The auditory training can be directed towards remediation of direct skills, such as targeting discrimination of frequency, intensity, or duration of the acoustic signal, discrimination of phonemes and syllables, dichotic listening or temporal processing tasks (Baran et al., 2006). The auditory training can also be computer-based. There exist various software programs for auditory training for the English-

speaking population (Earobics, Fast for Word, CAPDOTS and LiSN and Learn). Literature reviews of the existing research, concluded that there is weak evidence that intensive, short term interventions (e.g. traditional auditory interventions or computer-based training) can be beneficial for children with APD. There is less evidence that these interventions positively affect oral and written language performance. (Pokorni et al., 2004, Loo et al., 2010, Fey et al., 2011, Loo et al., 2016). However, much more research is needed to determine the full effect on patients with APD.

Top-down, strategy driven intervention approaches include training in improving central resources, such as language, cognitive and metacognitive strategies. These approaches can build listening strategies, promote allocation of perceptual and higher resources and provide compensatory methods to minimise functional listening difficulties (Kraus and White-Schwoch, 2015).

For the Norwegian speaking population, an auditory training program is developed from material used in rehabilitation after cochlear implantation, matched to the specific auditory deficits of each child. However, this is not a commercial software program, and audiological clinics or Statped West, a national service in Norway for special needs education, are responsible for the training.

Otoacoustic emissions measures

Otoacoustic emissions (OAE) are the result of outer hair cell motility in the inner ear, thought to reflect a combination of an active nonlinear distortion and a passive linear coherent reflection mechanism (Shera, 2004). The active element is associated with the motility of the OHCs and the passive element with stereocilia stiffness. Usually evoked by incoming sounds, the two OAE types most often used clinically are transient evoked otoacoustic emission (TEOAE) and distortion

product otoacoustic emissions (DPOAE), which differ on the basis of the stimulus (clicks vs pure tones).

Evoked OAEs typically become supressed (i.e., reduced in amplitude) when contralateral noise is introduced. This suppression effect results from activation of the auditory efferent system, called the medial olivocochlear reflex (Guinan, 2006). Specifically, OAE suppression is an indirect index of the MOC functionality (Collet et al., 1990, Veuillet et al., 1991).

There is growing evidence that the MOC efferent system could play functional roles in human hearing. Possible roles could include: a) aiding auditory perception in noise by antimasking and complex processing resulting in improved tone detection, and intensity and speech discrimination (Giraud et al., 1997, Micheyl et al., 1997, De Boer, 2012); b) mediating selective attention by modulating OHC activity in the ear to which the attention is directed (Puel et al., 1988, Giard et al., 1994, Garinis et al., 2011); c) protecting of the inner ear from acoustic injury (Maison et al., 2000). It is also thought that MOC function could be altered by auditory training, as shown by stronger MOC activity in musicians (Micheyl et al., 1995, Perrot et al., 1999, Brashears et al., 2003).

The inhibitory effect of the MOCR has been studied with evoked OAE measurements. Many experiments have employed a contralateral inhibition of OAEs technique, wherein OAEs are first measured in quiet conditions, and then during presentation of a contralateral acoustic stimulus (CAS). The OAE level, phase, and/or spectral differences between quiet and CAS conditions can be used to quantify the inhibitory effect of the MOCR (Velenovsky and Glattke, 2002). Various types of CAS have been employed to elicit contralateral inhibition of OAEs including continuous or pulsed broadband and narrowband noise, speech babble, and steady-state and amplitude modulated tones (Norman and Thornton, 1993, Maison et al., 1997, Maison et al., 1999, Smith et al., 2001). In general, broadband CAS is considered more effective as an inhibitor than narrowband CAS (Norman and Thornton, 1993, Berlin et al., 1993a, Williams and Brown, 1997). CAS can be presented in a steady-state fashion throughout OAE recordings (Hood et al., 1996) or in trials with

short duration CAS temporally preceding the evoking stimulus (Berlin et al., 1995). The strength of the MOC reflex shows inter-subject variability, and is dependent on contralateral stimuli frequencies, intensities and inter-stimulus intervals (Veuillet et al., 1991, Kawase et al., 2003, Lilaonitkul and Guinan, 2009).

Click evoked OAE inhibition can be quantified in both time and frequency domains (waveform and spectrum, respectively) and is typically reported as the difference in the overall OAE level with and without CAS. The maximum amount of click evoked OAE inhibition is seen within the 8-18 ms post-stimulus range of the waveform (Hood et al., 1996). Similarly, spectral analyses of OAE waveforms indicate maximum inhibition within the 1-4 kHz range (Collet et al., 1990). The preponderance of inhibition in the mid-frequencies is thought to reflect the relatively high density of radial efferent fibres terminating on the outer hair cells in this tonotopic range (Guinan, 2006).

There are two methods to evoke the TEOAEs; the linear and non-linear click method which differ by the stimulus (four identical clicks or three similar clicks and the fourth with larger size and inverted polarity, respectively). The linear click method captures both the linear and non-linear part of the emission, but the stimulus ringing artefacts from the ear canal and middle ear are not self-cancelling. The non-linear click method eliminates the stimulus ringing artefact, but miss the linear part of the emission, thus removing suppression information (Kemp, 1978, Bray and Kemp, 1987, Backus and Guinan, 2006).

Accumulating evidence suggests that active listening influences cochlear mechanics, making it possible for the brain to fine-tune peripheral auditory processing (de Boer and Thornton, 2007, Harkrider and Bowers, 2009, Garinis et al., 2011, Smith and Cone, 2015). This effect is thought to arise from an efferent coupling between the cortex and the MOC bundle, with inhibitory synapses terminating directly on the outer hair cells. Corticofugal effects of attention on the MOC reflex have been studied by combining contralateral inhibition of click-evoked OAE with active listening paradigms. While the attention tasks have differed across studies, it is apparent that attention can

influence MOCR strength. Most studies have found that active listening to tones or speech in the contralateral ear led to greater OAE inhibition (Maison et al., 2001, Garinis et al., 2011, Smith and Cone, 2015). However, some reports showed reduced OAE inhibition when attending to clicks or speech in the contralateral ear (Harkrider and Bowers, 2009).

Electrophysiological measures

Auditory evoked potentials (AEPs) are brain responses evoked by the presentation of auditory stimuli, and have been suggested as a means of determining the degree of involvement of auditory system versus non-auditory systems in APD and listening difficulties (Kraus et al., 1995, Ponton et al., 2000, Menning et al., 2000, Wunderlich et al., 2006, Martin et al., 2008, Schochat et al., 2010, Wilson et al., 2013). While not immune to influences from non-auditory systems, AEPs can provide means to elucidate the neurobiological factors contributing to AP and to identify smaller changes in CANS function related to volume (numbers) and synchrony (timing) of neural activity in response to an auditory stimulus (Hall, 2006).

Three AEPs that have been widely used to investigate both auditory and non-auditory systems are the auditory middle latency response (AMLR), the auditory late latency response (ALLR) and the auditory P300. The auditory middle latency response (AMLR) has been used to assess function in the thalamo-cortical pathways thought to be essential in processing speech and non-speech signals (Kileny et al., 1987, Jerger et al., 1988, Musiek and Lee, 1997). It consists of a series of vertex positive and negative waves (Po, Na, Pa, Nb and Pb) between 10 ms to 50 ms post-stimulus onset, although the most robust waves have proven to be Na and Pa. Each wave within the AMLR is thought to be generated by multiple temporally overlapping subcortical and cortical generators (Kraus and McGee, 1993). In particular, the early Na and Pa waves are thought to be generated by

subcortical structures including the inferior colliculus and thalamus, and cortical structures including the superior temporal gyrus (Kraus et al., 1982, Hall, 2006).

The auditory late latency response (ALLR) has been used to evaluate neural function in cortical structures thought to represent more elementary levels of auditory sensory coding and automatic processing (Naatanen and Picton, 1987). It consists of a series of vertex positive and negative waves (P1, N1, P2 and N2) between 50 ms to 250 ms post-stimulus onset, N1 and P2 showing best stability. Each wave within the ALLR is thought to be generated by multiple temporally overlapping subcortical and cortical sources (Onishi and Davis, 1968, Naatanen and Picton, 1987). The N1 component is generally thought to represent the initial extraction of information from sensory analyses of the stimulus, or the excitation associated with allocation of a channel for information processing out of the primary auditory cortex. The P2 component may represent inhibition of sensory input from further processing via automatic stimulus identification and discrimination (Hansen and Hillyard, 1988). The N1 is considered a passive, transient response evoked by short-term envelope change in the auditory stimulus (Onishi and Davis, 1968), while P2 is considered sensitive to attention and stimulus parameters such as pitch and intensity (Crowley and Colrain, 2004) as well as musical experience (Seppanen et al., 2012).

The P300 has been used to assess discriminative responses thought to represent cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli (Polich, 2007). It consists of a positive wave (P300) commonly largest over central parietal (Pz) regions of the head and occurring approximately 300 ms following stimulus onset of a target stimuli within a series of non-target stimuli. The P300 is thought to be mostly generated in non-auditory areas in the frontal and temporal cortices (Baudena et al., 1995, Halgren et al., 1995), although some contribution by auditory generators is suggested by evidence of lesions in the auditory cortex compromising both P300 latency and amplitude (Knight et al., 1989, Musiek et al., 1992).

The Norwegian APD test battery

APD is a relatively new disorder in Norway. It was not until January 2019 that APD was recognised by the Norwegian Health Authority, and given a diagnosis code. During the last decade, researchers and clinicians have worked together in spreading knowledge of APD, developing tests to assess the condition, and identifying interventions for children diagnosed with APD. Today, the larger public audiological clinics offer multi-professional APD assessments. However, it has been a long and winding road.

To address the need for an APD test battery for use in Norway, existing behavioural tests from the recommended auditory categories of auditory discrimination, auditory temporal processing and patterning, dichotic speech, monaural low redundancy speech, and binaural interaction were considered (American Speech-Language Hearing Assosiation, 2005). The choice of tests was based on several considerations, including their acoustic simplicity and reproducibility, high sensitivity and specificity to CANS dysfunction, relevance to more complex aspects of hearing, and the suitability for children above seven years of age. Interpretation of results of behavioural tests of AP in children under the age of seven years is difficult, due to the maturational variability of the CANS, the response demands of the task, and highly variable test results on children as young as six years of age (Stollman et al., 2004, Dawes and Bishop, 2008, Moore et al., 2011).

Based on the work of Brandt (Brandt, 2010), both the Danish and Norwegian APD test-batteries were developed (Pedersen et al., 2017, Mattsson et al., 2018). The words and numbers used were dialect neutral, spoken by a male first-language speaker of Norwegian, and widely used in the Norwegian Speech Audiometry (Quist- Hanssen). The test signals were modified and produced in Adobe Audition (Adobe Systems Incorporated) and compiled on a CD. On the CD, there is a signal with running speech for setting the most comfortable loudness levels of the test, and a Microsoft

Excel sheet to register the answers and automatically calculate the scores. The full test battery takes 30-40 minutes to complete, including preliminary instructions.

The Norwegian APD test-battery developed for a clinical evaluation consists of the following tests, covering each of the auditory categories recommended by ASHA (2005):

- *Monaural low redundancy speech:* the FW test (Keith, 2000).
- *Binaural integration of speech:* the CW test (Keith, 2000) and the DD test (Musiek, 1983a).
- *Temporal processing:* the GIN test (Musiek et al., 2005), the FP test (Musiek and Pinheiro, 1987), and the DP test (Musiek et al., 1990).
- *Binaural interaction:* the BMLD test (Wilson et al., 2003).

In addition, a subtest from the Norwegian Speech Audiometry from Sør-Trøndelag University College (HIST SIN) was chosen to assess the listener's speech intelligibility in noise (Øygarden, 2009). After evaluation of the tests in normal hearing children, the intention was to propose a educed test battery for clinical use in APD assessment in the Norwegian population. The test battery does not include cognitive or language tests, as these tests currently exist and are extensively used in Norway. Evaluation of cognition and language are also performed by psychologists and speech-language pathologists outside the audiological clinics.

The diagnostic criteria for use in Norway are as follows:

- participant performing two SD (or the lower 2.5 percentile) or more below age expectations, in at least one ear on at least two different auditory processing tests categories (American Academy of Audiology, 2010),
- with at least one of the failed tests having used speech stimuli and one having used non-speech stimuli (British Society of Audiology, 2018)

2. AIMS OF THE THESIS

General aims

- To provide a standardised battery of tests for auditory processing to the Norwegian population aged 7-12 years
- To study and compare the central auditory nervous system in children with APD, children with listening difficulties who did not meet the diagnostic criteria for APD and normal hearing children, by otoacoustic emissions and electrophysiological methods, to provide insight into the underlying pathophysiology of listening difficulties.

Specific aims

Paper 1

The aim of paper one was to develop age appropriate normative data and to measure test-retest reliability for the Norwegian behavioural auditory processing battery of tests for children.

- To propose which of the tests should remain in a final test battery for identifying APD.

Paper 2

The aim of paper two was to explore if the auditory efferent system, as reflected by TEOAE suppression, is compromised in children with APD.

- To estimate group differences in TEOAE suppression in children with listening difficulties, diagnosed with APD or not, and children with normal hearing.
- To determine if TEOAE may be used as a clinical tool for the diagnosis of APD.

Paper 3

The aim of paper three was to investigate if behavioural problems found in children with APD would translate into significant problems in the AEP results. Further, because the AMLR and ALLR are thought to originate predominantly from auditory areas in the thalamus and cortex, then these AEPs would be more sensitive to APD. Secondly, because the auditory P300 is thought to originate from non-auditory areas in the frontal and temporal cortices, then it would be more sensitive to broader listening difficulties not resulting from APD.

- To estimate group differences in thalamo-cortical function assessed by AMLR.
- To estimate group differences in cortical sensory coding and automatic processing, and cognitive processes involved in auditory processing, assessed by ALLR and P3.
- To explore associations between electrophysiological measures, behavioural AP tests and performance based measures of sustained attention.

3. MATERIALS AND METHODS

Study design

This thesis consists of three papers that differ to some extent in design and methods. A prospective, repeated measure design was used for paper 1, and a subgroup of participants was retested after 14 days. For papers 2 and 3, a prospective, three-group, repeated measure design was used. The studies were approved by the Scientific Committee in Ålesund Hospital and the Regional Committee for Medical and Health Research Ethics in the Central (number 2013/1130, paper 1) and West of Norway (number 278.08, paper 2 and 3). Written informed parental consent was obtained from all participants. The statistical analyses were performed using SPSS version 21.0 (paper 1) and 25.0 (paper 2 and 3), and the R programming environment (R Core Team, 2013). The subjects and examinations included in paper 1, 2 and 3 are shown in Figure 5.

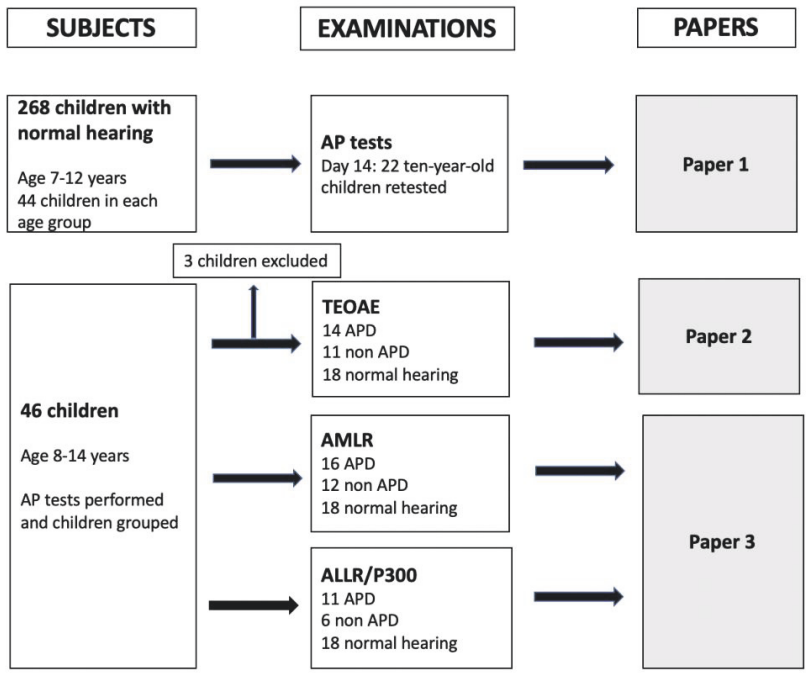

Figure 5. Study populations in paper 1, 2 and 3.

Test design

Behavioural tests of auditory processing

The Norwegian APD test battery was used on all the children. The tests were administered by headphones and the tasks reported orally. The scores for each test were calculated. An overview of the specifications in each test is given in Table 1.

Monaural low redundancy speech

In the **Filtered Words test (FW)**, the participant is presented 25 low-pass filtered monosyllabic words to the right and left ears separately. The same words are played in the two ears, but in different order. Before each test, a training series of 10 words which are easier to recognize is presented to each ear. The participant has to repeat each word, and the percentage of correctly repeated words determines the score for each ear.

Binaural integration of speech signals

In the **Dichotic Digits test (DD),** the participant is presented 20 sets of four monosyllable digits (1,2,3,5,6,7,12). In each set, two different digit pairs are presented dichotically. The two digits within each pair are different, the time from onset of the two digit pairs is one second. The participant has to repeat the digits in free-recall mode, the percentage of correctly repeated digits determines the score for each ear.

In the **Competing Words test (CW),** the participant is presented 20 sets of two different monosyllables. One word is presented to each ear dichotically, at equal intensities and durations. The participant has to repeat the words in free-recall mode, the percentage of correctly repeated words determines the score for each ear.

Temporal processing

In the **Gaps in Noise test (GIN)**, the participant is presented with 22 white noise segments monaurally. Each segment contains 0-3 silent intervals, gaps, ranging from 2-20 ms. Across segments, each gap duration is presented six times per ear. After each segment is played, the participant report the number of gaps heard. The shortest gap consistently detected four out of six times for each ear is the test score. A pre-test containing larger gaps, ranging from 5-70 ms for rehearsal and screening for major temporal difficulties is presented.

In the **Frequency Pattern test (FP),** the participant is presented with two series of 30 patterns monaurally. The patterns consist of various combinations of three sinusoids. The duration of each sinusoid is 200 ms, with either lower (880 Hz) or higher (1122 Hz) frequency. The time from onset of the sinusoids is 150 ms. Each participant has to describe the patterns, where one tone is different in frequency from the other two. The percentage of correctly repeated patterns determined the score for each ear.

In the **Duration Pattern test (DP),** the participant is presented with two series of 30 patterns monaurally. The patterns consist of various combinations of three sinusoids. The frequency of each sinusoid is 1000 Hz, with either shorter (250 ms) or longer (500 ms) duration. The time from onset of the sinusoids is 150 ms. Each participant has to describe the patterns, where one tone is different in duration from the other two. The percentage of correctly repeated patterns determines the score for each ear.

Binaural Interaction

In the **Binaural Masking Level Difference test (BMLD),** the participant is presented 31 bandpass filtered white noise segments containing five 500Hz tone beeps each. The two ears are tested jointly. The white noise (No) is always played in phase between the ears, while the tone bursts (S) are played either in phase (SoNo) or π radians (180 °) out of phase (SπNo). The two trial types are tested from +7 dB and -1dB signal-to-noise ratio (SNR), respectively, the SNRs decreases

2dB steps for each presentation. Besides the segments with beeps, the series contains eight “catch” trials with noise only, to confirm that the subject is not guessing. The masker level is dependent on the most comfortable sound level set. The participants are instructed to respond with a yes if they heard the tone beeps. The SNR thresholds for the in phase or out of phase conditions are identified and the binaural masking level difference calculated, (BMLD=SoNo – SπNo).

Speech in Noise

In the subtest from the Norwegian Speech Audiometry from Sør-Trøndelag University College (HIST SIN), age-appropriate utterances in the form numeral-adjective-noun are presented monaurally with background noise fixed at 45 dB HL. The first utterance starts at +25 dB signal-to-noise ratio. The SNRs decreases 1,5-dB steps for each sequence presented until the listener is unable to recognise four following utterances. The participant repeats the words heard and the threshold in dB SNR is obtained from a table based on the total number of recognized words.

Test	*Category*	*Test stimuli*	*Task*	*Test score*
FW	Monaural low-redundancy speech	Two series of 25 monosyllable nouns, low-pass filtered with a cut-off frequency of 1kHz, presented to one or both ears. ITI = 4 sec Training series of 10 words, filter cut-off frequency of 1kHz	Repeat words in any order	The percentage of correct words repeated
CW	Binaural integration of speech	Twenty sets of pairs of monosyllable nouns presented dichotic, at equal intensities and durations. ISI = 1 sec, ITI = 5 sec	Repeat words in free recall	The percentage of correct nouns repeated
DD	Binaural integration of speech	Twenty sets of four monosyllable digits (1,2,3,5,6,7,12), two different digit pairs were presented to each ear dichotic. ISI = 1s, ITI = 8 sec	Repeat digits in free recall	The percentage of correct digits repeated
DP	Temporal ordering	Two series of 30 patterns with combinations of three 1kHz sinusoids with shorter (250 ms) or longer (500 ms) duration, presented monaural. ISI = 200 ms	Verbally state pattern of 3 tones	The percentage correct patterns repeated
GIN	Temporal resolution	22 white noise segments of 6 s duration containing 2-3 gaps, presented monaural. Gap duration of 2,3,4,5,6,8,10, 12,15 and 20 ms (each presented six times per ear). Training series of five noise segments with gap duration from 5-70 ms. ITI = 11 sec.	Verbally count number of gaps	The shortest gap reported (at least four out of six times)
FP	Temporal ordering	Two series of 30 patterns with combinations of three 200 ms sinusoids with lower (880 Hz) or higher (1122 Hz) frequency, presented monaural. ISI = 150 ms.	Verbally state pattern of 3 tones	The percentage correct patterns repeated
BMLD	Binaural interaction	39 low-pass filtered 3 sec white noise segments. Of the segments, 31 contained five 0.5 kHz tones of 270 ms duration and eight did not. The tones were either in phase (SoNo) or π radians (180 °) out of phase (SπNo), presented from +7 dB and -1dB SNR, respectively. SNRs decreased 2dB steps for each presentation. ISI = 270 ms, ITI = 8 sec.	Verbally state when a tone is heard	BMLD = SoNo – SπNo, one score for the two ears
HIST SIN	Speech in noise	Three word utterances presented monaurally with background noise fixed at 45 dB HL. The first utterance started at +25 dB SNR, the SNR decreased 1,5-dB steps for each sequence until the listener was unable to recognise four following utterances.	Repeat the words heard	The threshold in dB SNR

Table 1. Specifications of the AP tests in the Norwegian APD test battery. Inter stimulus interval (ISI) = time from onset of one stimulus to the next, inter trial interval (ITI) = time from the last stimulus in one trial to first stimulus in the next trial. SNR = signal-to-noise-ratio.

Paper 1

Method

The study population was recruited from two primary schools in Aalesund, Norway between August 2013 to June 2014. A group of 268 normally developing children aged 7-12 years were enrolled in the study, with 44 participants in each age group.

Subjects

Children who were native speakers of Norwegian, had normal hearing based on pure-tone audiometry and tympanometry were eligible. Children with attention disorders or autism spectrum disorders potentially influencing the AP test performance were excluded. Of the participants included in this study, some had problems completing all APD tests due to difficulties understanding the task or lack of motivation. The results from these test occasions were excluded from the statistical analysis.

Procedure

The children were tested at school in a quiet room in a sound-isolated booth (Mini 250, Industrial Acoustics Company, UK). Hearing sensitivity and middle ear function were assessed and the previously described APD test battery was administered in all participating children. Pure tone hearing thresholds were obtained using a GSI61 (Grason Stadler Inc. USA) diagnostic audiometer with TDH 39P earphones (Telephonic, USA) calibrated to ISO 389 standards. Middle ear function and acoustic reflexes were examined using a GSI 38 (Grason Stadler Inc. USA) immittance unit. The behavioural auditory processing assessment was performed using a computer with DT 770 Pro headphones (Beyer Dynamic, Germany). All children underwent auditory processing assessment with the tests from the Norwegian AP test battery, as described in Table 2.

Auditory processing category	*Behavioural test*
Monaural low redundancy speech	the FW test, HIST speech in noise test
Binaural integration of speech	the CW test and the DD test
Temporal processing	the GIN test, the FP test, and the DP test
Binaural interaction	the BMLD test
Speech in noise	the HIST speech in noise test

Table 2: The behavioural processing tests performed in paper 2 and 3, depicted in their respective auditory category.

Statistics

The number of patients needed was calculated from a power analysis program. A sample size of 44 children in each age group would provide a power of 0.90 for ANOVA analyses for main effects amongst the groups, with an assumed standardised effect size (mean difference between the groups/SD) of 0.5 and a significance level of 0.05. Homogeneous groups were assumed. A high degree of power was requested as the results should be generalized and applied to the Norwegian population.

Linear mixed models (LMM) were used to identify any significant effects of age, ear and gender on the APD tests, as well as for interactions amongst these variables. To give some protection against false positive findings due to multiple testing, a significance level of 0.01 was used. Bonferroni corrections were applied for post-hoc pairwise comparisons for categorical variables with more than two levels.

The assumption of normality for each variable was examined by visual inspection of histograms and normal quantile-quantile (Q-Q) plots and tests for normality. When the normal assumptions were not met, the data were transformed or corresponding non-parametric analyses were used. Intra-class correlation coefficient (ICC) for consistency (McGraw and Wong, 1996) was used to

assess the test-retest reliability for each of the APD tests, supplemented by paired t-tests or Wilcoxon signed rank tests to check for learning effects. The uncertainty in the ICC was assessed by bootstrap percentile confidence intervals.

Paper 2 and 3

Method

The study population for papers 2 and 3 was recruited from Statped West, a national service in Norway for special needs education (28 children with confirmed listening difficulties) and from local schools and by word of mouth (18 children with no auditory, attentional, learning or language disorder confirmed by parental interview). Listening difficulties were confirmed by scores at or below the 15th percentile on the auditory processing (AP) scale of the auditory processing domains questionnaire (APDQ) (O'Hara and Mealings, 2018).

All children underwent auditory processing assessment with tests from the Norwegian AP test battery, as described in Table 3. Participants were diagnosed with APD if performance was:

- at least two SDs (or the lower 2.5 percentile) or more below age expectations, in at least one ear on at least two different auditory processing categories (American Academy of Audiology, 2010),
- with at least one of the failed tests having used speech stimuli and one having used non-speech stimuli (British Society of Audiology, 2018).

Auditory processing category	*Behavioural test*
Monaural low redundancy speech	the FW test
Binaural integration of speech	the CW test and the DD test
Temporal processing	the GIN test, the FP test, and the DP test
Binaural interaction	the BMLD test

Table 3: The behavioural processing tests performed in paper 2 and 3, depicted in their respective auditory category.

Subjects

Children aged 8 to14 years who were native speakers of Norwegian, were able to complete the Norwegian AP test battery and fulfilled the following inclusion criteria were eligible; pure-tone audiometry thresholds ≤20 dB at all octave frequencies from 0,25 to 8 kHz; word recognition score in quiet of >90% on speech audiometry; normal middle ear function as assessed by otomicroscopy and tympanometry (single peak and tympanometric peak pressure greater than -100 daPa, contralateral acoustic reflex thresholds between 70 and 100 dB HL; and normal auditory brainstem responses (ABR) to 75dB click stimuli at 11.1 clicks/sec. Children with other disorders that precluded completion of the AP test battery did not enter the study. Children were not excluded based on previous bouts of OME.

Three children were excluded from the study (paper 2) because the TEOAEs didn't meet the study's quality criteria (two from the APD group and one from the non APD group). The late CAEP measurements (paper 3) could only be done if personnel and equipment were available, therefore ALLR and P300 were not assessed in 11 children (five from the APD group and six from the non APD group).

Procedure

Hearing sensitivity and middle ear function were assessed and the previously described AP tests were administered in all participating children. All audiological testing was performed in sound isolated rooms. Pure tone hearing thresholds were obtained using a clinical audiometer (Aurical; GN Otometrics, DK) with TDH 39P earphones (Telephonic, USA), calibrated to ISO 389 standards. Middle ear function and acoustic reflexes were examined using a GSI 68 (Grason-Stadler, USA) or AZ26 (Interacoustic, DK) immittance unit using a 226 Hz probe tone. Ipsilateral and contralateral acoustic reflexes were tested at 500 and 1000 Hz. Eighth cranial nerve and auditory brainstem function were assessed using clinical ABR equipment running software version 2.6.0 (Audera; Grason-Stadler, USA). The behavioural auditory processing assessment was performed using a computer with DT 770 Pro headphones (Beyer Dynamic, Germany). Finally, TEOAE testing was performed using an Echoport ILO 292-II (Otodynamics, UK) with software ILO V6 and UGD TEOAE probe (Otodynamics, UK).

The children recruited from Statped West underwent neuropsychological and language evaluation because of the likelihood of comorbidity of APD and other neurodevelopmental disorders. Twenty-four of these children were tested on the Integrated Visual & Auditory Continuous Performance test+ (IVA+) (Sandford and Turner, 1995) to examine their continuous performance on the same auditory or visual task presented on a computer. The children were instructed to click the mouse-button when they saw or heard number 1, and ignore the number 2. The IVA+ test consisted of five sets of 100 trials each. Each set started with a high demand block of 50 trials when the target frequency (i.e., the 1s) was high followed by a low demand block of 50 trials when the foils (i.e., the 2s) were numerous compared to the targets.

The IVA+ assess performance with tasks that require the participant to remain prepared to respond to an infrequent target (i.e., the 1s) over an extended period of time and measures both the maintenance of attention and inhibitory control. The scores of auditory (ASust) and visual sustained

attention (Vsust) were used. The Asust and Vsust scores provide a measure of a person's ability to accurately and quickly respond in a reliable manner to auditory and visual stimuli under low demand conditions. In addition, it includes the ability to sustain attention and be flexible when things change under high demand conditions.

Otoacoustic emissions measures (paper 2)

Linear TEOAEs were recorded to clicks at 60 ± 3dB peSPL and 50 clicks/s, with altering conditions of contralateral broadband noise (CBBN) presented at 60 dB SPL. The test paradigm is described in Table 4**.** TEOAE validity criteria were set at reproducibility ≥70% and the signal-to-noise ratio (SNR) ≥3dB in the condition without CBBN. For the emission waveforms that met this requirement, the reproducibility values within the frequency bands from 1 to 4 kHz were 70% or higher. The TEOAE suppression effect was estimated in two ways:

1. Absolute suppression (ΔTEOAE) was calculated by subtracting the emission levels with CBBN from emission levels without CBBN , expressed in dB for the overall response and for the frequency bands centred around 1.0, 1.5, 2.0, 3.0 and 4.0 kHz (Veuillet et al., 1991).
2. Normalized index (ΔTEOAEn). The TEOAE amplitudes were converted into linear scale (re: 20μPa). The change in TEOAE amplitude due to CBBN was normalized to the TEOAE amplitude without CBBN (TEOAE baseline), and quantified as percentage change from baseline amplitude (ΔTEOAEn = ΔTEOAE/TEOAE baseline) (Guinan et al., 2003).

AMLR recordings (paper 3)

The participating children were evaluated by recordings of AMLR, ALLR and P300 measures. The test paradigms are described in Table 4.

Bipolar click stimuli were presented separately to the right and left ear, and responses were recorded both ipsi- and contralaterally for the stimulated ear. Measurements of component magnitude (peak amplitude) and timing (peak latency) in individual averages were made after

inspection of the waveform. Peak ERP amplitudes were defined as the maximum negative or positive value in the 10-24 ms (Na) and 20-38 ms (Pa) post stimulus onset intervals, measured from baseline to peak. Peak-to-peak amplitude was computed as the absolute difference in voltage between Pa and Na peak amplitude. Latency for Na and Pa was measured from the onset of the stimulus.

ALLR and P300 recordings (paper 3)

A single two-tone oddball ERP paradigm was used, with stimuli composed from spectrally composite tones of 80 dB with a 500 Hz fundamental frequency and harmonics at 1000 Hz (standard) and 1500 Hz (target), presented binaurally. The participants were instructed to respond to the target stimuli by pressing a response key as quickly as possible, with their reaction times being recorded. The hit rate was measured as the number of correct responses to the target stimuli, which was thought to reflect the difficulty level and the individual's focus on the task.

Continuous electroencephalographic (EEG) activity was recorded with a Brain Vision amplifier from 18 monopolar Ag/AgCl electrodes fixed on an Easycap, mounted according to the international 10-20 system. From the averaged EEG recordings, the N1 and P2 components elicited by standard stimuli, and the P300 component elicited by correctly identified target stimuli were identified. Peak ERP amplitudes were defined as the maximum negative/positive amplitude in the 70 – 140 ms (N1), 140 – 250 ms (P2), and 250 – 650 ms (P300) post stimulus onset intervals. Because of the slow wave nature of the P300 amplitude, especially in normally hearing subjects, the mean P300 amplitude of the post stimulus interval from 250 to 650 ms interval was also calculated.

Based on the results on the APD assessment, the participating children were divided into three groups: i) the APD group if they had reported listening difficulties and met the diagnostic criteria for APD, ii) the non APD group if they had listening difficulties and did not meet the diagnostic

criteria for APD, iii) the control group if they had no listening difficulties and were not diagnosed with APD.

Test	Test paradigm	Stimuli	Task
TEOAE	Standard linear differential stimulus paradigm with CBBN (ILO V6). Recordings time windowed from 2 to 20 ms.	80 µsec click stimuli, presented at 60 ± 3dB peSPL at 50 clicks/s, within frequency bands from 1 to 4 kHz. CBBN (white noise, 0.2 to 20 kHz) presented at 60 dB SPL, 3s duty cycle of noise. Responses averaged over 260 sweeps to 1040 clicks with and 1040 without CBBN. Noise artefact rejection level of 6 mPa.	Passive paradigm
AMLR	Standard AMLR paradigm (Audera). Electrode montages at Fz (high forehead) referred to A1 (left earlobe) or A2 (right earlobe), ground (mid forehead), recorded ipsi- and contralateral for stimulated ear.	100 µsec bipolar click stimulus with alternating polarity, presented monaurally at 70 dB nHL at 7.1 clicks/s. Impedances were kept below 10 kΩ. Rejection level set to ±45µV, measurements exceeding 10% rejection were manually discarded.	Passive paradigm
ALLR/ **P300**	Two-tone oddball 78aradigm (Brain Vision). 18 monopolar Ag/AgCl electrodes on Easycap, mounted according to the international 10-20 system. Data obtained from the midline electrodes (Fz, FCz, Cz and Pz) were analysed. Bipolar electrodes placed at the outer canti of the right eye for recordings of eye movements	200 stimuli composed from spectrally composite tones of 80 dB with a 500 Hz ff, presented binaurally at a rate of 1 Hz, onset asynchrony of 1000 ms • 160 standard (harmonics at 1000 Hz); • 40 target (harmonics 1500 Hz presented randomly) • Impedances were kept below 10 kΩ, EEG data were baseline (-100 to 0 ms) corrected, low pass filtered and corrected for eye movements artefacts (Brain Vision Analyser 2). Epochs containing amplitudes exceeding ± 100 µV were rejected before averaging.	Respond to the target stimuli by clicking a response key

Table 4. Summary of test paradigms for the TEOAE, AMLR, ALLR and P300 measures. ff = fundamental frequency

Statistical analyses

When planning the study, the number of patients needed was calculated from a power analysis program. A general effect size of 0.5 between the groups was considered a clinical effect based on previous studies of TEOAE suppression (Sanches and Carvallo, 2006) and AEP (Jirsa and Clontz, 1990, Liasis et al., 2003). The study's final sample size of 43 participants provided a power of 0.81 for ANOVA analyses for main effects amongst the three groups, with an assumed effect size (mean difference between the groups/SD) of 0.5 and a significance level of 0.05.

Analyses of variance (ANOVA) were used to identify any significant effects of participant group on each of the behavioural AP tests.

LMMs were used to identify any significant effects of participant group, ear, age or electrode montage on otoacoustic emissions (paper 2) and electrophysiological values (paper 3), as well as for interactions amongst these variables. Heterogeneity in variance across age groups was allowed for. P-values for the overall effects for group or frequency were obtained by likelihood ratio tests, and pairwise differences were assessed by t-tests. Similar LMMs that included frequency as an independent variable were fitted to assess differences between response frequencies (paper 2). For the N1, P2, P300 latencies, linear regression analyses were conducted to assess the main effects of group and age, as well as for interactions amongst these variables (paper 3). Bonferroni corrections were applied for post-hoc pairwise comparisons. Statistical analyses were performed both with two groups (normal hearing (NH) and listening difficulties) and three groups (NH, APD and non APD). As the grouping did not have a major effect on the results, the group effects were presented for the model with 3 groups.

To give some protection against false positive findings due to multiple testing, a significance level of 0.01 was used in paper 2. In paper 3, p-values <0.05 were considered to be statistically significant. Bonferroni-Holm corrections were applied to adjust for multiple comparisons in the

correlation analyses in paper 3. For a categorical description of the level of correlation, we used the suggestions by Cohen: low r= 0.10 to 0.29, moderate r= 0.30 to 0.49, strong r=0.50 to 1.0 (Cohen, 1988).

The assumption of normality for each variable was examined by visual inspection of histograms and normal Q-Q plots and tests for normality. When the normal assumptions were not met, the data were transformed or corresponding non-parametric analyses were used.

In paper 2, Pearson's correlation analyses were used to assess associations between TEOAE measures and SNR for each ear, and between MOC suppression and the behavioural AP measures. In paper 3, Pearson's correlation analyses were used to investigate the relationships amongst the AEPs, continuous performance measures and behavioural AP measures. As the separate ear results were moderately to highly correlated for each of the behavioural AP measures of CW, DD, FP, DP and GIN (r 0.536 to 0.934, $p<0.001$), the ear scores were averaged for use in the correlation analyses. This was not required for the FW or BMLD tests as these had already been conducted binaurally.

4. MAIN RESULTS

Paper 1

The results from the APD tests are presented by boxplots, split by age and ear in Figure 6. No significant gender differences in test performance were found. With the exception of GIN and BMLD, the test performance increased by age, with no pairwise difference found between the 11- and 12-year-olds. The seven-year-olds had lower performance compared to age groups 9-12 years, with large variability between individuals and low performance on many tests. For the dichotic speech tests CW and DD there appeared to be a ceiling effect for the oldest age groups, and significant better results in the right ear. For the DD test the REA decreased by age. There was a tendency towards decreasing REA for CW as well, but this effect was not statistically significant (p=0.054). For the FP and DP tests, there seemed to be a floor effect for the youngest age groups.

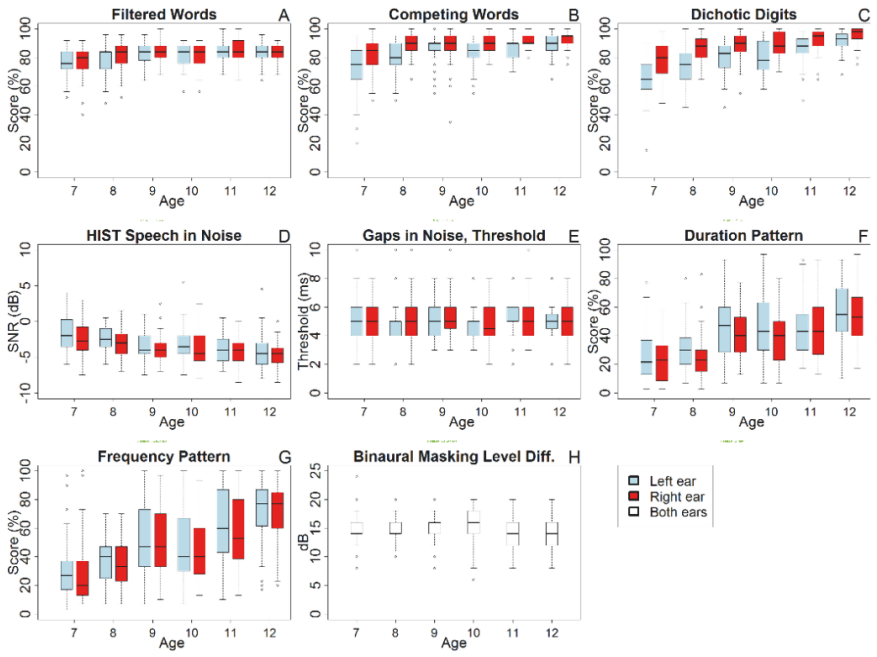

Figure 6. Boxplots of the scores on the APD tests among children aged 7 to 12 years of age. The centre line in each box indicates the median value, the box contains 50% of cases. The whiskers

represent the overall range in scores. Outliers, which are defined as values extending more than 1.5 box-lengths from the edge of the box, are indicated with circles.

The reliability of individual performance between the first and second test session for the 10-year-old children was excellent for the DP tests and DD left ear, and from fair to good for the remaining tests. There was no learning effect found for the non-speech tests. For the speech test FW, performance improved after two weeks, indicating a learning effect.

The normative values were presented by the age categories seven years, eight years, 9-10 years, and 11-12 years. For the GIN and BMLD tests, data were pooled across ear and age. Age groups were combined to reduce the estimate uncertainty per age category and to ensure that the number of observations within each age category was sufficient for obtaining a smooth profile across the age groups. The results from the statistical analysis of age differences were also considered. The 7 year olds had larger variability and lower scores on most tests results, thus we chose to present the results for the children aged seven and eight years separately.

Paper 2

The data for TEOAE amplitudes, absolute contralateral TEOAE suppression and normalised TEOAE suppression are presented by boxplots in figure 7. Overall, mean TEOAE amplitude decreased significantly after adding CBBN. The mean TEOAE amplitude (groups collapsed) was 9.6 dB SPL (SD 4.1dB). As contralateral noise was introduced, the mean TEOAE amplitude decreased by 1dB SPL (SD 0.6dB). The mean normalized index (ΔTEOAEn) was 10.5% (SD 6.5%). No significant group, age or ear differences were observed for contralateral TEOAE suppression in dB or as a normalized index ($p > 0.01$). The non APD children showed weaker contralateral suppression compared to the APD children and control participant groups, but the group differences were not significant.

There were no differences in suppression between groups or ears on the various response frequencies. However, an overall decrease in TEOAE suppression with increased response frequency from 1 through 4 kHz was observed. No significant group, ear or age effect were observed on SNR.

Overall, low correlations between MOC suppression and the AP tests, and between TEOAE amplitude and the suppression measures were found (Pearson correlation coefficient (r) ranged from-0.23 to 0.04, $p > 0.01$). However, the results indicated a strong correlation between SNR and TEOAE baseline amplitude (right ear $r = 0.78$, left ear $r = 0.83$, $p < 0.001$), but low correlation to MOC suppression.

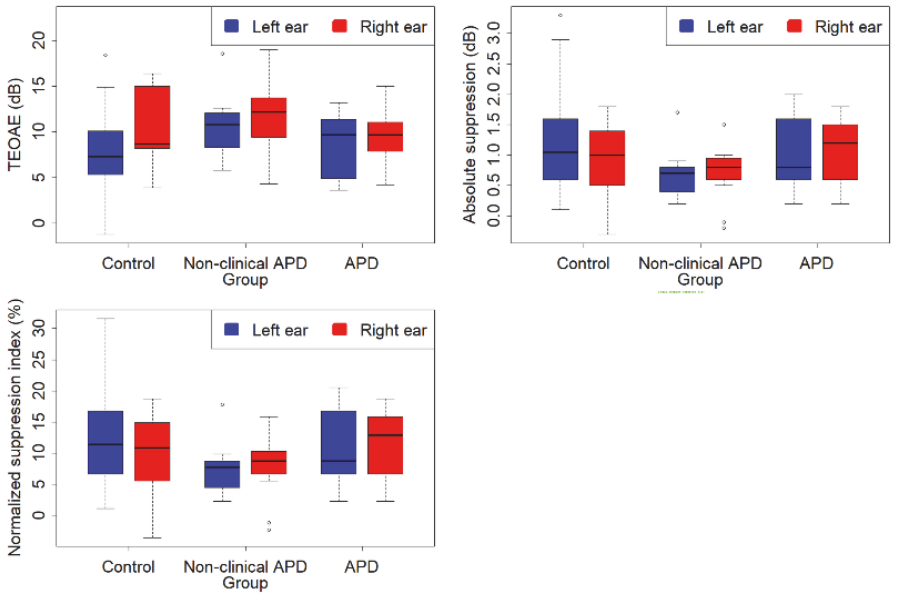

Figure 7. Boxplots of TEOAE amplitudes (top left), absolute contralateral TEOAE suppression values (top right), and normalized TEOAE suppression values (bottom left) for all participating children.

Paper 3

The results from the MLR measurements are presented as boxplots, split by ear and group in Figure 8. The results from the ALLR and P300 measurements are presented as average waveforms in Figure 9. No significant interaction effects were found, and the results from models with main effects only are presented.

In the case of Sustained Auditory Attention Quotient, the non APD group mean (86.0 ± 32.2) fell in the slightly impaired range while the APD mean (64.3 ± 38.0), fell in the moderately to severely impaired range, according to the interpretation manual (Sandford and Turner, 2004). However, the difference was not statistically significant (p= 0.109). When standardizing the Norwegian version of the IVA+ scales, normal hearing children performed with a mean of 100, with a standard deviation of 15 (Ukvitne and Nicholas, 2017).

A significant group effect (p <0.001) was observed for the Na latencies, with the APD and non APD groups showing similar Na latencies that were prolonged relative to the NH group. Larger Na-Pa amplitudes were observed for left versus right ear stimulation (p = 0.009).

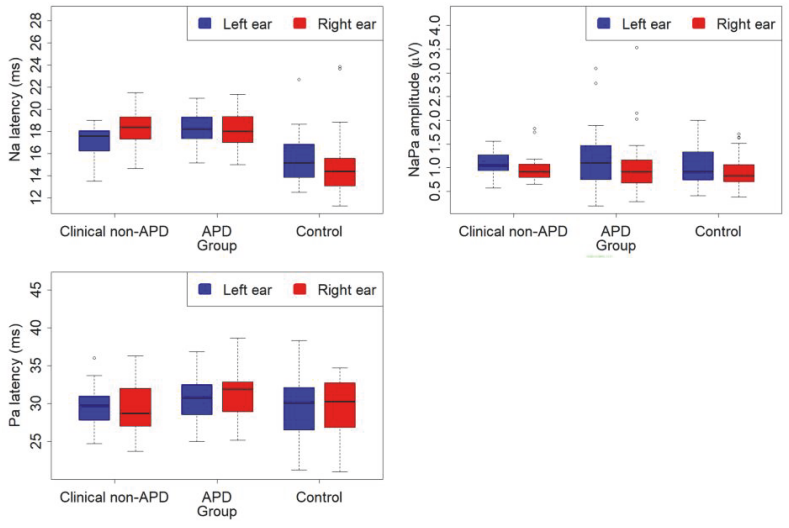

Figure 8. Boxplots of Na latency, Pa latency and NaPa amplitudes for the three groups.

A significant group effect was observed for the P300 mean amplitude ($p = 0.019$) and latency ($p = 0.021$), with attenuated amplitudes and prolonged latencies for the APD and non APD groups compared to the NH group. The group effect for the P300 amplitude was not significant ($p = 0.053$). However, when comparing two groups (listening difficulties and NH) the group effect was significant, with 5.9 μV lower amplitudes in children with listening difficulties ($p = 0.008$). Significant within-subject effects ($p < 0.001$) of midline electrodes on ALLR and P300 results showed the expected topographical anterior-posterior effect, with largest responses in Cz and Pz, respectively. Hit rates and reaction time for the P300 measurements were generally high, with median hit rates of 39 to 40 and a mean reaction time of 376.9 ms (SD 103.9), with no significant group differences, indicating focus on the task.

Overall, mostly non-significant or low to moderate correlations were found between the AEP, AP tests and continuous performance tests. Significant moderate correlations were observed between Na latency and the AP tests CW left ear and DD, between P2 latency and DP, P2 amplitude and GIN (p 0.01 to 0.05), and between most P300 measures and CW left ear, FP, DP and DD ($p < 0.001$ to 0.05). Significant moderate correlations were observed between auditory sustained attention and DD and Pa latency left ear, and between visual sustained attention and DP and DD.

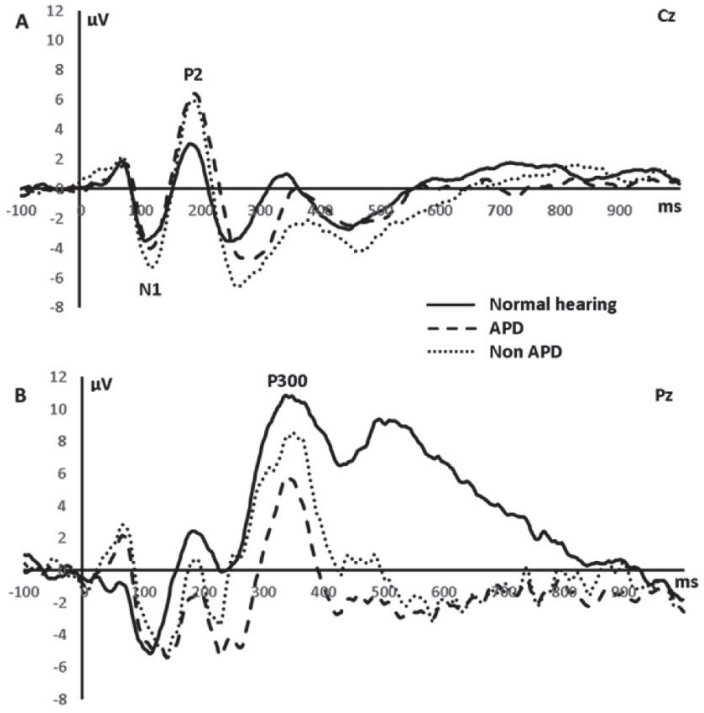

Figure 9. Grand average AEP waveforms for the ALLR (A) and P300 (B) for the normal hearing, APD and non APD groups. ALLR and P300 results are shown for recordings from Cz and Pz, respectively.

5. DISCUSSION

Study Design

A prospective, repeated measure design was chosen for our studies, with one group of children for paper 1 and three groups for papers 2 and 3. In repeated measure designs, multiple measurements of each participant are performed. This allows the researcher to exclude the effects of individual differences that could occur if different subjects were used (Howitt, 2011). Factors such as working memory, age, hearing and other important variables remain the same in repeated measures as one person is taking part in all measurements. A repeated measure design can use fewer subjects to detect a desired effect size due to greater statistical power. However, in papers 2 and 3, we compared three independent groups.

On the other hand, repeated measure designs have some disadvantages. The biggest drawbacks are known as order effects caused by multiple measurements. Order effects are due to the order in which the measurements are performed, not due to the measurement itself. For example, scores could decrease over time due to fatigue, boredom affecting concentration and performance in reaction times or accuracy, or increase due to learning (Collie et al., 2003). Order effects can interfere with the analyst's ability to correctly estimate the effect of the variables measured, but can be reduced by counterbalancing. In paper 1, this was accounted for by randomizing the test order in respect of test order and ear order.

The study population

Paper 1

The normative values were collected in one part of the country, and the local dialect might have introduced bias towards the results. However, the words and numbers used were dialect

neutral and familiar to children aged seven and above, reducing the potential geographical bias. In addition, a one-centre study reduces the methodological variations often seen in multicentre studies.

Children with previously diagnosed attention disorder or autistic spectrum disorder possibly precluding completion of the AP test battery, were excluded from the study population. The diagnostic process for attention disorder takes approximately four years in Norway (Andersson et al., 2004). It is likely that the study sample included a representative number of children with neurodevelopmental disabilities, thus reflecting a population cross-section and avoiding truncated norms.

Papers 2 and 3

When the work behind this thesis started, APD was a new disorder in Norway. The AP test battery was available for this study only, and the APDQ had recently been translated and standardized in Norwegian. Inclusion of participants was time consuming due to limited knowledge of the disorder in the general population, the lack of available AP tests in audiological clinics and a limited study population. Eleven of the included participants were not assessed by ALLR and P300 due to lack of personnel and equipment, which limited the population for these measures (paper 3). However, the statistical analyses were performed both with two groups (NH and children with listening difficulties) and three groups (NH, APD and non APD) with similar results, indicating that the sample size or grouping had no significant impact on the results.

Study protocol

Various measures were performed to assess auditory processing, the central auditory nervous system and cognitive tests, providing valuable insight to the dynamic process of listening. The design differentiates this study from previous studies on children with APD and listening difficulties, which have focused on either AP tests, otoacoustic emissions or electrophysiological

measures. The study design, including children with confirmed listening difficulties diagnosed with APD or not, is unique and identifies the heterogeneous group underlying listening difficulties. The multidisciplinary perspective is also important, determining the potential nature of each child's listening difficulties with respect to APD and comorbid developmental disorders (papers 2 and 3).

The AP tests used were the same in all papers. The AP testing was performed by three different audiologists in paper 1, and two different speech-language therapists in papers 2 and 3. TEOAE and AMLR measurements were done by two examiners, ALLR and P300 measurements were done by one examiner. This variability in testers could increase the variability of test results. However, settings and test instructions were uniform as decided upon in the protocols.

Paper 1

The final CD recording of the Norwegian APD test battery contained a calibration tone and a short story for setting the most comfortable sound level, usually around 50dB SPL. This may have introduced methodological variability, since the stimulus level was not standardized.

The potential order effect from the repeated measure design was accounted for by randomizing the AP test order in regard to test and ear order, to minimise the influence on variation in attention and learning effects. Within each age group and gender, ear order and test order was alternated between subjects with the right ear tested first in half the participants and the left ear tested first in half the participants. Nevertheless, the duration and order of the test session may have had impact on the results in the youngest age group, requiring more time to complete all the testing due to their greater susceptibility to fatigue. Despite randomizing test order to account for a potential fatigue effect, a learning effect influenced the outcome for FW and CW left ear, with better performance when the speech tests were administered last.

Paper 2

The TEOAE assessments followed the standard ILO V6 procedure ensuring minimal methodological variation. The recording and stimulus parameters were chosen based on previous research, facilitating comparison of results.

The linear paradigm was chosen based on the advantage of keeping the linear part of the emission and the suppression information intact, providing optimal MOCR magnitude (Kemp, 1978). The TEOAEs were recorded in alternating conditions of quiet and contralateral broadband noise (CBBN) to minimize effects of subject and stimulus level changes over time. The stimulus paradigm was chosen based on reports of largest TEOAE suppression observed when CBBN was around 60dB SPL (Collet et al., 1990, Ryan et al., 1991, Veuillet et al., 1991, Lilaonitkul and Guinan, 2009), and stimuli were lower intensity level clicks around 60dB SPL (Hood et al., 1996), both of which reduced confounding effects of the middle ear muscle reflex (MEMR) (De Boer, 2012). All participants had clinical acoustic reflexes between 70 and 100dB HL. Given previous reports showing that the MEMR affected lower frequency signals more than signals above 1 kHz (Collet et al., 1990, Veuillet et al., 1991, Berlin et al., 1993b), and tone activators of 1-2 kHz yielded higher auditory reflex thresholds compared to wideband acoustic reflectance methods (Feeney et al., 2003), the confounding effect of the MEMR on suppression was expected to be minimal.

TEOAE response was accepted as valid if the reproducibility was ≥70% and the TEOAE signal-to-noise ratio (SNR) was ≥3dB in the condition without CBBN. More stringent criteria of 80% rejection could have been set. However, the statistical analyses were conducted using a reproducibility cut-off of both 70% and 80%. As this criterion did not have a major effect on the results, only the 70% reproducibility figures were presented, since more data were included. A more stringent SNR criteria of 6 dB SNR could have resulted in increased TEOAE amplitudes (Backus, 2007, Mishra and Lutman, 2013), and less bias and variability errors (Francis and Guinan, 2010,

Goodman et al., 2013). Nonetheless, the lack of group effect and the robust grand overall mean SNR of 9.8 dB despite a relatively low stimulus level, could reflect sufficient SNR in the present study.

Paper 3

The morphology and latency of the obligatory components of AEPs is highly dependent upon the stimulus and acquisition parameters (Hall, 2006). Stimulus changes, such as rise time, duration, inter-stimulus interval (ISI), intensity level, stimulus complexity and tone burst frequency, may affect the AEPs (Naatanen and Picton, 1987, Roberts et al., 2000). The AMLR and ALLR measures were performed in a passive paradigm to avoid modulating concentration and motivation, which may affect the AEPs. Stimuli such as clicks and tones were used to avoid confounding effects from linguistic load.

For the AMLR, the default Audera protocol was used, which both generated the acoustic stimuli, recorded neuro-electrical activity from the scalp and derived the waveforms, ensuring minimal methodological variation. Electrode placement over hemispheric electrode sites ensured neuropathology being more evident (Mason and Mellor, 1984). The relatively high intensity of the click stimulus (70 dB nHL), the repetition rate (7.1 clicks/second) providing a relatively long ISI, and low impedances (<10 kΩ) enhanced the AEP amplitudes and improved the SNR. Eye movements were identified visually together with the inspection of myogenic potentials (temporalis or frontalis muscles). The lack of recordings for eye movements with bipolar electrodes and corrections for eye movements artefacts could have introduced a potential confounding and variability error of measurements.

For the ALLR and P300, the relatively high intensity of the spectral composite tones (80 dB), the repetition rate (1 Hz) providing long ISI, and low impedances (<10 kΩ), enhanced the AEP amplitudes and improved signal to-noise-ratio. All data were baseline (-100 to 0 ms) corrected, low pass filtered, and corrected for eye movement artefacts for optimal quality (Gratton et al., 1983).

One of the strengths of the ALLR and P300 was that one observer did all the measurements, thus reducing the variability of settings and measurements.

Interpretation and comparison with other studies

Paper 1

Gender and age effects

The lack of gender effect observed in this study is consistent with previous reports (Keith, 2000, Fuente and McPherson, 2006, McDermott et al., 2016, Pedersen et al., 2017), indicating that separate norms based on gender were not required.

The increasing test performance and reduced variability with age in the participating children, with the exception of the BMLD and GIN test, support a maturational course of auditory processing. The lack of age effect on BMLD and GIN were consistent with results from the Danish test battery (Pedersen et al., 2017), indicating that neural connections underlying binaural processing and temporal resolution are present at birth, but mature during early childhood (Moore, 1985, Kapfer et al., 2002, Shinn et al., 2009, Amaral and Colella-Santos, 2010). Whether an age effect should be expected for tests of binaural processing and temporal resolution in general remains the topic of much debate, with varying reports of maturational courses (Roush and Tait, 1984, Irwin et al., 1985, Wightman et al., 1989, Hall and Grose, 1990, Grose et al., 1993, Hall and Grose, 1994a, Hall et al., 2004, Moore et al., 2011). Much of this variation is thought to result from differences in tests and methods used to assess binaural processing and temporal resolution.

Binaural speech tests

The CW and DD test results all showed age effects, eventually reaching overall ceiling effects in the older aged participants. The presence of a ceiling effect is often found on AP tests and are

accepted, as the goal is to diagnose a patient with scores worse than normal (Arnst, 1981, Bellis, 2003, Fuente and McPherson, 2006, Bellis et al., 2011).

The REA found in the present study for DD and CW decreased with age. However, only the DD showed significant age-ear interaction. Interestingly, these findings were consistent with results reported by Pedersen et.al (2017). The tendency towards an REA for dichotic tests has been widely reported in younger subjects for linguistically loaded stimuli, with larger REA with higher linguistic loads (Broadbent, 1954, Kimura, 1961b, Kimura, 1961a, Hugdahl et al., 1990). The reason for this phenomenon is widely discussed, and is thought by many to reflect the specialisation of the left hemisphere for language, together with the suppressed ipsilateral auditory pathways under dichotic listening (Rosenzweig, 1951, Kimura, 1961a, Musiek and Weihing, 2011, Hugdahl and Westerhausen, 2016, Moore et al., 2018).

Monosyllable words are thought to involve the highest verbal workload for dichotic testing, and are thus optimal for reflecting hemispheric dominance for language (Moncrieff, 2011). In addition, an increase in working memory load on the dichotic tasks results in larger ear advantage (Penner et al., 2009). The decrease in REA with age may reflect the maturation of language skills combined with more developed working memory (Penner et al., 2009). The diminishing right ear advantage by age in the CW and DD tests might also be partly due to the ceiling effect.

Temporal ordering tests

Overall, the scores obtained on the FP and DP tests were worse than those reported on these and similar tests in other age-equivalent studies (Musiek et al., 1982, Stollman et al., 2004, Schochat and Musiek, 2006, McDermott et al., 2016). These differences could have been related to participant preparation (e.g. instructions and use of practice trials), or to participant language, whereby different phonetic features could contribute to distinct developmental courses for temporal processing in speakers of different languages (Chermak and Musiek, 1997). The high inter-subject

variability and poor results in the youngest age groups indicate influence from linguistic experience and working memory (Cacace et al., 1992, Talcott et al., 2000, Bellis et al., 2011).

Despite the high inter-subject variability, with a probable floor effect in the younger participants, a general improvement across all age groups was noted. This suggests the maturational course for FP and DP processing could continue beyond 12 years, generally consistent with previous reports of frequency and duration discrimination reaching a mature state by 10 years of age and adulthood, respectively (Maxon and Hochberg, 1982, Sinnott and Aslin, 1985, Olsho et al., 1987, Elfenbein et al., 1993, Jensen and Neff, 1993, Moore et al., 2011).

Test-retest reliability

Evaluating test-retest reliability is difficult, and no clear agreement on how to do it exists. The Intra-class correlation coefficient (ICC) reflects both the degree of correlation and agreement between measurements. For the DD left and DP tests, excellent reliability was found, while the other AP tests showed fair to good reliability (Fleiss, 1986). The ICC increases with the variance of the population, and the number of subjects. In this study, the ICC was determined by a relatively small, homogenous group, thus it may be underestimated. Therefore, the test-retest reliability for the 10-year-old children was found to be satisfactory for all tests, generally consistent with reports of test-retest reliabilities for children aged 8-11 years (Keith, 2000), children aged 6-16 years (Pedersen et al., 2017), and significant learning effects in CW and FW scores in six- and nine-year old children (Amos and Humes, 1998). Different age groups and statistical methods complicate detailed comparisons between the above studies.

Recommendation for final test battery

When recommending a final battery of tests for APD, we have considered the task requirements, including auditory categories, and the linguistic and cognitive demands of the tasks. The varying results obtained on the tests of AP evaluated in this study also have implications for the choice of tests remaining in the final test battery for identifying APD in Norwegian children.

Test performance can be highly influenced by age, auditory experience, or the cognitive skills used on the task, such as attention (Riccio et al., 1994, Riccio et al., 1996, Tillery et al., 2000, Gyldenkaerne et al., 2014), cognitive abilities (Tomlin et al., 2015), motivation (Silman et al., 2000) and linguistic factors (Richard, 2007). Behavioural tests using non-verbal or simple speech stimuli (e.g. GIN, DD), as well as tests with minimal memory load and a simple response mode (e.g. GIN, BMLD), reduce the influence of language and cognitive factors. However, there is some ambiguity concerning the influence of verbal working memory and linguistic experience on dichotic tests, with reports of higher working memory load on DD compared to CW, requiring the storage of four words before repeating the words heard (Penner et al., 2009, Cacace and McFarland, 2013). On the other hand, digits represent a closed set of highly learned verbal stimuli, thus engaging the language dominant hemisphere less then single syllable words (Porter and Berlin, 1975, Moncrieff, 2011).

In order to supply the audiologists with the possibility to select behavioural auditory tests that are appropriate to the child's age, linguistic experience and cognitive ability, we included both the CW and the DD tests. We do not recommend the use of FP and DP testing in the final test battery due to the high variance, low scores and poor compliance observed with these tests in our study.

The specificity of a battery of tests generally decreases as tests are added, and it is advisable to select the minimum number of tests necessary to provide the overall best sensitivity and specificity, while assessing the major auditory processes (Musiek et al., 1982, Wilson and Arnott, 2013). The goal of an efficient behavioural AP test battery, in regard to time consumption and cost-effectiveness must be kept in mind, and it is advised to choose one test from each auditory category. The final Norwegian test battery available for the clinicians to choose from consists of five tests involving both speech and non-speech stimuli; CW, DD, FW, GIN and BMLD. In addition, the HIST SIN may be used to assess speech in noise.

Paper 2

The absence of a group effect on the contralateral TEOAE suppression suggests that the MOC function was not compromised in the participants of this study, despite confirmed listening difficulties. This was consistent with reports from children with APD (Burguetti and Carvallo, 2008, Smart et al., 2019, Morlet et al., 2019) and SLI (Clarke et al., 2006), who had been tested with suppression of linear TEOAE. However, the results were inconsistent with reports from children with APD (Muchnik et al., 2004, Sanches and Carvallo, 2006) and listening difficulties (Yalcinkaya, 2010), in studies using a non-linear ipsilateral stimulus. It should be noted that reports comparing linear and non-linear TEOAE paradigms in children with APD, showed reduced suppression for both methods (Sanches and Carvallo, 2006).

The lack of association between contralateral TEOAE suppression and performance on individual AP tests was consistent with previous reports (Muchnik et al., 2004, Boothalingam et al., 2015), including those reporting a lack of association between MOCR and speech-in-noise performance (Mishra and Lutman, 2014), possibly due to top-down influences on task dependent attentional control of MOC function (de Boer and Thornton, 2007, Garinis et al., 2011). At least two potential reasons can be offered for this. First, behavioural measures of AP involve the coordination of several neural mechanisms that could be influenced by non-auditory factors (Allen and Allan, 2014). Previous studies have also shown MOC reflex strength to change with attention (de Boer and Thornton, 2007, Garinis et al., 2011, Harkrider and Bowers, 2009, Smith and Cone, 2015). Thus, investigations using suppressors other than white noise and active rather than passive test paradigms (such as listening conditions that require active attention), could reduce the variability seen in MOC function (De Boer, 2012) so that OAE suppression might better differentiate children with and without APD. The effect of attention was not controlled for in the current study, and hence cannot be used to explain the variability seen here. Second, the APD population is heterogeneous with a wide variety of deficits contributing to the diagnosis of APD and

the individuality of symptoms. In the present study, the participating children with listening difficulties were grouped into APD and non APD groups based on the results on the AP test battery used, and not on confirmed site(s)-of-lesion or sub-type of APD. If the participants had confirmed lesions involving specific brain regions associated with the MOC function or had been diagnosed with APD based on test specifically assessing those brain regions, the findings might have revealed abnormal MOC function.

Methodological comparisons across studies

Much of the variation seen in studies of MOC function is thought to result from methodological differences, which makes comparisons across studies difficult. Normalization of the suppression gave similar results as absolute suppression regarding effects of age, ear, group or frequency, implying similar measures of MOC functioning regardless of computational methods. This finding is contrary to reports of varying emission amplitudes across frequencies and ears affecting the ΔTEOAE, thus advocating the need for a normalized index (Guinan et al., 2003, Backus and Guinan, 2007, Garinis et al., 2011, Mishra and Lutman, 2013).

The use of absolute versus SNR methods for reporting OAE amplitudes varies. Some studies have reported higher TEOAE SNR resulting in increased TEOAE amplitudes (Muchnik et al., 2004, Butler et al., 2011, Mishra and Lutman, 2014). Others reported low or unspecified SNR, or did not assess SNR differences between the groups (Clarke et al., 2006, Sanches and Carvallo, 2006, Burguetti and Carvallo, 2008), which may have led to misinterpreting shifts in TEOAE levels due to noise as being true physiological inhibition.

The middle-ear muscle reflex could potentially confound the MOCR magnitude by influencing the stimulus and/or TEOAE as both are transmitted through the middle-ear. As previously discussed, the confounding effect of MEMR was likely minimal in this study. Comparable studies either did not report tests for MEMR (Sanches and Carvallo, 2006, Veuillet et al., 2007) or used clinical acoustic reflex procedures (Muchnik et al., 2004, Clarke et al., 2006, Burguetti and

Carvallo, 2008, Garinis et al., 2008, Yalcinkaya, 2010, Butler et al., 2011). However, the estimation of MOCR might have been influenced by MEMR in studies that used high click levels to evoke OAEs (Muchnik et al., 2004, Sanches and Carvallo, 2006, Yalcinkaya, 2010) and/or high CBBN levels (Muchnik et al., 2004, Yalcinkaya, 2010).

Paper 3

The present study showed AMLR Na latency and P300 latency and amplitude measures were sensitive to listening difficulties, but not exclusive to APD in children. These results only partly supported the study's hypothesis that the AMLR and ALLR would be more sensitive to APD whereas the auditory P300 would be more sensitive to broader listening difficulties not resulting from APD.

The prolonged Na latencies of 2.6 ms observed in the children with listening difficulties (APD and non APD groups collapsed) suggest slower processing and possibly more asynchronous neural firing in the auditory thalamo-cortical pathways that contribute to the Na wave (Naatanen and Picton, 1987). Neural dysfunction causing slower conduction times in the CANS cannot be ruled out, but the later waves N1 and P2 would also be expected to show a prolonged effect (although the present study's limited sample size and resulting effect on statistical power is noted).

The act of processing the P300 stimulus is complex and involves the intertwining of auditory, cognitive (including attention and memory), and language mechanisms (Medwetsky, 2011). The delayed P300 latencies of 113.9 ms and reduced mean amplitudes of 3.7 μV in the children with listening difficulties (APD and non APD groups collapsed), suggest neurocognitive dysfunctions related to allocation of attentional resources and working memory (Polich and Herbst, 2000). Research has shown that cognitive abilities like working memory and attention are linked to sensory perception and can affect speech comprehension, particularly in challenging listening conditions or when the signal is deteriorated (e.g., by hearing loss) (Arbogast and Kidd, 2000, Woods et al., 2001, Ronnberg, 2003, Ronnberg et al., 2008, Ronnberg et al., 2010, Rudner et al.,

2012, Ronnberg et al., 2013, Classon et al., 2013). Factors reducing the quality of the bottom-up signal may increase the required top-down cognitive capacities to interpret the signal (Rudner et al., 2009, Kramer et al., 2009). Despite normal peripheral hearing, this could also be the case for children with listening difficulties, independent of APD diagnosis.

The observed AEP differences amongst the groups, suggest these AEP measures were sensitive to listening difficulties but not to APD. On first consideration, these findings appeared to be inconsistent with previous reports of AMLR measures (Schochat et al., 2010), ALLR measures (Jirsa and Clontz, 1990, Jirsa, 1992, Liasis et al., 2003, Tomlin and Rance, 2016, Koravand et al., 2017) and P300 measures (Jirsa and Clontz, 1990, Jirsa, 1992) being sensitive to APD. However, the AP tests and criteria used to diagnose APD varied among studies, and none of those previous studies included a group of children with confirmed listening difficulties without APD. On closer consideration, these findings identify the long-standing challenge posed by the absence of universally accepted definitions and diagnostic criteria for APD, and the arbitrary effect this has on diagnosis (Wilson and Arnott, 2013). Of the children with listening difficulties which did not fulfil the present study's diagnostic criteria for APD (the non APD group), five and six children scored 2SDs or more below the age appropriate mean for at least one ear on at least one or two of the speech or non-speech tests, respectively. Only one child in the present study had all AP tests within the age expectations. If more liberal AP diagnostic criteria had been used, higher rates of APD diagnosis would have occurred, increasing the APD group. This reinforces calls to clearly consider differences in AP testing and diagnostics across studies of AP and APD (Medwetsky, 2011, Wilson and Arnott, 2013, Wilson, 2018).

On a broader consideration, the present findings were consistent with reports of AMLR, ALLR and P300 abnormalities in children with a range of disorders that include (or are likely to include) listening difficulties. Typical findings of prolonged Na and/or Pa latency in children with learning impairments (Arehole et al., 1995, Purdy et al., 2002) or language impairments (Milicic et al.,

1998), prolonged latency and/or attenuated amplitude for the waves N1, P2 or P300 in children with learning impairments (Purdy et al., 2002, Gilley et al., 2006), language impairment (Tonnquist-Uhlen, 1996, Bishop and McArthur, 2004), or dyslexia (Mazzotta and Gallai, 1992). These reports suggest that the problems related to listening difficulties are multimodal, and may be caused by cognitive, memory, attention, and language deficits.

Overall, the mostly non-significant or low to moderate correlations between the AEP and behavioural AP measures, indicate that the AMLR and ALLR are not measures of a particular AP ability assessed by these behavioural AP measures. The six significant correlations (p from 0.01 to 0.05) observed should be interpreted with caution as they could be incidental findings due to multiple comparisons. The moderate correlations observed between the P300 measures and the AP tests CW left, DD, FP, and DP suggest cognitive functions (such as attention and working memory) could influence the AP tests performance, consistent with previous reports of top-down modulation of the CANS (Riccio et al., 1994, Riccio et al., 1996, Tillery et al., 2000, Tomlin et al., 2015). However, the direction of causality is still not clear. Top-down cognitive mechanisms are linked to speech-perception in noise, and as the listening situation becomes poorer, the amount of cognitive capacity to comprehend speech will increase, requiring more listening effort (Kramer et al., 2009, Pichora-Fuller et al., 2016).

Auditory processing and cognition

In the case of sustained auditory attention quotient, the non APD group means fell in the slightly impaired range, while the APD group means fell in the moderately to severely impaired range. It is to be noted that the diagnosed attention disorder in some of the children may have influenced the ASust quotient. Thus, the decreased score in the APD tests could be associated by impaired auditory sustained attention. However, the correlations observed between AP tests and the

continuous performance tests were mostly low, and at best moderate, indicating that additional factors influenced AP performance in these participants.

The moderate correlations between auditory sustained attention and the dichotic digits test were consistent with previous reports from children with APD (Gyldenkaerne et al., 2014) or suspected of having APD (Sharma et al., 2009), and children with attention disorders (Keith and Engineer, 1991), indicating that dichotic listening involves some auditory attentional processes. Previous research on dichotic listening has shown the influence of cognitive functions like attention and working memory (Penner et al., 2009, Hugdahl and Westerhausen, 2016). Although auditory sustained attention correlated significantly with the DD test in the present study, the correlation was no longer significant when the Bonferroni-Holm adjustment was applied (although Bonferroni-Holm correction may lead to possible Type II errors due to lower critical p-value for significance).

The low correlations between auditory sustained attention and the P300 may reflect the complexity of the tasks, with the continuous performance test paradigms requiring multiple cognitive operations, and the allocation of more cognitive resources, compared to the oddball paradigm. Hence, the decline in test performance in the IVA +, may be attributed to the high mental workload for processing of information and the decrement reflective of the depletion of information-processing resources over time (Mishra et al., 2013b, Mishra et al., 2013a).

Correlations across abilities may reflect the complex processing of auditory information in the CANS, involving both serial and parallel processing within the auditory structures of the CANS itself, as well as shared processing with other sensory or higher order brain structures and systems (language, attention and executive control) (Ghazanfar and Schroeder, 2006, Peelle, 2012, Specht, 2014). The present findings show that top-down cognitive processes significantly influence, or are at least correlated with, auditory processing abilities.

Validity of the results

The internal validity of a study refers to the extent to which confounding factors might explain the observed results. The selection of subjects for participation represents a possible selection bias, and is relevant for all three papers. In developing norms for the AP test battery (paper 1), children from one part of the country were selected. This allows for linguistic bias due to the various dialects in the Norwegian language as previously discussed. However, the words and numbers used were dialect neutral and familiar to children aged seven and above and widely used in Norwegian speech audiometry (Quist-Hanssen). In papers 2 and 3, the children in the APD and non APD groups were referred for AP assessment based on listening difficulties, and some of the children had comorbid developmental disorders, possibly influencing the results.

In paper 1, the order of the APD tests was randomized between children in regard to test and ear order, to avoid confounding of attention and learning effect. In papers 2 and 3, age was accounted for in the LMMs, to minimize confounding of maturational changes due to age differences between the groups.

The external validity refers to the extent to which the study results can be generalized and applied to populations other than the one included in the study, at another time and place. In paper 1, a representative number of children from the general population was chosen based on power analyses, in order to allow extrapolation to the general population.

In papers 2 and 3, the children in the APD and non APD groups were referred for AP assessment based on listening difficulties. Given the similarity of the results to those described in other studies including children with listening difficulties, as previously discussed, the results are likely to be representative for this population. The children with normal hearing, reporting no auditory, attentional, learning, speech or language disorders, were recruited from local schools on a random basis, and were therefore thought to be representative of the normally hearing population.

The results from this study may serve as grounds for larger sample-sized trials including AEPs and attention tests to clarify which neuronal networks are impaired in children with APD, and the relationship between attention and APD.

Limitations

Paper 1

The linguistic background of the participants could have influenced their test results. In addition to speaking Norwegian fluently, all children were bilingual to varying degrees, with their knowledge of English increasing with age. The present study did not control for possible effects of bilinguism in its participants, which could have been assessed by a questionnaire about linguistic experience and exposure.

Papers 2 and 3

The possibility to generalise from the results of this study are limited for several reasons. First, the small sample size, particularly for the ALLR and P300 measures, limits the power to find significant differences, especially given the complex multifactorial relationships being addressed. Second, a caveat in the correlation analyses is the small and varying sample sizes for different sets of variables, which complicates direct comparisons of p-values and its limited power to reveal smaller associations. In addition, the large number of comparisons (paper 3) could inflate type 1 errors, leading to false positive findings. Finally, the known intra-subject variability of the TEOAE and the dominance of male participants could influence the results. Caution is needed when interpreting minor variations in ERP amplitudes as abnormal or as neural biomarkers of listening difficulties and/or APD.

The fact that the children with listening difficulties participating in the study were clinically referred is worth noting. While the use of a multidisciplinary approach to assess the participants

allowed for a range of developmental disorders to be identified, these other disorders were not the focus of the present study. The presence of comorbidities (to varying degrees) in the participants could have contributed to the homogeneity of the APD and non APD groups. Measures of general intelligence quotient (IQ) was not accounted for in the present study. However, measures of general IQ do not explain auditory processing deficits in reports of children diagnosed with APD (Iliadou et al., 2009, Weihing et al., 2015b) or referred for AP assessment (Brenneman et al., 2017). It is noted that the TEOAEs were recorded in a passive test paradigm, which could have reduced the potential influence of attention on the MOCR.

The control group of 18 children was recruited from local schools and by word of mouth on the basis of their presenting with no auditory, attentional, learning, speech or language disorders, confirmed by parental interview. In particular, they had no experience of auditory processing difficulties in everyday life, thus the APDQ was not performed. This may serve as a study limitation.

6. CONCLUSIONS

Paper 1

A new AP test battery was evaluated as to normative data and test-retest reliability in children with normal hearing aged 7-12 years. For a first-time evaluation for APD in Norwegian speaking children, a test battery consisting of CW, DD, FW, GIN and BMLD (in addition to a peripheral auditory evaluation, including speech-in-noise tests) was recommended.

Paper 2

The present study did not support the hypothesized link between reduced medial olivocochlear (MOC) function and listening difficulties in background noise in children with APD.

Paper 3

The present study showed AMLR Na latency and P300 latency and amplitude measures were sensitive to listening difficulties, but not exclusive to APD in children. The results, indicated neural dysfunction in the thalamo-cortical level (bottom-up) and neurocognitive dysfunctions (top-down) related to allocation of attentional resources and working memory in the children with listening difficulties. The central auditory system may be less efficient and unable to dynamically adapt to adverse listening conditions because it is unable to facilitate greater neural effort in sound perception processes in noise.

General conclusions of the thesis

Our findings provide standardization of an AP test battery in children with normal hearing. Cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli could contribute to listening difficulties in general and to APD in particular.

Implications and future perspectives

As the sample sizes in paper 2 and 3 were small, future studies with larger sample sizes are needed to assess the validity of our findings. We have however brought forward findings of mechanisms regarding level of neurobiological problems in the CANS in children with listening difficulties. Our findings are a contribution to the continuously developing theories on how auditory stimuli are processed by the human brain in children with listening difficulties, with or without APD, and could contribute to developing hypothesis and future experiments.

The hypothesis of reduced MOCR function in children with APD was not supported, however the study demonstrated the feasibility of doing such tests along with caveats regarding methodology. In particular, further studies are warranted into the possible role of other stimulation and recording parameters in determining whether contralateral TEOAE suppression might reveal a possible mechanism for impaired speech in noise perception. After all, continuous steady broad band noise is rare in educational settings.

Also, ripe for future research are further studies on the relationships between hearing and other cognitive functions (e.g., attention, memory, language, intelligence, executive function. Future electrophysiological and neuroimaging studies including children with listening difficulties (with and without APD) and various comorbid disorders might further contribute to the understanding of brain function.

Any final diagnosis of APD depends on the diagnostic criteria being used. There are concerns of the arbitrary nature of the current requirements for APD diagnosis and the need for a more holistic approach in addressing the reported listening difficulties (Dillon et al., 2012, Moore et al., 2013). BSA (2018) argue that “rather than labelling a person with APD, it is more helpful and appropriate to describe the presenting hearing and/or listening problem, and to outline an evidence-based approach to address the specific needs of the particular patient”. Objective AEP measures can

inform clinicians about the potential accuracy with which the auditory system is able to process sounds supporting good hearing and listening, and may explain some of the subtle listening difficulties these children experience. Using the presence of abnormal AEPs to indicate CANS dysfunction rather than to diagnose APD by specific criteria would be consistent with such an approach.

When assessing children with listening difficulties, interpretation of AP tests requires consideration of the child's cognitive abilities and their potential impact on listening difficulties and AP test results. Minimising confounding factors by ensuring optimal cooperation and attention in test situations is important for reliable AP results. The comorbidity observed in these participants, reflects the growing concept that APD may include both auditory and cognitive elements, thus advocating the need for a multi-disciplinary approach in diagnosing APD (BSA 2018).

In addition, a better understanding of the relationship between AP results and listening problems is warranted. The majority of the AP tests used are designed to be sensitive to a specific auditory processing domain, which in turn relies on a range of abilities to perform the test (attention, language, memory). The relationship between AP test results and real life listening, and how deficient any auditory ability (as assessed by a score on some test) has to be before it is associated with increased difficulties in real life, is largely unknown. It is therefore crucial to avoid diagnosing children using standardized AP tests alone. Evaluation of cognitive abilities like working memory, attention, processing abilities and language are important, and should be performed prior to AP assessment. A clinical audiological evaluation including a structured case report, and the use of well-validated behavioural questionnaires may help in understanding the extent of listening difficulties in real-life. Finally, all results should be evaluated from a multidisciplinary perspective, to describe the listening difficulties and potential influence from cognition and language, in order to outline an approach in which the needs of the child are fully in focus.

Author contributions

This PhD project is based on an idea of the candidate herself. The work has been performed as part-time work, combined with the job as a senior consultant at the Department of Otorhinolaryngology, Head and Neck surgery at Ålesund Hospital.

Paper 1 is research performed as a result of the project "Normative data for the Norwegian APD test battery", designed and conducted by Mattsson. The testing was performed at local schools by three audiologists from the Department of Otorhinolaryngology, Head and Neck surgery at Ålesund Hospital.

The study protocols behind Papers 2 and 3 were carried out as part of the project "Children with auditory processing disorder - diagnostics and differential diagnostics in a multidisciplinary perspective". The children were included and examinations were conducted at Bergen University Hospital, Haukeland University and Statped West. The co-authors Lind, Grøndahl, Nicholas and Andersson made substantial contributions to the extensive testing, in their various disciplines. The electrophysiological testing of the children was performed by Andersson and Mattsson.

The writing of all three papers and the thesis has been conducted by Mattsson, with contributions from the co-authors in varying degrees. Final approval of the versions to be published were provided by all the listed authors. The statistical analyses were conducted by Mattsson, with substantial contributions from Follestad in the choice of methods.

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Paper 1

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Normative data for diagnosing auditory processing disorder in Norwegian children aged 7–12 years

Tone Stokkereit Mattsson, Turid Follestad, Stein Andersson, Ola Lind, Jon Øygarden & Ståle Nordgård

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Contralateral suppression of otoacoustic emissions in a clinical sample of children with auditory processing disorder

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Paper 3

Electrophysiological characteristics in children with listening difficulties, with or without auditory processing disorder

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Abstract

Objective: To determine if the auditory middle latency responses (AMLR), auditory late latency response (ALLR) were sensitive to APD. Secondly, to determine if the auditory P300 was more sensitive to broader listening difficulties in children not resulting from APD.

Design: Three-group, repeated measure design.

Study sample: Forty-six children aged 8 to14 years were divided into three groups: children with reported listening difficulties fulfilling APD diagnostic criteria, children with reported listening difficulties not fulfilling APD diagnostic criteria, and normally hearing children.

Results: AMLR Na latency and P300 latency and amplitude were sensitive to listening difficulties. No other auditory evoked potential (AEP) measures were sensitive to listening difficulties, and no AEP measures were sensitive to APD only. Moderate correlations were observed between P300 latency and amplitude and the behavioural AP measures of competing words, frequency patterns, duration patterns, and dichotic digits.

Conclusions: Impaired thalamo-cortical (bottom up) and neurocognitive function (top down) may contribute to difficulties discriminating speech and non-speech sounds. Cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli could contribute to listening difficulties in general and to APD in particular.

Introduction

Children having difficulties understanding speech in complex listening environments are a heterogeneous group with a wide variety of deficits that could affect auditory processing (AP). Several definitions of AP have emerged during the past decades with perhaps the most cited being: "the perceptual processing of auditory information in the central nervous system (CNS) and the neurobiological activity that underlies that processing and gives rise to electrophysiologic auditory potentials" (American Speech-Language-Hearing Association (ASHA), 2005, American Academy of Audiology (AAA), 2010). This definition goes on to state that AP includes the auditory mechanisms that underlie abilities or skills including sound localization and lateralization, auditory discrimination, auditory pattern recognition, temporal aspects of audition, auditory performance in competing acoustic signals, and auditory performance with degraded acoustic signals (ASHA, 2005, AAA, 2010).

Disorders of AP have been called Auditory Processing Disorders (APDs). Universal agreement on differential definitions and diagnostic criteria for APD remains elusive despite its long history of research and clinical investigation and the presence of multiple position statements and professional guidelines from around the world (Wilson, 2018). Earlier definitions of APD as being a disorder in the bottom-up processing of sound inside the traditional auditory system (ASHA, 2005, AAA, 2010), have been challenged by more recent definitions that seek to expand APD to include disorders in the top-down processing of sound outside the traditional auditory system, with particular interest in processes related to auditory attention (British Society of Audiology (BSA), 2018). This has led some authors to argue that rather than assessing an individual for the purpose of diagnosing APD, the assessment should determine the specific nature of the reported listening difficulties so that those difficulties can be managed appropriately (Dillon et al., 2012, BSA, 2018).

The difficulties arising from APD have also been referred to as listening difficulties (e.g., Moore et al., 2010). Listening difficulties, however, is a broad categorisation. There are several distinctions

between hearing, listening and comprehension. Hearing is often regarded as a passive function providing access to audition via automated perception of sound (e.g., when referring to sub lexical tasks such as syllable discrimination). Listening is often viewed as a higher order function requiring attention and processes loading on cognitive resources that puts demands on mental effort (Pichora-Fuller and Singh, 2006). Speech comprehension is a complex, multifunctional task that requires hearing, AP, attention, memory, and integrative processes in order to understand single words, sentences and narratives (Anderson et al., 2013, Shinn-Cunningham, 2008, Ronnberg et al., 2008). Engaging all of these systems is thought to strengthen the neural circuits that facilitate listening (Kraus et al., 2012). Within the larger context of listening, AP is thought to be the link between sound detection and the extraction of meaning from the sound signal. Inefficient AP is seen by some as a risk factor that could compromise listening ability (Bamiou et al., 2006).

Recent evidence also supports close links between listening difficulties in children and language and cognitive processing (Moore et al., 2010, Moore et al., 2013). Attention and working memory have also been linked to sensory perception in a manner that could affect speech comprehension, particularly in background noise (Rudner et al., 2011, Ronnberg et al., 2013, Lunner et al., 2009, Zekveld et al., 2013). A consequence of such links is individuals with higher cognitive function are likely to cope better with adverse listening conditions than individuals with lower cognitive function (Larsby et al., 2005, Lunner, 2003, Rudner et al., 2009).

Defining which neuronal networks are impaired in APD and listening difficulties has been a topic of long standing investigation. In clinical settings, the assessment of AP and the diagnosis of APD has traditionally been done using behavioural tests such as competing words (CW), dichotic digits (DD), filtered words (FW), frequency patterns (FP), duration patterns (DP), gaps in noise (GIN), and binaural masking level difference (BMLD; ASHA, 2005, AAA, 2010). These tests all present auditory stimuli that have been modified to challenge the listener's ability to process those stimuli. The use of such tests stems from previous research showing high sensitivity and specificity to different sites-of-lesion

in the central auditory nervous system (CANS, Musiek et al., 2011). However, many of these tests can be influenced by factors outside of the CANS including higher order cognitive functions (Tomlin et al., 2015) such as attention (Riccio et al., 1994, Riccio et al., 1996, Tillery et al., 2000, Gyldenkaerne et al., 2014), motivation (Silman et al., 2000) and linguistic ability (Richard, 2007). If an individual fails a behavioural tests of AP such as those described above, it can be challenging to determine if that failure resulted from a disorder within and/or outside the traditional auditory system.

Auditory evoked potentials (AEPs) have been suggested as a means of determining the degree of involvement of auditory system versus non-auditory systems in APD and listening difficulties (Kraus et al., 1995, Ponton et al., 2000, Menning et al., 2000, Wunderlich et al., 2006, Martin et al., 2008, Schochat et al., 2010, Wilson et al., 2013). While not immune to influences from non-auditory systems, AEPs can provide an opportunity to elucidate the neurobiological factors contributing to AP by identifying small changes in neural function related to volume (numbers) and synchrony (timing) of neural activity in response to auditory stimulus (Hall, 2006). As well as investigating APD, AEPs have been used to investigate CANS function in a range of disorders including (but not limited to) language impairment (Tonnquist-Uhlen, 1996, Milicic et al., 1998, Bishop and McArthur, 2004), dyslexia (Mazzotta and Gallai, 1992), and learning impairment (Arehole et al., 1995, Hayes et al., 2003, Gilley et al., 2006).

Three AEPs that have been widely used to investigate both auditory and non-auditory systems are the auditory middle latency response (AMLR), the auditory late latency response (ALLR) and the auditory P300. The AMLR has been used to assess neural function in the thalamo-cortical pathways thought to be essential in processing speech and non-speech signals (Kileny et al., 1987, Jerger et al., 1988, , Musiek and Lee, 1997). It consists of a series of vertex positive and negative waves (Po, Na, Pa, Nb and Pb) between 10 ms to 50 ms post-stimulus onset, although the most robust waves have proven to be Na and Pa. Each wave within the AMLR is thought to be generated by multiple temporally overlapping subcortical and cortical sources (Kraus and McGee, 1993). In general, the

early Na and Pa waves are thought to be generated by subcortical structures including the inferior colliculus and thalamus, and cortical structures including the superior temporal gyrus in auditory cortex (Kraus et al., 1982, Hall, 2006).

The ALLR has been used to evaluate neural function in cortical structures thought to represent more elementary levels of auditory sensory coding and automatic processing (Naatanen and Picton, 1987). It consists of a series of vertex positive and negative waves (P1, N1, P2 and N2) between 50 ms to 250 ms post-stimulus onset, with waves N1 and P2 being most stable. Each wave within the ALLR is thought to be generated by multiple temporally overlapping subcortical and cortical sources (Onishi and Davis, 1968, Naatanen and Picton, 1987). The N1 is considered a passive, transient response evoked by short-term envelope change in the auditory stimulus (Onishi and Davis, 1968), while P2 is considered to be sensitive to attention and stimulus parameters such as pitch and intensity (Crowley and Colrain, 2004) as well as musical experience (Seppanen et al., 2012).

The P300 has been used to assess discriminative responses thought to represent cognitive processes involved in conscious recognition, attention and discrimination of the acoustic characteristics of the stimuli (Polich, 2007). It consists of a positive wave (P300) commonly largest over central parietal (Pz) regions of the head and occurring approximately 300 ms following stimulus onset of a target stimuli within a series of non-target stimuli. The P300 is thought to be mostly generated in non-auditory areas in the frontal and temporal cortices (Baudena et al., 1995, Halgren et al., 1995), although some contribution by auditory generators is suggested by evidence of lesions in the auditory cortex compromising both P300 latency and amplitude (Knight et al., 1989, Musiek et al., 1992).

Adding AEPs to the test battery for APD would allow mechanisms regarding level of neurobiological problems in the CANS to be elucidated, assisting clinicians using behavioural measures of AP to better separate APD from broader listening difficulties. We hypothesized that because the AMLR and ALLR are thought to originate predominantly from auditory areas in the thalamus and cortex, then these AEPs would be more sensitive to APD. Secondly, because the

auditory P300 is thought to originate from non-auditory areas in the frontal and temporal cortices, then it would be more sensitive to broader listening difficulties not resulting from APD.

Method

Participants

Forty-six children aged 8 to14 years (mean age 10.6 years) who met the inclusion criteria described below were prospectively included in this study. The children were informed in writing of the requirements of participating in the study, and written consent were given by their guardians. The study was approved by the Regional Committee for Medical and Health Research Ethics West (number 278.08).

All participants were native speakers of Norwegian, were able to complete the Norwegian AP test battery, and fulfilled the following inclusion criteria: pure-tone audiometry thresholds ≤20 dB from 0.25 to 8 kHz; word recognition score in quiet of >90% on speech audiometry; normal middle ear function as established by otomicroscopy and tympanometry (single peak and tympanometric peak pressure greater than -100 dPa), contralateral acoustic reflex thresholds between 70 and 100 dB HL; and normal auditory brainstem responses (ABR) to 75dB click stimuli at 11.1 clicks/sec. Children with comorbid disorders (e.g. the presence of one or more additional disorders co-occurring with the primary disorder) that precluded completion of the AP test battery did not enter the study.

Twenty-eight of the 46 participating children were included based on observed listening difficulties and the results of the Norwegian version of the auditory processing domain questionnaire (APDQ). The parents filled out the APDQ questionnaire form in paper, with scores ≤15th percentile on the auditory processing (AP) scale indicating listening difficulties (O'Hara and Mealings, 2018). These children were referred to Statped West (a national service in Norway for special needs education) for auditory processing assessment, and underwent cognitive and language evaluation in a

multidisciplinary approach. This assessment included the cognitive tests Wechsler Intelligence Scale for Children (WISC III; Wechsler, 1991), Leiter International Performance Scale-revised (Roid and Miller, 1997), Integrated Visual and Auditory Continuous Performance Test plus (IVA+; Sandford and Turner, 2004), Benton Visual Retention test (Sivan, 1991), Children´s Auditory Verbal Learning Test (CAVLT-2; Talley, 1992) in addition to the language tests of the British Picture Vocabulary Scale (BPVS II; Dunn et al., 1997), Clinical Evaluation of Language Fundaments (CELF IV; Semel et al., 2006) and the Tests for Reception of Grammar (TROG; Bishop, 2009). Finally, the questionnaires Behaviour Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) and the Children's Communication Checklist (CCC-2; Bishop, 2003) were also performed when deficits in executive functions and communication skills were indicated, respectively.

The control group of 18 children were recruited from local schools and by word-of-mouth on the basis of their presenting with no auditory, attentional, learning, speech or language disorders. This was confirmed by parental interview. In particular, they had no experience of auditory processing difficulties in everyday life, thus the APDQ was not performed. This is a noted limitation of the present study.

Following an AP assessment (described below), the 46 participating children were divided into three groups: i) an APD group consisting of 16 children with reported listening difficulties who met this study's diagnostic criteria for APD ii) a non APD group**,** consisting of 12 children with reported listening difficulties who did not meet this study's diagnostic criteria for APD, and iii) a normal hearing group presenting with no reported listening difficulties and no reports of auditory, attentional, learning, speech or language disorders. This study's diagnostic criteria for APD were performing two SDs or more below age expectations in at least one ear on two or more tests of AP (ASHA, 2005), with at least one test having used speech stimuli and at least one having used non-speech stimuli (BSA, 2018). The participant characteristics, including APDQ results and comorbid conditions, are summarized by group in Figure 1.

Equipment

All audiological testing was performed in sound isolated rooms. Pure tone hearing thresholds were obtained using a clinical audiometer (Aurical; GN Otometrics, DK) with TDH39 ear phones (Telephonics, USA) calibrated to ISO 389 standards. Middle ear function and acoustic reflexes were examined by a GSI 68 immittance unit (Grason Stadler Inc. USA) or AZ26 (Interacoustics, DK) using a 226 Hz probe tone. Ipsilateral and contralateral acoustic reflex thresholds (ART) were tested at 500 and 1000 Hz. Eighth cranial nerve, auditory brainstem function and middle latency responses were assessed using Audera clinical evoked potential system, running software version 2.6.0 (Grason-Stadler, USA). APD testing was performed using a computer with DT 770 Pro headphones (Beyer Dynamic, Germany). Finally, TEOAE testing was performed using an Echoport ILO 292-II (Otoynamics, UK) with software ILO V6 and UGD TEOAE probe (Otodynamics, UK).

Procedure

Following audiological examination, all participating children were evaluated using a behavioural auditory processing assessment and the three electrophysiological measures of AMLR, ALLR and P300. The behavioural AP assessment consisted of a monaural low redundancy speech test (FW, conducted binaurally), dichotic speech tests with free recall (DD and CW), auditory temporal processing and patterning tests (FP, DP, GIN), and a binaural interaction test (BMLD). These tests were drawn from the Norwegian APD test battery developed by Mattsson et al. (2018), with norms for Norwegian-speaking children. Prior to each test, oral instructions and trial sequences were provided, and the children were given breaks when needed to minimize confounds related to fatigue. After each assessment, all test results were discussed in a multidisciplinary team to determine the potential nature of each child's listening difficulties with respect to APD and comorbid developmental disorders.

Sustained attention

Twenty-four children from the clinical group were tested on the Integrated Visual and Auditory Continuous Performance Test Plus (IVA+) (Sandford and Turner, 1995), to examine their continuous performance on the same auditory or visual task for a period of 15 minutes. The test was presented on a laptop with the sound set to a comfortable level. The numbers 1 and 2 were presented in a pseudorandom order as either a visual or an auditory stimulus. The children were instructed to click the mouse-button when they saw or heard number 1, and ignore the number 2. During testing, the children received no feed-back. The IVA+ test consisted of five sets of 100 trials each. Each set started with a high demand block of 50 trials when the target frequency (i.e., the 1s) was high followed by a low demand block of 50 trials when the foils (i.e., the 2s) were numerous compared to the targets.

The IVA+ assess performance with tasks that require the participant to remain prepared to respond to an infrequent target (i.e., the 1s) over an extended period of time and measures both the maintenance of attention and inhibitory control. This study used the IVA+ scores of auditory (ASust) and visual sustained attention (VSust). Sustained attention is the vigilant focus on stimuli and is considered a basic function that determines selective and divided attention (Sarter et al., 2001). The ASust and VSust scores of the IVA+ provide a measure of a person`s ability to accurately and quickly respond in a reliable manner to auditory and visual stimuli under low demand conditions. In addition, it includes the ability to sustain attention and be flexible when things change under high demand conditions.

AMLR recordings

The AMLR was recorded with the default Audera AMLR protocol, which both generated the acoustic stimuli, recorded neuro-electrical activity from the scalp and derived the waveforms. Responses were evoked using 100 μs bipolar click stimulus with alternating polarity, presented separately for the right and left ear at 70 dB nHL and a repetition rate of 7.1 clicks/second. EEG activity was filtered using a 10-250 Hz band-pass filter, with a 12 dB/octave roll-off.

Electrode montages at Fz (high forehead) referred to A1 (left earlobe) or A2 (right earlobe), mid forehead was ground for all recordings. Responses were recorded both ipsi- and contralaterally for the stimulated ear. Impedances were kept below 10 kΩ, all subjects were awake during testing. Rejection level was set to ±45μV, measurements exceeding 10% rejection were manually discarded.

The time window for all recordings was 90 ms. One thousand accepted trials contributed to each waveform, which were repeated once. Each set of two measurements were averaged after analysis. Measurements of component magnitude (peak amplitude) and timing (peak latency) in individual averages were made after inspection of the waveform and identification of peaks within the appropriate latency range. Peak AEP amplitudes were defined as the maximum negative or positive value in the 10-24 ms (Na) and 20-38 ms (Pa) post stimulus onset intervals, measured from baseline to peak. Peak-to-peak amplitudes were computed as the absolute difference in voltage between Pa and Na peak amplitudes. Latencies for Na and Pa were measured from onset of stimulus.

ALLR and P300 recordings

The ALLR and auditory P300 measurements could only be done if personnel and equipment were available at the time, therefore ALLR and P300 were not assessed on 11 children (five from the APD group and six from the non APD group). The ALLR and P300 were recorded within a single two-tone oddball AEP paradigm. A total of 200 stimuli, composed from complex tones of 80 dB with a 500 Hz fundamental frequency and harmonics at 1000 Hz and 1500 Hz, windowed with a 5 ms rise/fall time, were presented binaurally through headphones at a rate of 1 Hz to each participant. Of these stimuli, 160 were defined as standard stimuli (the complex tone containing the 1000 Hz harmonic) and 40 defined as target stimuli (the complex tone containing the 1500 Hz harmonic). Stimuli were quasi-randomly presented with target stimuli presented randomly but not sequentially, with a fixed stimuli onset asynchrony of 1000 ms. Participants were instructed to respond to the target stimuli by pressing a response key as quickly as possible, with their reaction times (RTs) being recorded. The hit rate was measured as the number of correct responses to the target stimuli, which was thought to reflect the

difficulty level and the individual's focus on the task. All participants were given five example trials of the oddball paradigm for practice and to ensure their ability to discriminate targets from standards.

Continuous electroencephalographic (EEG) activity was recorded with a Brain Vision amplifier from 18 monopolar Ag/AgCl electrodes fixed on an Easycap, mounted according to the international 10-20 system (F7, F3, Fz, F4, F8, FC3, FCz, FC4, C3, Cz, C4, T7, T8, P3, Pz, P4, TP9, TP10) with ground electrode attached to the nose tip and linked mastoid electrodes (TP9/TP10) as reference. Eye movements were recorded with bipolar electrodes placed at the sub- and supraorbital regions and at the outer canthi of the right eye. Impedances were kept below 10 kΩ, and EEG activity was sampled at 500 Hz, high pass filter of 0.05 Hz.

Off-line EEG data processing was conducted using Brain Vision Analyser 2 software with EEG activity epoched into 1100 ms bins. All data were baseline (-100 to 0 ms) corrected, low pass filtered (30 Hz, 12 dB per decade attenuation), and corrected for eye movements artefacts (Gratton et al., 1983). Epochs containing amplitudes exceeding ± 100 μV were rejected before averaging.

From the averaged EEG recordings, the N1 and P2 components elicited by standard stimuli, and the P300 component elicited by correctly identified target stimuli were identified. Peak AEP amplitudes were defined as the maximum negative/positive amplitude in the 70 – 140 ms (N1), 140 – 250 ms (P2), and 250 – 650 ms (P300) post stimulus onset intervals. Because of the slow wave nature of the P300 amplitude, especially in normal hearing subjects (Figure **2b**), the mean P300 amplitude of the post stimulus interval from 250 to 650 ms was also calculated.

Data analysis

Analyses of variance (ANOVA) were used to identify any significant differences by participant group for each of the behavioural AP tests. Pearson's correlation analyses were used to investigate the relationships amongst the AEPs and behavioural AP measures for all participants combined. Bonferroni-Holm corrections were also applied to adjust for multiple comparisons, these results are

given in the text. As the separate ear results were moderately to highly correlated for each of the behavioural AP measures of CW, DD, FP, DP and GIN (r 0.536 to 0.934, $p<0.001$), the ear scores were averaged for use in the correlation analyses. This was not required for the FW or BMLD tests as these had already been conducted binaurally. For a categorical description of the level of correlation, we used the suggestions by Cohen: low r= 0.10 to 0.29, moderate r= 0.30 to 0.49, strong r=0.50 to 1.0 (Cohen, 1988).

Linear mixed models (LMM) were used to compare each of the AEP measures by groups allowing for heterogeneity across age groups. Bonferroni corrections were applied for post-hoc pairwise comparisons. For the AMLR measures, LMMs were used to test for the main effects of group (APD, non APD and NH), stimulus ear (left or right), electrode montage (ipsilateral or contralateral) and age, as well as for two-factor interactions amongst these variables. For the ALLR measures, LMMs were used to test for the main effects of group, electrode montage (Fz, FCz, Cz and Pz) and age, as well as for three-factor interactions amongst these variables. For the N1, P2, P3 latencies, linear regression analyses were conducted to assess the main effects of group and age, and their interaction. While AMLR wave amplitudes were recorded for Na, Pa and Na-Pa, only the results of the analyses of the Na-Pa data were reported as similar results were obtained on analyses of the Na and Pa data separately. For the ALLR and P300, data obtained from central electrodes (Fz, FCz, Cz and Pz) were analysed. Data from Cz for the N1 and P2 and Pz for the P300 were reported for descriptive statistics and correlation analyses. These reported electrodes show the largest amplitude values, and hence are more susceptible to reveal statistical findings.

The normal assumptions for the LMM for each variable were assessed using tests for normality, and visual inspection of histograms and normal Q-Q plots. When normal assumptions were not met, the data were transformed or corresponding non-parametric analyses were used.

Nonparametric tests and linear regression analyses were used to examine the hit rate and reaction time measures from the oddball paradigm, respectively. All data analyses were performed using IBM

SPSS Statistics software, version 25. P-values <0.05 were considered to be statistically significant. The analyses were performed with two groups (normal hearing (NH) and listening difficulties) and three groups (NH, APD and non APD). As the grouping did not have a major effect on the results, the group effects were presented for the model with 3 groups.

Results

The descriptive statistics for all behavioural AP tests and attention measures for each participant group are shown in Table 1, in addition to the results of the ANOVAs for group comparisons. Significant effects for group were observed for CW left, DD, DP and FP. In the case of Sustained Auditory Attention Quotient, the non APD group mean fell in the slightly impaired range, while the APD group mean fell in the moderately to severely impaired range, according to the Interpretation manual (Sandford and Turner, 2004). When standardizing the Norwegian version of the IVA+ scales, normal hearing children performed with a mean of 100, with a standard deviation of 15 (Ukvitne and Nicholas, 2017).

The descriptive statistics for the AMLR, ALLR and P300 recordings are presented in Table 2. The MLR amplitude and latency values are presented in Figure 2. The grand mean ALLR and P300 waveforms for each group are displayed in Figure 3.

The results for the analyses of the effects of group (APD, non APD and NH), stimulus ear (left or right), electrode montage (ipsilateral or contralateral) and age on the AMLR results are shown in Table 3. No significant interaction effects were found, and the results from models with main effects only are presented. A significant ($p < 0.001$) effect for group was observed on the Na latencies with the APD and non APD groups showing similar Na latencies that were prolonged relative to the NH group. An ear effect was also observed on Na-Pa amplitude ($p = 0.009$), with larger amplitudes observed for left versus right ear stimulation.

The results for the analyses of the effects of group (APD, non APD and NH) and age on the ALLR and P300 results, are shown in Table 4. No significant interaction effects were found, and the results from models with main effects only are presented. A significant effect for group was observed on the P300 mean amplitude ($p = 0.019$) and latency ($p = 0.021$), with attenuated amplitudes and prolonged latencies for the APD and non APD groups compared to the NH group. The group effect for the P300 amplitude was not significant ($p = 0.053$). However, when comparing two groups (listening difficulties and NH) the group effect was significant, with 5.9 μV lower amplitudes in children with listening difficulties ($p = 0.008$). Significant within-subject effects of midline electrodes on ALLR and P300 results were observed ($p <0.001$), showing the expected topographical anterior-posterior effect with largest responses in Cz and Pz, respectively. An effect for age was also observed on P300 mean amplitude ($p =0.029$) and latency ($p = 0.008$). Hit rates and reaction time for the P300 measurements were generally high, with median hit rates of 39 to 40 and a mean reaction time of 376.9 ms (SD 103.9), with no significant group differences.

The Pearson`s product moment correlations for behavioural AP and attention measures against AEP measures are shown in Table 5. Significant moderate correlations were observed between Na latency and the AP tests CW left ear and DD, between P2 latency and DP, P2 amplitude and GIN, between P300 measures and CW left ear, FP, DP and DD. Significant moderate correlations were observed between auditory sustained attention and DD and Pa latency left ear, and between visual sustained attention and DP and DD. The association between auditory and visual sustained attention was strong ($r=0.79$, $p<0.001$).

Discussion

The present study showed AMLR Na latency and P300 latency and amplitude measures were sensitive to listening difficulties, but not exclusive to APD in children. These results only partly

supported the study's hypothesis that the AMLR and ALLR would be more sensitive to APD whereas the auditory P300 would be more sensitive to broader listening difficulties not resulting from APD.

AEPs and APD

On first consideration, these findings appear to be inconsistent with previous reports of AMLR measures (Schochat et al., 2010), ALLR measures (Jirsa and Clontz, 1990, Jirsa, 1992, Liasis et al., 2003, Tomlin and Rance, 2016, Koravand et al., 2017) and P300 measures (Jirsa and Clontz, 1990, Jirsa, 1992) being sensitive to APD. However, the AP tests and criteria used to diagnose APD varied among studies, and none of those previous studies included a group with listening difficulties without APD. On closer consideration, these findings identify the long-standing challenge posed by the absence of universally accepted definitions and diagnostic criteria for APD (Wilson, 2018) and the arbitrary effect this has on its diagnosis (Wilson and Arnott, 2013). This reinforces calls to clearly consider differences in AP testing and APD diagnoses across studies of AP and APD (Medwetsky, 2011, Wilson and Arnott, 2013, Wilson, 2018).

On a broader consideration, the present study's findings are consistent with reports of AMLR, ALLR and P300 abnormalities in children with a range of disorders that include (or are likely to include) listening difficulties. Typical findings are prolonged Na and/or Pa latency in children with learning impairments (Arehole et al., 1995, Purdy et al., 2002) or language impairments (Milicic et al., 1998), prolonged latency and/or attenuated amplitude for the waves N1, P2 or P300 in children with learning impairments (Purdy et al., 2002, Gilley et al., 2006), language impairment (Tonnquist-Uhlen, 1996, Bishop and McArthur, 2004), or dyslexia (Mazzotta and Gallai, 1992). These reports suggest that the problems related to listening difficulties are multimodal, and may be caused by cognitive, memory, attention, and language deficits.

The prolonged Na latencies of 2.6 ms observed in the children with listening difficulties (APD and non APD groups collapsed) suggest slower processing and possibly more asynchronous neural firing

in the auditory thalamo-cortical pathways that contribute to the Na wave (Naatanen and Picton, 1987). Neural dysfunction causing slower conduction times in the CANS cannot be ruled out, but the later waves N1 and P2 would also be expected to show a prolonged effect (although the present study's limited sample size and resulting effect on statistical power is noted).

The act of processing the P300 stimulus is complex and involves the intertwining of auditory, cognitive (including attention and memory), and language mechanisms (Medwetsky, 2011). The delayed P300 latencies of 113.9 ms and reduced mean amplitudes of 3.7 μV in the children with listening difficulties (APD and non APD groups collapsed) suggest neurocognitive dysfunctions related to allocation of attentional resources and immediate memory (Polich and Herbst, 2000). Research on persons with hearing impairment has shown that cognitive abilities like working memory and attention play an important role in speech understanding in challenging listening conditions (Ronnberg et al., 2008, Ronnberg, 2003, Ronnberg et al., 2013, Ronnberg et al., 2010, Rudner et al., 2012, Classon et al., 2013, Woods et al., 2001, Arbogast and Kidd, 2000). This could also be the case for children with listening difficulties, independent of APD diagnosis.

AEP and auditory processing

Overall, the mostly non-significant or low to moderate correlations between the AEP and behavioural AP measures, indicate that the AMLR and ALLR are not measures of a particular AP ability assessed by these behavioural AP measures. The six significant correlations (p from 0.01 to 0.05) observed should be interpreted with caution as they could be incidental findings due to multiple comparisons.

The low to moderate correlations observed between Na and P2 measures and the AP tests CW left, DD, DP, and GIN, could indicate more elementary, bottom-up levels of auditory processing (such as sensory coding and automatic processing) being represented in the AP tests. However, when Bonferroni-Holm adjustment was applied, these correlations were no longer significant.

The significant, moderate correlations observed between the P300 measures and the AP tests CW left, DD, FP, and DP suggest an association between cognitive functions (such as attention and memory) and the AP tests performance, consistent with previous reports of top-down modulation of the CANS (Riccio et al., 1994, Riccio et al., 1996, Tillery et al., 2000, Tomlin et al., 2015).

Auditory processing and cognition

Overall, the correlations observed between AP tests and the continuous performance tests were mostly low, and at best moderate. It is to be noted that the ASust quotient for the non APD group means fell in the slightly impaired range, while the APD group means fell in the moderately to severely impaired range. The diagnosed attention disorder in some of the children may have influenced the ASust quotient. Thus, the decreased score in the APD tests could be associated by impaired auditory sustained attention. However, the correlations observed between AP tests and the continuous performance tests were mostly low, and at best moderate, indicating that additional factors influenced AP performance in this study's participants. The significant correlation between auditory and visual sustained attention was high (as expected) ($r=0.79$, $p<0.001$), suggesting the existence of some common factors underlying attention in the auditory and visual modalities.

The moderate correlations between auditory sustained attention and the dichotic digits test were consistent with previous reports from children with APD (Gyldenkaerne et al., 2014) or suspected of having APD (Sharma et al., 2009) and children with attention disorders (Keith and Engineer, 1991), indicating that dichotic listening involves some auditory attentional processes. Previous research on dichotic listening has shown influence of cognitive functions like attention and working memory (Penner et al., 2009, Hugdahl and Westerhausen, 2016). It should be noted that Tomlin et al. (2015) found associations between AP tests, working memory and non-verbal IQ, but no associations with attention. Although auditory sustained attention correlated significantly with the DD test in the present study, the correlation was no longer significant when Bonferroni-Holm adjustment was applied.

The low correlations between auditory sustained attention and the P300 may reflect the complexity of the tasks, with the continuous performance test paradigms requiring multiple cognitive operations, and the allocation of more cognitive resources compared to the oddball paradigm. Hence, the decline in test performance in the IVA + may be attributed to the high mental workload for processing of information and the decrement reflective of the depletion of information-processing resources over time.

In particular, the fact that AP tests are low to moderately correlated with various AEP measures and continuous performance tests, suggest a variance associated with each test indicating that the AP is not merely governed by cognitive influence. The processing of auditory information in the CANS is complex, involving both serial and parallel processing within the auditory structures of the CANS itself, as well as shared processing with other sensory or higher order brain structures and systems (language, attention and executive control) (Ghazanfar and Schroeder, 2006, Peelle, 2012, Specht, 2014). Given the organisation of the CANS and the nature of processing, the symptoms of children with APD are often diverse and heterogeneous.

A caveat in this correlation analyses is the varying sample sizes for different pairs of variables, which complicates direct comparisons of p-values, in addition to the small sample size. In addition, applying Bonferroni-Holm correction may be problematic for multiple correlations, leading to possible Type II errors due to lower critical p-value for significance.

Ear, electrode and age effects

The overall ear asymmetry found in the AMLR Na-Pa amplitude (with attenuated amplitude values when sound was presented to the right ear) were contradictory to previous reports of a right ear advantage in clinical populations (Purdy et al., 2002). Whether an ear asymmetry of the Na-Pa amplitude should be expected in general remains the topic of much debate, with reports of no difference between the ears in adults (de Almeida et al., 2006), children (Schochat and Musiek, 2006) or clinical groups (Kraus et al., 1985). Others have reported prolonged left ear Pa latencies in learning

impaired children (Arehole et al., 1995). It is widely accepted that the left auditory cortex is dominant for processing fast temporal information, and the right auditory cortex is dominant for processing tonal information such as pitch processing (Zatorre et al., 2002, Schonwiesner et al., 2005, Boemio et al., 2005).

The absence of an electrode montage effect on the AMLR was consistent with previous reports of bilateral symmetric functions in the Na and Pa generators in normal populations (McGee and Kraus, 1996, Schochat and Musiek, 2006, de Almeida et al., 2006). These findings were inconsistent with reports of inter-individual variation in the MLR components affecting the results, and the need for relative measures of ear and electrode effects (Musiek et al., 1999, Weihing et al., 2012). The amplitudes of midline electrodes in the ALLR and P300 was similar across all participating groups, reflected in midline topographical anterior-posterior effects, consistent with previous research (Ponton et al., 2002).

The presence of an age effect for P300 latencies only was consistent with the age of the present study's participants and the maturational courses of the thalamo-cortical pathways, with Pa and Nb waves reaching adult values at six to 12 years of age (Kraus et al., 1985, Suzuki and Hirabayashi, 1987, Ponton et al., 2002, Schochat and Musiek, 2006), N1 and P2 waves reaching adult like values in adolescence (Ponton et al., 1996, Tonnquist-Uhlen, 1996, Sharma et al., 1997, Eggermont and Ponton, 2003, Sussman et al., 2008), and the P3 wave maturing later from ages five through 16 (Polich et al., 1985).

Clinical implications

The prolonged Na latency and P300 amplitude and latency suggest clinicians should consider abnormalities in AEPs as being indicative of broader listening problems rather than of an APD diagnosis using specific diagnostic criteria. In this regard, the presence of abnormal AEPs indicate dysfunctions in the CANS While any final diagnosis of APD will depend on the diagnostic criteria

being used, the presence of dysfunction in the CANS indicated by abnormal AP results should not be ignored. This is consistent with concerns of the arbitrary nature of the current requirements for APD diagnosis and the need for a more holistic approach in addressing the reported listening difficulties (Dillon et al., 2012, Moore et al., 2013). BSA (2018) argue that "rather than labelling a person with APD, it is more helpful and appropriate to describe the presenting hearing and/or listening problem, and to outline an evidence based approach to address the specific needs of the particular patient". Using the presence of abnormal AEPs to indicate CANS disorder (or at least dysfunction) rather than to diagnose APD by specific criteria would be consistent with such an approach.

The moderate correlations observed between P300 measures and a subgroup of AP tests suggest that listening difficulties in children may be related to problems allocating attentional resources in demanding listening situations. This is consistent with reports of a complex interaction between AP scores and cognition (Tomlin et al., 2015). However, the direction of causality is still not clear. Top-down cognitive mechanisms are linked to speech-perception in noise, and as the listening situation becomes poorer, the amount of cognitive capacity to comprehend speech will increase, requiring more listening effort (Kramer et al., 2009, Pichora-Fuller et al., 2016). It is difficult to separate purely auditory from cognitive disorders, because the use of listening tasks with complex stimuli such as degraded speech or dichotic listening, renders it impossible to suppress cognitive skills. When assessing children with listening difficulties, interpretation of AP tests requires consideration of the child's cognitive abilities and potential impact on listening difficulties and AP test results. Minimising confounds by ensuring optimal cooperation and attention in test situations are important for reliable AP results. The comorbidity observed in the study's participants, reflect the growing concept arguing that APD may include both auditory and cognitive elements, thus advocating the need for a multi-disciplinary approach in diagnosing APD (BSA 2018).

Limitations

The present study's findings have several limitations. First, the small sample size, particularly for the ALLR and P300 measures, limits the power to find significant differences especially given the complex multifactorial relationships being addressed. Second, the large number of comparisons could inflate type 1 error, leading to false positive findings. Third, the dominance of male participants could influence on the results. This prevents generalisation of the results across levels of cognitive function, age or gender. Caution should be taken when interpreting minor variations in AEP results as abnormal or as neural biomarkers of listening difficulties and/or APD.

The fact that the children with listening difficulties participating in the current study were clinically referred is also worth commenting. The use of a multidisciplinary approach to assess the study's participants allowed for a range of developmental disorders to be identified, but these other disorders were not the focus of the present study. The presence of attention disorders in particular could have contributed to homogeneity of the APD and non APD groups, with influence on the P300. However, the use of a passive oddball paradigm could have reduced the potential influence of attention on the P300 measures. This notion is supported by the low correlations between the continuous performance tests and the P300 waveforms.

Conclusion

The present study showed AMLR Na latency and P300 latency and amplitude measures were sensitive to listening difficulties but none of the AMLR, ALLR or auditory P300 measures were sensitive to APD in children. These results in this study's clinical sample of children with listening difficulties, with or without APD, indicate neural dysfunction in the thalamo-cortical level (bottom up) and neurocognitive dysfunctions (top down) related to allocation of attentional resources and immediate memory. Impaired cortical and cognitive function may contribute to difficulties

discriminating speech and non-speech sounds, indicating listening difficulties being a reflection of the overall development of CANS.

The observed significant correlations between the P300 measures and the AP tests CW left, DD, FP, and DP suggest associations between cognitive functions (such as attention and working memory) and the AP tests performance, consistent with previous reports of top-down modulation of the CANS. The results from this study may serve as grounds for larger sample-sized trials including AEPs and attention tests to clarify which neuronal networks are impaired in children with APD, and the relationship between attention and APD.

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Declaration of interest

The authors report no declaration of interest.

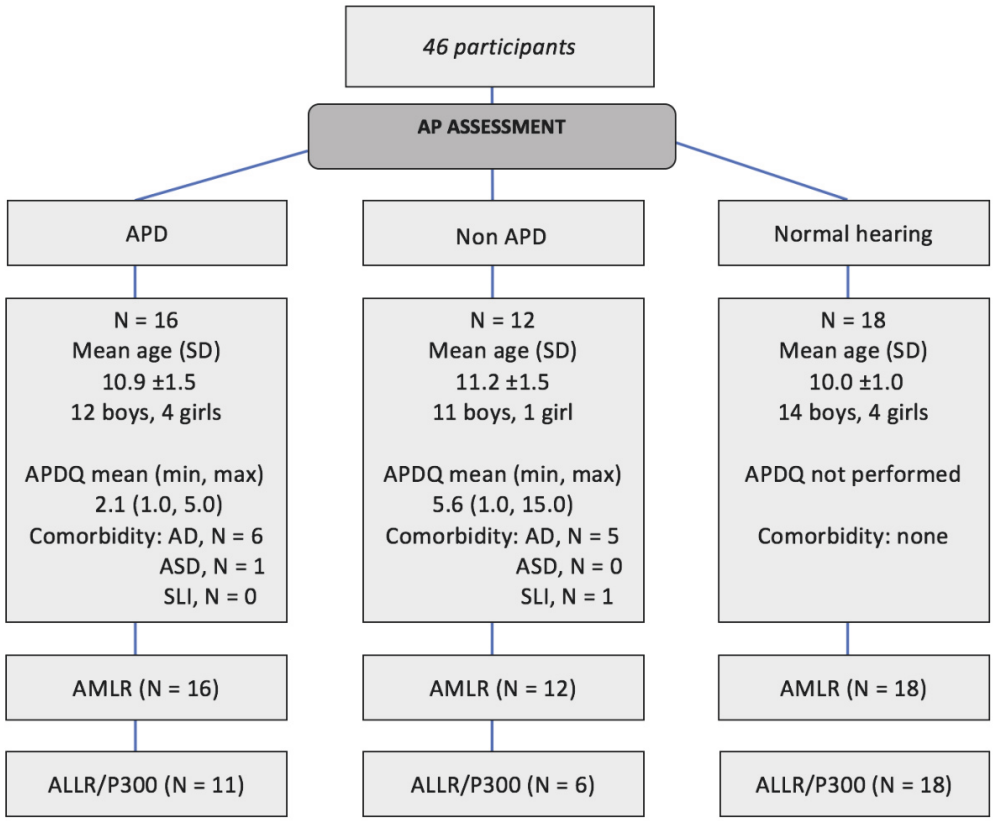


Figure 1. Characteristics of the study population, displayed by three groups.

The numbers of participants in each group and measure are displayed. The results from the Auditory processing domain questionnaire (APDQ, subscale Auditory processing), demonstrate the participants listening difficulties, values are given in percentiles. The frequencies of comorbid disorders are shown for each group.

AD: attention disorder, ASD: autism spectrum disorder, SLI: speech-language impairment.

Groups		***APD***		***Non APD***		***Control***		ANOVA
	Ear	Mean	SD	Mean	SD	Mean	SD	p value
Filtered words (%)	Both	73.1	9.7	75.3	7.4	75.8	10.1	0.690
Competing words (%)	Right	82.1	13.8	85.4	4.5	86.1	8.3	0.500
	Left	70.3	12.7	73.9	12.3	84.2	9.1	0.002
Dichotic digits (%)	Right	77.5	12.3	85.7	12.1	92.3	9.3	0.002
	Left	64.1	14.2	73.5	14.2	85.3	9.6	<0.001
Duration patterns (%)	Right	25.7	22.9	46.1	21.2	49.4	30.1	0.029
	Left	32.7	22.2	52.1	21.7	54.3	27.5	0.035
Frequency patterns (%)	Right	28.6	19.8	52.4	28.8	57.1	30.2	0.011
	Left	37.3	22.6	54.1	29.6	60.6	30.2	0.146
Gaps in noise (ms)	Right	6.2	1.7	6.3	1.4	6.8	1.1	0.508
	Left	5.9	2.1	6.8	1.9	7.1	1.4	0.131
BMLD (dB)	Both	10.3	2.9	13.3	2.9	11.2	2.9	0.034
A-Sust		64.3	38.0	86.0	32.2			0.109*
		77.6	28.6	82.7	33.8			0.543*

Table 1. Descriptive statistics for the tests of auditory processing (AP) and attention measures for the groups APD, non APD and normal hearing (NH). The p-values for analyses of variance of group differences are given. ANOVA: one-way analyses of variance, BMLD: binaural masking level difference, A-Sust: Auditory sustained attention, V-sust: Visual sustained attention, LE: left ear, RE: right ear, B: both. * independent sample t-test

Groups	***APD***		***Non APD***		***NH***	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
			AMLR			
Amplitude (μV)						
Na-Pa (RE)	1.01	0.63	0.97	0.23	0.93	0.33
Na-Pa (LE)	1.17	0.63	1.05	0.25	1.04	0.36
Latency (ms)						
Na (RE)	17.98	1.45	18.10	1.55	14.75	2.68
Na (LE)	18.38	1.11	17.11	1.55	15.56	1.90
Pa (RE)	31.39	2.96	29.32	3.15	29.53	3.48
Pa (LE)	31.0	2.29	29.65	2.24	29.50	4.00
			ALLR			
Amplitude (μV)						
N1	-4.95	2.63	-6.67	4.24	-5.06	3.05
P2	7.21	4.23	6.61	5.61	4.46	5.87
Latency (ms)						
N1	115.27	10.25	123.00	12.44	115.89	16.89
P2	187.27	15.37	185.67	8.34	187.68	30.84
			P300			
Amplitude (μV)						
P300	11.33	4.18	10,09	2.41	15.55	6.57
P300 mean	2.94	3.94	2,69	3.29	6.01	4.76
Latency(m)						
P300	485.64	129.11	480.33	162.78	417.47	88.34

Table 2. Descriptive statistics for the AEP measures.

AMLR results are for monaural stimuli and are shown as the average of the values from the ipsilateral and contralateral electrode montages. ALLR and P300 results are for binaural stimuli and are shown for recordings from Cz for the ALLR and Pz for the P300. NH: normal hearing, LE: left ear, RE: right ear.

	Group				***Ear***		***Electrode montage***		***Age***
	NH-APD	*NH-non APD*	*APD-non APD*		*LE - RE*		*Ipsilateral-contralateral*		
	Est. (95% CI)	Est. (95% CI)	Est. (95% CI)	p-value	Est. (95% CI)	p-value	Est. (95% CI)	p-value	p-value
Amplitude (μV)									
NaPa	-0.2 (-0.5, 0.2)	-0.1 (-0.5, 0.4)	0.1 (0.3, 0.5)	0.564	0.1 (0.01, 0.2)	0.009	0.04 (-0.1, 0.1)	0.384	0.966
Latency (ms)									
Na	-2.8 (-4.2, -1.5)	-2.2 (-3.7, -0.6)	0.6 (-0.9, 2.1)	<0.001	17.0 (16.5, 17.6)	0.521	16.9 (16.4, 17.5)	0.991	0.267
Pa	-1.6 (-3.9, 0.8)	0.0 (-2.7, 2.7)	1.5 (-1.1, 4.2)	0.191	-0.2 (-1.0, 0.6)	0.663	-0.2 (-1.0, 0.6)	0.663	0.928

Table 3. Results from linear mixed models (LMMs) for the AMLR measures for models with no interaction effects included.

Differences, confidence intervals and p values are shown for the main effects of group (APD, non APD and NH), ear (left or right), and montage (ipsilateral or contralateral). Only p values are shown for the main effects of age.

NH: normal hearing, APD: auditory processing disorder as per BSA (2018), LE: left ear stimulus, RE: right ear stimulus.

	Group				***Electrode montage***	***Age***
	NH-APD	*NH-non APD*	*APD-non APD*			
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p value	p value	p value
Amplitude (μV)						
N1	-1.1 (-3.9, 1.8)	1.1 (-2.3, 4.3)	2.1 (-1.3, 5.6)	0.304	<0.001	0.06
P2	-2.3 (-7.1, 2.5)	-2.3 (-7.8, 3.3)	0.1 (-5.8, 5.8)	0.407	<0.001	0.458
P300	5.8 (-0.5, 12.1)	5.2 (-2.2, 12.5)	-0.7 (-8.3, 7.0)	0.053	<0.001	0.215
mean P3	3.1 (-0.4, 6.5)	4.2 (0.3, 8.3)	1.2 (-3.0, 5.4)	0.019	<0.001	0.029
Latencies (ms)						
N1	-1.2 (-13.6, 11.3)	-8.5 (-22.9, 6.0)	-7.3 (-22.5, 7.8)	0.484		0.491
P2	-0.7 (-(-21.9, 20.5)	1.2 (-23.5, 25.8)	1.9 (-23.9, 27.7)	0.989		0.803
P300	-120.9 (-210.0, -31.8)	-102.6 (-206.4, 1.2)	18.3 (-90.3, 126.9)	0.021		0.008

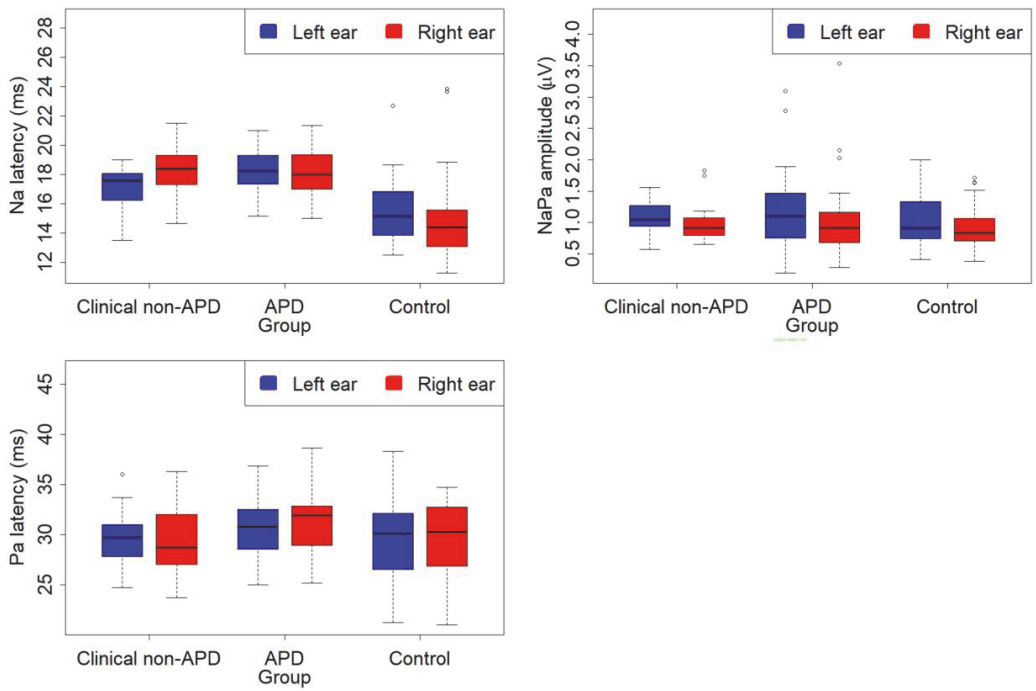
Table 4. Results from linear mixed models (LMMs) for the ALLR and P300 measures for models with no interaction effects included, over the electrode montages Fz, FCz, Cz and Pz. Differences, confidence intervals and p values are shown for the main effects of group (APD, non APD and NH). Only p values are shown for the main effects of electrode montage and age. No significant interaction effects were observed.

NH = normal hearing, APD = auditory processing disorder as per BSA (2018), LE = left ear stimulus, RE = right ear stimulus.

		Amp. Na-Pa	*Amp. Na-Pa*	*Lat. Na*	*Lat. Na*	*Lat. Pa*	*Lat. Pa*	*Amp. N1*	*Amp. P2*	*Lat. N1*	*Lat. P2*	*Amp. P300*	*Mean P300*	*Lat. P300*	*A-Sust.*	*V-Sust*
		LE	***RE***	***LE***	***RE***	***RE***	***LE***									
CW	LE	-0.11 (41)	-0,06 (42)	-0.31 (41)*	-0.30 (42)*	-0.15 (45)	-0.05 (45)	0.02 (35)	-0.02 (35)	0.04 (35)	0.05 (35)	0.47 (35)**	0.61 (35)**	-0.28 (35)	0.28 (24)	0.24 (24)
CW	RE	-0.18 (40)	-0.17 (41)	-0.19 (40)	-0.07 (41)	0.00 (44)	-0.01 (44)	0.06 (34)	0.16 (34)	0.22 (34)	0.04 (34)	-0.04 (34)	0.07 (34)	0.12 (34)	0.32 (23)	0.21 (23)
BMLD	B	0.09 (40)	-0.04 (41)	-0.09 (40)	-0.09 (41)	-0.38 (44)	-0.28 (44)	-0.01 (35)	-0.15 (35)	0.09 (35)	-0.06 (35)	-0.07 (35)	0.05 (35)	0.12 (35)	-0.04 (23)	-0.12 (23)
FP	B	0.01 (41)	-0.05 (42)	-0.18 (41)	-0.29 (42)	0.03 (45)	-0.03 (45)	-0.22 (35)	0.02 (35)	0.08 (35)	0.25 (35)	0.52 (35)**	0.34 (35)*	-0.39 (35)*	-0.05 (24)	-0.09 (24)
DP	B	-0.14 (41)	-0.02 (42)	-0.20 (41)	-0.28 (42)	-0.01 (45)	-0.09 (45)	-0.16 (35)	0.08 (35)	0.24 (35)	0.42 (35)*	0.48 (35)**	0.34 (35)*	-0.31 (35)	0.32 (24)	0.41 (24)**
GIN	B	-0.02 (40)	0.10 (42)	-0.16 (40)	-0.12 (42)	-0.08 (44)	-0.16 (44)	-0.01 (34)	-0.39 (34)*	-0.23 (34)	-0.22 (34)	0.09 (34)	0.22 (34)	-0.20 (34)	0.03 (24)	-0.02 (24)
DD	B	0.19 (41)	0.07 (42)	-0.35 (42)*	-0.30 (42)*	-0.15 (45)	-0.13 (45)	-0.06 (35)	-0.06 (35)	0.16 (35)	0.17 (35)	0.46 (35)**	0.49 (35)**	-0.43 (35)**	0.53 (24)**	0.56 (24)**
FW	B	-0.15 (41)	0.08 (42)	0.01 (41)	-0.02 (42)	-0.09 (45)	-0.05 (45)	-0.15 (35)	-0.04 (35)	-0.08 (35)	0.03 (35)	-0.03 (35)	0.07 (35)	-0.26 (35)	0.37 (24)	0.05 (24)
A-Sust.		0.07 (19)	0.15 (20)	0.11 (19)	0.21 (20)	-0.14 (23)	0.45 (23)*	0.13 (16)	0.10 (35)	0.19 (16)	0.21 (16)	0.37 (16)	0.03 (16)	0.40 (16)		0.79 (23)**
V-Sust.		0.32 (19)	0.25 (20)	0.02 (19)	0.32 (20)	-0.01 (23)	0.35 (23)	0.46 (16)	0.25 (16)	0.34 (16)	0.30 (16)	0.41 (16)	0.11 (16)	0.40 (14)	0.79 (23)**	

Table 5. Pearson`s product moment correlations (and sample sizes following case-wise deletion of missing data) for behavioural AP and attention measures against AEP measures. The reported values are not Bonferroni-Holm corrected. ALLR and P300 results are shown for recordings from Cz for the ALLR and Pz for the P300. *p ≤0.05. **p≤0.01. A-Sust: Auditory sustained attention, V-sust: Visual sustained attention, Ampl: amplitude, LE: left ear, RE: right ear, B: both ears

Figure 2. Boxplots of MLR Na latency values (top left), Pa latency values (bottom left), and NaPa amplitude values (top right) for all participating children. The centre line in each box indicates the median value and the box contains 50% of the cases. The whiskers represent the overall range in scores, except outliers, which are indicated by circles.



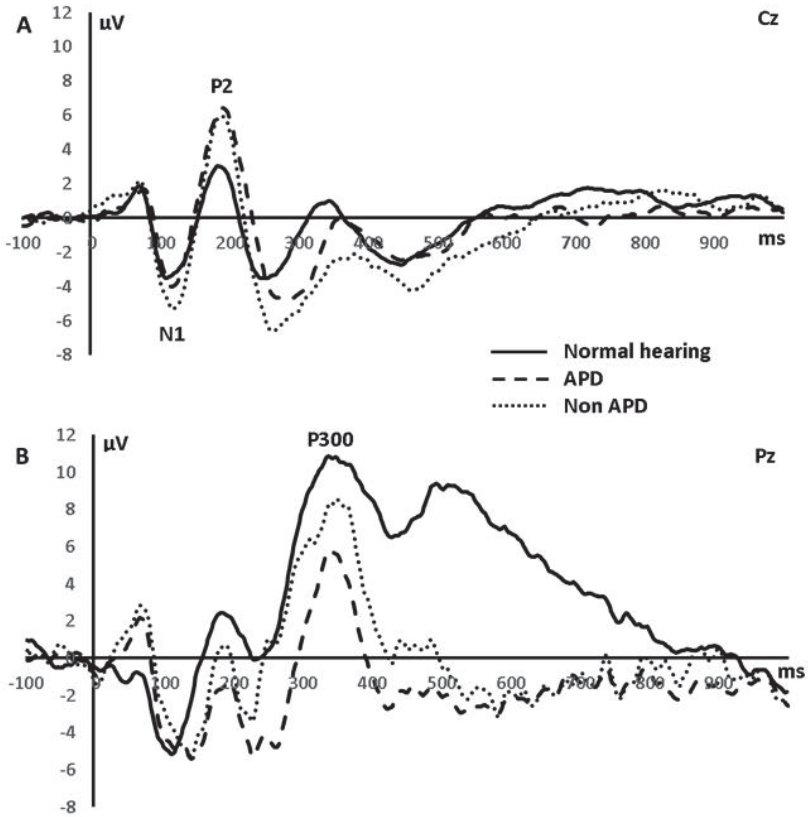


Figure 3. Grand average AEP waveforms for the ALLR (A) and P300 (B) for the normal hearing, APD and non APD groups. ALLR and P300 results are shown for recordings from Cz and Pz, respectively.

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