Cortical processing of speech and non-speech sounds in autism and Asperger syndrome

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CONTENTS

ABSTRACT

Autism and Asperger syndrome (AS) are neurodevelopmental disorders characterised by deficient social and communication skills, as well as restricted, repetitive patterns of behaviour. The language development in individuals with autism is significantly delayed and deficient, whereas in individuals with AS, the structural aspects of language develop quite normally. Both groups, however, have semantic-pragmatic language deficits. The present thesis investigated auditory processing in individuals with autism and AS. In particular, the discrimination of and orienting to speech and non-speech sounds was studied, as well as the abstraction of invariant sound features from speech-sound input. Altogether five studies were conducted with auditory event-related brain potentials (ERP); two studies also included a behavioural sound-identification task. In three studies, the subjects were children with autism, in one study children with AS, and in one study adults with AS.

In children with autism, even the early stages of sound encoding were deficient. In addition, these children had altered sound-discrimination processes characterised by enhanced spectral but deficient temporal discrimination. The enhanced pitch discrimination may partly explain the auditory hypersensitivity common in autism, and it may compromise the filtering of relevant auditory information from irrelevant information. Indeed, it was found that when sound discrimination required abstracting invariant features from varying input, children with autism maintained their superiority in pitch processing, but lost it in vowel processing. Finally, involuntary orienting to sound changes was deficient in children with autism in particular with respect to speech sounds. This finding is in agreement with previous studies on autism suggesting deficits in orienting to socially relevant stimuli.

In contrast to children with autism, the early stages of sound encoding were fairly unimpaired in children with AS. However, sound discrimination and orienting were rather similarly altered in these children as in those with autism, suggesting correspondences in the auditory phenotype in these two disorders which belong to the same continuum. Unlike children with AS, adults with AS showed enhanced processing of duration changes, suggesting developmental changes in auditory processing in this disorder.

TIIVISTELMÄ

Autismi ja Aspergerin oireyhtymä (Asperger syndrome, AS) ovat kehityksellisiä neurologisia häiriöitä, joiden keskeisiä piirteitä ovat vaikeudet sosiaalisessa vuorovaikutuksessa ja viestinnässä sekä käyttäytymisen toistavuus ja kapea-alaisuus. Autismiin liittyy huomattava kielen kehityksen vaikeus, kun taas AS:ssa kieli kehittyy melko normaalisti. Sekä autistisilla että AS-henkilöillä on kuitenkin vaikeuksia kielen vuorovaikutuksellisessa käytössä. Tässä väitöskirjassa tutkittiin, miten autistiset ja AS-henkilöt erottelevat puheäänteissä ja ei-kielellisissä äänissä tapahtuvia muutoksia, sekä miten vahvasti heidän tahaton tarkkaavuutensa suuntautuu näihin äänimuutoksiin. Lisäksi tutkittiin, miten autistiset lapset erottelevat puheäänteitä silloin, kun äänten akustiset piirteet vaihtelevat jatkuvasti yhden äänierottelulle epäolennaisen piirteen osalta. Väitöskirjan viidessä osatutkimuksessa tutkimusmenetelmänä käytettiin aivojen tapahtumasidonnaisia kuuloherätevasteita. Kahteen tutkimukseen sisältyi lisäksi äänten erottelutehtävä.

Tulosten mukaan ääntenpiirteiden peruskäsittely on autistisilla lapsilla heikentynyttä, ja heillä on vaikeutta äänten keston erottelussa. Sen sijaan äänten taajuuden erottelu on näillä lapsilla voimistunutta, mikä saattaa selittää autismissa yleistä kuuloyliherkkyyttä ja lisäksi vaikeuttaa olennaisen kuulotiedon valikoimista epäolennaisesta. Viimeisen osajulkaisun mukaan autististen lasten kyky erotella vokaaleja heikentyikin puhetta muistuttavassa tilanteessa, jossa äänten akustiset piirteet vaihtelivat jatkuvasti. Tutkimukset myös osoittivat autististen lasten tahattoman tarkkaavuuden kääntyvän tavanomaista heikommin erityisesti puheäänissä tapahtuviin muutoksiin. Tämä tulos on yhtenevä aiempien tutkimusten kanssa, joiden mukaan autismiin liittyy vaikeus suunnata tarkkaavuutta sosiaalisesti merkityksellisiin ärsykkeisiin.

Lapsilla, joilla oli AS, ei havaittu erityisempää vaikeutta ääntenpiirteiden peruskäsittelyssä. Sen sijaan tulokset äänten erottelun ja tahattoman tarkkaavuuden kääntymisen suhteen olivat heidän osaltaan varsin samanlaiset kuin autistisilla lapsilla. Tämä korostaa sitä, että autismi ja AS kuuluvat samaan tautikirjoon. Lisäksi tutkimukset viittasivat siihen, että AS-henkilöiden tavassa käsitellä kuulotietoa tapahtuu kehityksen myötä muutoksia.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals.

I Čeponienė, R., Lepistö, T., Shestakova, A., Vanhala, R., Alku, P., Näätänen, R., & Yaguchi, K. (2003) Speech-sound –selective auditory impairment in autism: They can perceive but do not attend. *Proceedings of the National Academy of Sciences of the United States of America,* 100:5567-5572.

II Lepistö, T., Kujala, T., Vanhala, R., Alku, P., Huotilainen, M., & Näätänen, R. (2005) The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Research,* 1066:147-157.

III Lepistö, T., Silokallio, S., Nieminen-von Wendt, T. Alku, P., Näätänen, R., & Kujala, T. (2006) Auditory perception and attention function as reflected by brain event-related potentials in children with Asperger syndrome. *Clinical Neurophysiology,* 117:2161-2171.

IV Lepistö, T., Nieminen-von Wendt, T., von Wendt, L., Näätänen, R., & Kujala, T. (2007) Auditory cortical change detection in adults with Asperger syndrome. *Neuroscience Letters,* 414:136-140.

V Lepistö, T., Kajander, M., Vanhala, R., Alku, P., Huotilainen, M., Näätänen, R., & Kujala, T. (2008) The perception of invariant speech features in children with autism. *Biological Psychology,* 77:25-31.

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ABBREVIATIONS

ANOVA	analysis of variance
AS	Asperger syndrome
ASD	autism spectrum disorders
BAEP	brainstem auditory evoked potential
EEG	electroencephalogram
ERP	event-related potential
LLAEP	long-latency auditory evoked potential
MEG	magnetoencephalography
MLAEP	middle-latency auditory evoked potential
MMF	magnetic mismatch field
MMN	mismatch negativity
p	probability
PIQ	performance intelligence quotient
SOA	stimulus onset asynchrony
SPL	sound pressure level
SSG	Semisynthetic Speech Generation method
TSC	tuberous sclerosis complex
VIQ	verbal intelligence quotient
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WISC-III	Wechsler Intelligence Scale for Children, 3rd edition
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence - Revised

1 INTRODUCTION

1.1. Clinical characteristics of autism and Asperger syndrome

Autism and Asperger syndrome (AS) (Asperger, 1944/1991; Kanner, 1943) are neurodevelopmental disorders that belong to the autism spectrum disorders (ASD)[1]. Their main characteristics are deficient social and communication skills, as well as restricted, repetitive patterns of behaviour (Table 1). However, individuals with autism and AS differ from each other in particular with respect to language development.

Individuals with autism show significant delays and deficits in language development, with about a half remaining essentially nonverbal or with little functional spoken language (Gillberg & Coleman, 2000; Landa, 2007). The profile of language performance in the majority of verbal children with autism with respect to phonological, semantic, and grammatical abilities parallels with that reported for children with specific language impairment (Bishop et al., 2004; Kjelgaard & Tager-Flusberg, 2001; Rapin & Dunn, 2003). Furthermore, semantic-pragmatic deficits are universal in autism (Rapin & Dunn, 2003), entailing, for example, impaired understanding of nonliteral language, poor conversation skills, and deficits in interpreting and producing prosody (Landa, 2000; McCann & Peppé, 2003; Paul et al., 2005).

In contrast, the current diagnostic criteria (DSM-IV, American Psychiatric Association, 1994; ICD-10, World Health Organization, 1993) for AS allow no significant delay in general language or cognitive development. Although the structural aspects of language develop quite normally in individuals with AS (Volkmar & Klin, 2000), these individuals have, however, similar semantic-pragmatic deficits as those with autism (Gillberg & Coleman, 2000). Furthermore, some individuals with AS have initial mild deficits in their language development that later subside (Cederlund & Gillberg, 2004; Gillberg & Coleman, 2000; Wing, 1981).

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[1] The term "autism spectrum disorder" is commonly used to collectively refer to autism, AS, and Pervasive Developmental Disorder - Not Otherwise Specified (a condition with some – but not all – features of autism). In the present thesis, ASD is used to refer to autism and AS.

Table 1. DSM-IV/ICD-10 Diagnostic criteria for autism and Asperger syndrome (adapted from Lord et al. 2000).

	Autism	**Asperger syndrome**
Age of onset	Delays or abnormal functioning in social interaction, language, and/or play by age 3.	No clinically significant delay in language, cognitive development, or development of age appropriate self-help skills, adaptive behaviour, and curiosity about the environment in childhood.
Social Interaction	Qualitative impairment in social interaction, as manifested by at least two of the following:* a) marked impairment in the use of multiple nonverbal behaviours, i.e., eye-to-eye gaze; b) failure to develop peer relationships appropriate to developmental level; c) lack of spontaneous seeking to share enjoyment with other people; d) lack of social or emotional reciprocity.	Same as autism.
Communication	Qualitative impairments in communication as manifested by at least one of the following: a) delay in, or total lack of, the development of spoken language; b) marked impairment in initiating or sustaining a conversation with others, in individuals with adequate speech; c) stereotyped and repetitive use of language or idiosyncratic language; d) lack of varied, spontaneous make-believe or imitative play.	No clinically significant general delay in language.
Behaviour	Restricted, repetitive, and stereotyped patterns of behaviour, as manifested by at least one of the following: a) preoccupation with one or more stereotyped or restricted patterns of interest; b) adherence to non-functional routines or rituals; c) stereotyped and repetitive motor mannerisms; d) persistent preoccupation with parts of objects.	Same as autism.

*A total of six or more items are required for diagnosis.

Social impairment has been traditionally regarded as the primary dysfunction in ASD, and deficits in communication as its secondary consequence (Mundy & Neal, 2001; Wing, 1988). It has, however, become evident that impaired auditory processing also contributes to the language deficits observed in these disorders (Bomba & Pang, 2004; Rapin, 2002). Both the structure and function of the brain areas involved in language processing are atypical in individuals with autism in several ways. Magnetic resonance imaging has revealed abnormal asymmetry patterns in frontal and temporal regions related to language (De Fosse et al., 2004; Herbert et al., 2002; Rojas et al., 2002), and studies using regional cerebral blood flow during rest as a measure of cortical activation have indicated bilateral hypoperfusion in the superior temporal gyrus (Gendry Meresse et al., 2005; Ohnishi et al., 2000; Zilbovicius et al., 2000). Furthermore, individuals with autism show diminished activation in the left-hemisphere language-related areas during listening of sounds as well as during sentence comprehension (Boddaert et al., 2003, 2004; Müller et al., 1999). Recently, Gervais et al. (2004) reported that adults with autism failed to activate bilateral superior temporal sulcus voice-selective areas in response to vocal sounds, but showed a normal activation pattern in response to non-vocal sounds.

1.2. Auditory processing in autism and Asperger syndrome

1.2.1. Auditory sensory sensitivities

Atypical reactions to sensory stimuli are very common both in autism (Dahlgren & Gillberg, 1989; Kern et al., 2006; Kientz & Dunn, 1997; Leekam et al., 2007; O'Neill & Jones, 1997; Talay-Ongan & Wood, 2000) and AS (Dunn et al., 2002; Gillberg & Coleman, 2000). All the modalities, but particularly the auditory one, are affected (Dahlgren & Gillberg, 1989). On one hand, individuals with ASD frequently show signs of auditory hypersensitivity. For example, they get easily distressed by sounds, often try to avoid sounds by covering their ears, and may appear to have a better-than-normal hearing. On the other hand, auditory hyposensitivity is also fairly common: a child may fail to attend to his name, may ignore loud sounds, or may seek auditory stimulation by producing sounds by himself.

Recent studies have shown that children with ASD have, however, normal peripheral auditory functions – for example, their pure tone hearing sensitivity thresholds are similar to those of typically developing peers (Gravel et al., 2006; Khalfa et al., 2004). Therefore, the atypical reactions to sounds in ASD seem to represent a higher-level perceptual or cognitive dysfunction.

1.2.2. Auditory discrimination skills

Only a few studies have directly investigated speech sound discrimination in ASD. Bartolucci and Pierce (1977) reported that children with autism showed a similar delayed pattern in consonant perception tasks as children with mental retardation did. More recent studies (Bishop et al., 2004; Kjelgaard & Tager-Flusberg, 2001) have confirmed that children with ASD have impaired phonological processing skills as assessed with non-word repetition tasks. Furthermore, individuals with ASD have difficulty in perceiving speech in noisy environments (Alcantara et al., 2004).

Clinical observations of relatively good musical skills in autism, case descriptions of musical savants with ASD (Heaton et al., 1999; Mottron et al., 1999), as well as a survey study suggesting increased prevalence of absolute pitch in autism (Rimland & Fein, 1988), stimulated the emergence of studies on non-speech discrimination skills in ASD. These studies have revealed that musically untrained individuals with ASD outperform their controls in various tasks requiring pitch-memory and -discrimination skills (Bonnel et al., 2003; Heaton, 2003, 2005; Heaton et al., 2001; Mottron et al., 2000; O'Riordan & Passetti, 2006). Individuals with ASD are better than their controls also in discriminating pitch changes in words and sentences, suggesting that the enhanced sensitivity to pitch in autism is not restricted to non-speech stimuli (Hudry et al., 2006; Järvinen-Pasley et al., 2008). The perception of loudness, too, appears to be enhanced in children with autism (Khalfa et al., 2004).

The enhanced performance in low-level perceptual tasks in ASD is not specific to the auditory domain. Rather, studies in the visual modality have clearly demonstrated superior performance in various low-level tasks, including discrimination learning, visual search, and visual disembedding tasks (for a review, see Dakin & Frith, 2005; Happé & Frith, 2006). Two theories have been proposed to explain these findings. According to the Weak Central Coherence theory (Frith, 1989; Happé & Frith, 2006), ASD are characterised by a detail-focused cognitive style that might be paralleled by the deficient processing of global, contextual aspects of information. The Enhanced Perceptual Functioning model (Mottron & Burack, 2001; Mottron et al., 2006), in turn, proposes that low-level perceptual functions are enhanced in individuals with ASD, resulting in superior performance in tasks requiring stimulus detection, discrimination and categorisation.

Importantly, the enhanced low-level auditory processing has been suggested to have negative consequences on language development (Gustafsson, 1997; O'Riordan & Passetti, 2006). For perceiving speech, one has to both discriminate sounds and to identify phonemes despite the variation in their acoustical features caused by, for example, the speaker, background noise, and speech rate (Bishop, 1997). Enhanced low-level perceptual abilities in autism may result in a too focussed processing of these irrelevant features, which might impair the perception of the common, invariant features important for the identification of the phonemes (Gustafsson, 1997; O'Riordan & Passetti, 2006). This might affect the formation of appropriate phoneme categories, and thus impair the language development in autism. Enhanced low-level processing may also contribute to the auditory hypersensitivity, as well as to the difficulties reported in individuals with ASD in perceiving speech in noisy environments (Alcantara et al., 2004) and in separating competing sound sources from each other (Teder-Sälejärvi et al., 2005).

1.2.3. Orienting and attending to auditory events

Research on auditory attention functions in individuals with ASD has mainly focussed on involuntary and voluntary orienting, revealing a striking impairment in the ability of these individuals to orient and attend to socially relevant stimuli. Retrospective analyses of home videos of infants later diagnosed with ASD have indicated that as early as at the age of 6 to 12 months, these infants have deficient auditory (and visual) social orienting and attention, but do not differ from typically developing controls with regard to non-social attention (Maestro et al., 2002; Osterling et al., 2002; Werner et al., 2000). Furthermore, diminished orientation to voice was one of the most robust predictors of a later diagnosis of autism in two-year-old children with developmental disorders (Lord, 1995).

Dawson et al. (1998, 2004) observed that preschoolers with ASD, as compared with typically developing and developmentally delayed children, were impaired in their orienting to both social and non-social auditory stimuli. This impairment was, however, more severe for social stimuli. Furthermore, children with ASD prefer non-speech input over speech input (Blackstock, 1978; Klin, 1991; Kuhl et al., 2005). For example, these children preferred cafeteria noise to their mother's speech (Klin, 1991). In striking contrast, typically developing infants appear to prefer speech as compared with acoustically similar non-speech sounds as early as at birth (Vouloumanos & Werker, 2007). Furthermore, Gervais et al. (2004) reported that when adults with autism and their controls were presented with vocal and non-vocal sounds, and afterwards asked to describe sounds that they had heard, controls reported hearing equally many vocal and non-vocal sounds. In contrast, subjects with autism had a better recall of non-vocal stimuli, suggesting an attentional bias towards non-vocal sounds. Also visual orienting in autism is affected particularly with respect to social stimuli (Klin et al., 2003; Maestro et al., 2002; Swettenham et al., 1998).

Deficient orienting to social input in autism has been suggested to reflect a failure to find social stimuli inherently rewarding (Dawson et al., 2004; Mundy & Neal, 2001), and/or to attain significance to them because of their complex and unpredictable nature (Dawson & Levy, 1989; Dawson et al., 2005). Impairment in social orienting is likely to have far-reaching implications on the social and communicative development of individuals with ASD (Dawson et al., 2004; Mundy, & Neal 2001).

1.3. Auditory event-related potentials as a means to study autism and Asperger syndrome

The present thesis addresses auditory processing in individuals with autism and AS by using event-related brain potentials (ERP). In particular, the discrimination of and orienting to speech and non-speech sounds were investigated, as well as the abstraction of invariant sound features from speech sound input. In the following, the ERPs and the previous ERP findings in autism and AS are reviewed.

1.3.1. Auditory event-related potentials (ERPs)

Event-related potentials (ERPs) provide a non-invasive and accurate way of monitoring the timing and stages of auditory perception (Coles & Rugg, 1995). Auditory ERPs are transient voltage changes in the electroencephalogram (EEG) that are triggered by, and time-locked to, acoustic or cognitive events. Auditory ERPs are divided into three groups according to their latency and site of generation. *Brainstem auditory evoked potentials (BAEP)* occur at 0–10 ms after stimulus onset and are generated in the brainstem and subcortical structures (Legatt et al., 1988). *Middle-latency auditory evoked potentials (MLAEP)* represent the initial activation of the auditory cortex and occur at ca. 10–50 ms after stimulus onset (Liegeois-Chauvel et al. 1994). *Long-latency auditory evoked potentials (LLAEP)* have a peak latency of ca. 50 ms or more and are generated in the auditory cortex and related cortical areas. *Exogenous* LLAEP components are obligatorily elicited by all stimuli, and mainly reflect the physical features of the stimuli, whereas *endogenous* components also reflect cognitive processes, and are not obligatorily evoked by every stimulus (Näätänen, 1992).

In the present thesis, central auditory processing in ASD was studied with LLAEPs. Although early abnormalities in central auditory processing may be present in some individuals with ASD (Rosenhall et al., 2003), in the majority of them, auditory information is relayed in a relatively normal fashion from the acoustic nerve to the auditory cortex (Bomba & Pang, 2004; Buchwald et al., 1992; Grillon et al., 1989; Klin, 1993; Tharpe et al., 2006).

1.3.1.1. ERPs reflecting acoustic feature processing

In adults, the obligatory long-latency ERP waveform to any sound consists of P1, N1, and P2 peaks. The P1 is generated in the primary auditory cortex and peaks at ca. 50 ms (Liegeois-Chauvel et al., 1994). The N1 peaking at ca. 100 ms consists of at least three subcomponents: N1b and N1c are specific to auditory modality and mainly generated in the temporal lobes, whereas the third, modality non-specific component (N1a) reflects the activation of a widespread neural network related to general arousal response (Näätänen & Picton, 1987). The P2 peaks at ca. 150–200 ms, and is sometimes followed by N2. These sensory responses reflect sound detection and the encoding of physical stimulus features (Näätänen & Winkler, 1999). Their amplitude and latency strongly depend on the physical features of the stimulus input (Wunderlich & Cone-Wesson, 2006).

The obligatory ERP waveform in school-age children is quite different from that in adults. In children the waveform is typically dominated by the P1 and N2 peaks, which are often followed by the N4 response (Čeponienė et al., 1998, 2001; Cunningham et al., 2000; Ponton et al., 2000). With slow stimulus rates (> 1 sec), also the N1 and P2 are obtained, resulting in a waveform more similar to that in adults (Čeponienė et al. 1998; Wetzel et al., 2006). Although insufficiently studied, the childhood obligatory ERPs are considered to reflect similar cortical processes as those in adults (Čeponienė et al., 2001).

1.3.1.2. Mismatch negativity (MMN)

The mismatch negativity (MMN; Näätänen et al., 1978; for a review, see Näätänen et al., 2007) reflects early cortical stages of sound discrimination. It is elicited by any perceptibly different sound (“deviant”) in a sequence of repetitive sounds (“standards”), or by a sound violating an abstract rule or regularity of auditory input (Näätänen et al., 2001). The MMN is extracted from a deviant minus standard difference waveform, and peaks between 100 and 250 ms after the onset of the change. The MMN amplitude increases and its latency decreases with increasing deviation from the standard stimulus (Novitski et al., 2004; Sams et al., 1985). The MMN is associated with behavioural discrimination abilities, as its amplitude and latency to a particular stimulus contrast closely parallel the individual's discrimination ability of that contrast (Amenedo & Escera, 2000; Kujala et al., 2001; Lang et al., 1990; Novitski et al., 2004). Thus, unlike the ERPs reflecting acoustic features (Cunningham et al., 2000; Näätänen & Winkler, 1999), the MMN appears to be an index of neural sound representations underlying conscious auditory perception (Näätänen & Winkler, 1999). Importantly, the MMN requires no behavioural response, and it can even be recorded when the subject is ignoring the sound stimuli (Näätänen et al., 1993; Paavilainen et al. 1993). These features have made it a popular tool for investigating sound discrimination processes in various clinical groups (*e.g.,* Baldeweg et al., 1999; Ilvonen et al., 2003; Michie, 2001; for a review, see Näätänen, 2003). In particular, the MMN is well-suited for studying difficult-to-test populations such as children with autism.

According to Näätänen (1992), MMN is elicited when an incoming sound does not match with the sensory memory trace integrating the physical and temporal attributes of the recent, frequently presented stimulus. This sensory memory representation is abstract in nature: the MMN is not only elicited by changes in the physical sound features such as frequency and duration, but also by sounds that violate abstract rules or regularities of auditory input (Kujala et al., 2007b; Näätänen et al., 2001). For example, the MMN is elicited even when the standard sound constantly varies with respect to one or more irrelevant features, and the sound discrimination requires the detection of the relevant invariant features characterising the standard (Aulanko et al., 1993; Huotilainen et al., 1993; Jacobsen et al., 2004; Paavilainen et al., 2001). Although the MMN operates at the sensory memory level (Näätänen & Winkler, 1999), it is affected by long-term sound representations such as those formed for the native phonemes (Näätänen et al., 1997). For non-speech changes, the MMN typically reaches its largest amplitude over the right hemisphere (Levänen et al., 1996; Paavilainen et al., 1991); for phoneme changes it often predominates over the left hemisphere (Alho et al., 1998; Näätänen et al., 1997; Shtyrov et al., 2000).

The main MMN sources are located in the left and right supratemporal auditory cortices (for a review, see Alho, 1995). These generators probably reflect activity directly related to sensory memory traces, as the exact source location varies depending on the sound feature to be discriminated (Giard et al. 1995; Molholm et al., 2005). The MMN also has a generator in the right frontal lobe (Giard et al., 1990; Rinne et al., 2000). Therefore, in addition to sound discrimination, the process generating the MMN has been proposed to play an important role in initiating involuntary attention switch to changes in auditory environment (Escera et al., 1998; 2000). Consistent with this, the MMN is usually followed by P3a, an ERP-index of the actual involuntary attention switch.

1.3.1.3. P3a and P3b

Infrequently presented deviant stimuli in a sequence of repetitive standard sounds elicit two main varieties of positive deflections, the P3a and P3b, peaking at about 300 to 400 ms from stimulus onset (Polich & Criado, 2006; Squires et al., 1975). When stimuli are attended, the P3b is elicited by targets in discrimination tasks, and it reflects attention and memory-related operations associated with target detection (Polich, 1998). The auditory P3b is usually largest parietally, and its sources include the temporal cortices, hippocampal region and thalamus (Picton, 1992). The P3b is diminished in amplitude in various disorders with deficits in attention allocation or immediate memory or both, for example in schizophrenia (Bramon et al., 2004) and attention-deficit/hyperactivity disorder (Barry et al., 2003).

The P3a, in turn, is elicited by deviant unexpected sounds both when these sounds are attended and unattended. As compared with the P3b, the P3a is smaller in amplitude, more frontally distributed, and earlier in latency (Friedman et al. 2001; Squires et al., 1975). The P3a is especially large in response to novel, surprising sounds, and its amplitude diminishes as the novelty value of the stimulus decreases (Cycowicz & Friedman, 1997). The neural sources of the auditory P3a include prefrontal, temporal, and parietal cortices, as well as the posterior hippocampus (for a review, see Escera et al., 2000).

The P3a is considered to reflect involuntary shifting of attention to infrequent, attention-catching stimuli, thus being closely related to the orienting response (Escera et al., 2000; Sokolov, 1975). Consistent with this, P3a-eliciting unattended deviant and novel sounds disturb the performance in simultaneous visual or auditory discrimination tasks (Alho et al., 1997; Escera et al., 1998; Gumenyuk et al., 2001; Wetzel et al., 2006). Consequently, abnormally large P3a amplitude can be interpreted as a sign of a lowered threshold for involuntary attention switch, which manifests as increased distractibility by task-irrelevant events. Consistent with this, an enhanced P3a has been reported in patients with closed-head injuries (Kaipio et al., 1999), in chronic alcoholics (Polo et al., 2003), and in children with attention deficit/hyperactivity disorder (Gumenyuk et al., 2005). Diminished P3a responses, in turn, have been reported in patients with prefrontal (Knight, 1984), temporo-parietal (Knight et al., 1989), and posterior hippocampal (Knight, 1996) lesions.

1.3.2. Review of the previous auditory ERP studies in autism and Asperger syndrome

1.3.2.1. ERPs reflecting acoustic feature processing in autism and Asperger syndrome

Several studies investigated the N1 response in individuals with autism, with rather inconsistent results (for a review, see Bomba & Pang, 2004). Most studies have reported similar N1b responses for both non-speech and speech stimuli in participants with autism and their controls (*e.g.,* Erwin et al., 1991; Kemner et al., 1995; Lincoln et al., 1995; Oram Cardy et al., 2004). However, some studies found diminished N1b amplitudes (Bruneau et al., 1999; Courchesne et al., 1985) and prolonged latencies (Dawson et al., 1986; Gage et al., 2003), whereas some observed increased amplitudes (Oades et al., 1988) and shortened latencies (Ferri et al., 2003). The N1c responses were smaller in amplitude and longer in latency in children with autism as compared with those in both age-matched typically developing and mentally retarded children (Bruneau et al., 1999).

Other obligatory responses have received considerably less attention so far. The P1 was diminished in amplitude in high-functioning adults with autism for clicks presented with a slow rate, but enhanced for clicks presented with a fast rate (Buchwald et al., 1992). The P2 for tones was unaffected in the study of Lincoln et al. (1995), whereas Novick et al. (1980) observed diminished P2 responses for clicks and tones. In addition, Dunn et al. (1999) reported delayed P2 responses for words in children with autism. Further, the N2 for tones was similar in children with autism and their controls (Gomot et al., 2002).

In children with AS, the P1 was diminished in amplitude for both tones and syllables (Jansson-Verkasalo et al., 2003). Furthermore, the N2 for tones was delayed in latency and diminished over the right central scalp areas, whereas the N4 was unaffected. In their subsequent study, Jansson-Verkasalo et al. (2005) observed delayed P1 responses in children with AS for tones over the left hemisphere. Moreover, the N2 amplitude was diminished, whereas its latency was shortened centroparietally. The N4 for tones was diminished in amplitude and prolonged in latency.

In summary, the majority of the studies on the obligatory ERPs found differences between the individuals with autism or AS and their controls. However, the variability of the results makes it difficult to draw conclusions on their clinical significance.

1.3.2.2. MMN in autism and Asperger syndrome

The majority of the MMN studies on autism have investigated pitch discrimination. Gomot et al. (2002) reported shortened MMN latencies for tone pitch changes (1000 Hz vs. 1100 Hz) in children with autism and mental retardation as compared with age-matched controls. Consistent with this, the MMN amplitude for tone-pitch changes (1000 Hz vs. 1300 Hz) was larger in mentally retarded autistic children and adolescents than in their age-matched controls (Ferri et al., 2003). These studies are in agreement with behavioural ones suggesting enhanced pitch discrimination processes in autism (*e.g.,* Bonnel et al., 2003; Heaton, 2003; Mottron et al., 2000; O'Riordan & Passetti, 2006). In contrast, the MMN amplitude for pitch changes (1000 Hz vs. 1500 Hz) was diminished in children with autism and tuberous sclerosis complex (TSC) as compared with children with TSC only (Seri et al., 1999). However, in this study, all the subjects with autism had lesions involving one or both temporal lobes, which may have confounded the results as the main MMN generators reside in the temporal lobes.

Two studies have investigated phoneme discrimination in children with autism with MMN. Kemner et al. (1995) reported similar MMN amplitudes for vowel changes (/oy/ vs. /ay/) in high-functioning children with autism and their controls. Kuhl et al. (2005) recorded MMN for consonant changes in syllables (/wa/ vs. /ba/) in a large group of preschool children with ASD and in their age-matched controls. The MMN was absent in the ASD group, suggesting deficits in the discrimination of consonants in ASD. However, when the children were assigned into subgroups on the basis of whether they showed a listening preference for speech or non-speech in a separate experiment, the MMN of those children with ASD who preferred speech was equal to that of the control children.

The magnetic counterpart of the MMN (magnetic mismatch field; MMF), recorded by magnetoencephalography (MEG), has also been studied in autism. Tecchio et al. (2003) observed no MMF for tone pitch changes (1000 Hz vs. 1200 Hz) in individuals with autism and mental retardation with a broad age range (8–32 years). In contrast, Kasai et al. (2005) and Oram Cardy et al. (2005b) reported that the MMF power was similar in participants with autism as in their age-matched controls. However, Kasai et al. (2005) found that the MMF in adults with autism was delayed in latency in the left hemisphere for phoneme changes (/a/ vs. /o/), but not for speech (150 ms vs. 100 ms) or non-speech duration (100 ms vs. 50 ms) changes. Oram Cardy et al. (2005b), in turn, reported that children with ASD had delayed MMF latencies for tone pitch (300 Hz vs. 700 Hz) and phoneme-category (/a/ vs. /u/) changes.

Recent MMN studies have suggested that individuals with AS, too, have cortical sound-discrimination deficits. Jansson-Verkasalo et al. (2003) recorded MMN for tone pitch changes (1000 Hz vs. 1100 Hz) and for consonant changes (/taa/ vs. /kaa/) in children with AS. The MMN latency was delayed over the right hemisphere for consonant changes, and over both hemispheres for tone changes in the AS group as compared with age-matched controls. Consequently, the authors suggested that there are sound discrimination deficits particularly in the right hemisphere in AS. Moreover, whereas the controls tended to have larger-amplitude MMNs over the left than the right hemisphere, the opposite trend was observed in the AS group. In their subsequent study, Jansson-Verkasalo et al. (2005) observed that the MMN for tone-pitch changes (280 Hz vs. 320 Hz) had two separate peaks. The “MMN1” was frontocentrally smaller in amplitude in children with AS than in their controls, whereas the “MMN2” was delayed in latency in the AS group.

Finally, two studies have investigated the discrimination of prosodic contrasts with the MMN in individuals with AS. Kujala et al. (2005) recorded MMN for words spoken with commanding, sad, or scornful voice, and found fewer significant MMNs in adults with AS than in their controls. Furthermore, diminished MMN amplitudes as well as prolonged latencies particularly over the right hemisphere were evident in the AS group. Further, Korpilahti et al. (2007) recorded MMN for words spoken with commanding voice in children with AS. The first peak of the MMN was enhanced in these children, whereas the second one was delayed. Taken together, these results suggest altered neural processing of prosody in AS.

1.3.2.3. P3a and P3b in autism and Asperger syndrome

The P3b for target stimuli in sound discrimination tasks has been consistently found to be diminished in individuals with autism, for both non-speech (Ciesielski et al., 1990; Courchesne et al., 1989; Lincoln et al., 1993; Novick et al., 1980; Oades et al., 1988) and speech stimuli (Courchesne et al., 1984, 1985; Dawson et al., 1988; Dunn et al., 1999). Based on these results, Courchesne (1987) suggested that individuals with autism are impaired in selectively attending to the target stimuli and in recognising them as important. However, some studies on individuals with autism who have average-range cognitive abilities have reported typical P3b responses (Erwin et al., 1991; Kemner et al., 1995; Salmond et al., 2007).

The P3a amplitude is diminished in individuals with autism in response to novel, surprising stimuli embedded among attended target and standard stimuli in sound discrimination tasks (Courchesne et al., 1984, 1985; Kemner et al., 1995)[2]. This result was interpreted as suggesting a limited or selective capacity to orient to new and significant information (Courchesne, 1987). In contrast, Ferri et al. (2003) reported similar P3a amplitudes for unattended novel sounds in individuals with autism and mental retardation (aged 6–19 years) and their controls. However, in subjects with autism, the P3a tended to decrease in amplitude with age, whereas in the control group, it tended to increase with age (Ferri et al., 2003). Lincoln et al. (1993) found no P3a differences for non-speech target stimuli between school-age children with autism and their controls either when the sounds were responded to or only listened to. Finally, Gomot et al. (2002) reported that the MMN for tone-pitch changes was followed by a small P3a in mentally retarded autistic children but not in control children, but this response was not analysed statistically. In sum, the P3a studies have indicated that individuals with autism are impaired in their involuntary orienting to attended novel sounds, whereas their orienting to unattended novel or non-speech sounds appears to be fairly intact. None of these studies addressed the P3a for speech stimuli in autism.

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[2] In their original papers, Courchesne et al. (1984, 1985) labelled this response as A/Pcz/300, ("an auditory positive response that is largest at Cz and peaks at about 300 ms after stimulus onset"). They have later interpreted it as the P3a (Courchesne et al., 1992).

2 THE AIMS OF THE STUDIES

The present thesis addressed cortical discrimination of and orienting to, speech and non-speech sounds in individuals with autism and Asperger syndrome.

Study I aimed at determining whether children with autism have deficits in sound discrimination and orienting, and, if so, whether these deficits are affected by stimulus complexity and "speechness" quality. To this end, the MMN and P3a responses were recorded to pitch changes in acoustically matched simple tones, complex tones, and vowels. It was hypothesised that children with autism would have deficits particularly in speech-sound processing.

Study II aimed at providing a more comprehensive account of speech and non-speech processing in children with autism by recording the MMN and P3a for pitch, duration and phoneme (or phoneme-counterpart) changes. The same paradigm was also applied to children (**Study III**) and adults with AS (**Study IV**), allowing an indirect comparison of the perceptual functions in autism and AS, as well as a preliminary evaluation of developmental changes in these functions in AS. The individuals with AS were expected to have considerably milder deficits than individuals with autism. **Studies III** and **IV** also included a behavioural sound-identification task.

Study V determined whether children with autism are able to extract invariant sound features from speech-sound input. To this end, the MMN was recorded for pitch and phoneme changes in speech sounds under two different experimental conditions: (a) when all the other features of the standard and deviant stimuli were kept constant, and (b) when constant variation with respect to an irrelevant feature was introduced to the standard and deviant stimuli. It was hypothesised that because of their enhanced discrimination abilities, children with autism might have difficulties in extracting invariant sound features.

3 METHODS

3.1. Subjects

The subjects were children with autism (**Studies I, II, & V)**, children with AS (**Study III)**, and adults with AS **(Study IV)** (Table 2). Each clinical group was compared with an age-matched control group. The children with autism were recruited from the Helsinki University Central Hospital (HUCH) and from the Central Hospital of Central Finland. The subjects with AS were recruited from the HUCH and from the Helsinki Asperger Center (Dextra Medical Center). All the clinical participants had undergone a rigorous multidisciplinary diagnostic assessment and they fulfilled the DSM-IV (American Psychiatric Association, 1994) and the ICD-10 (World Health Organization, 1993) diagnostic criteria for autism (**Studies I, II, & V**) or AS (**Studies III & IV**). The studies were approved by the Ethics Committees of the HUCH and/or the Department of Psychology, University of Helsinki. Informed written consent was obtained from the parents (**Studies I-III, & V**) or participants (**Study IV**), and assent from the children.

3.2. Event-related potential measurements

3.2.1. Stimuli and experimental conditions

In **Study I**, ERPs were recorded with an oddball paradigm for pitch changes (probability (p) = .07) in a simple tone, complex non-speech sound, and vowel /ö/. There were also duration changes in the sequences, but as the article reported pitch processing only, the results on duration processing are not included here either. The deviant sounds were 10% higher in frequency than the standard sounds. The duration of the stimuli was 260 ms and the sound onset asynchrony (SOA) was 700 ms.

Table 2. The characteristics of the subjects.

	N	Male/Female ratio	Mean age in years (range)	Mean PIQ* (range)	Mean VIQ* (range)
Study I	9 children with autism	8/1	8.9 (6.3–12.4)	86 (70–113)	†
	10 control children	9/1	8.4 (6.6–12.4)	‡	‡
Study II	15 children with autism	13/2	9.4 (7.3–11.10)	95 (77–119)	59 (40–90)§
	15 control children	13/2	9.4 (7.5–11.11)	115 (96–131)¶	107 (87–141) ¶
Study III	10 children with AS	8/2	8.11 (7.7–10)	112 (87–137)	108 (86–129)
	10 control children	8/2	8.10 (7.9–10.2)	114 (96–131) ¶	107 (92–141) ¶
Study IV	9 adults with AS	7/2	27 (20–37)	108 (82–126)	104 (90–126)
	9 control adults	8/1	30 (20–41)	116 (106–123)	113 (93–126)
Study V	10 children with autism	9/1	9.1 (7.0–11.0)	89 (77–105)	54 (41–70) §
	16 control children	15/1	9.0 (6.11–10.10)	108 (80–131)	120 (91–148)

* PIQ and VIQ were assessed with WPPSI-R (Wechsler, 1990), WISC-III (Wechsler, 1991), or WAIS-R (Wechsler, 1981), depending on the participant's age. With respect to the children with autism, the PIQ was sometimes obtained with Leiter (Leiter, 1980), and in one case with Raven (Raven et al., 1996).

† VIQ unavailable for 5 children with limited expressive language. The VIQ of the remaining 4 children ranged between 57 and 66.

‡ Not assessed.

§ VIQ unavailable for 3 children with limited expressive language.

¶ One child was unavailable for testing.

In **Studies II-IV**, ERPs were recorded with an oddball paradigm for pitch (p = .08), duration (p = .08), and phonetic (p = .08) changes in phonemes (/a/, /o/), and for the corresponding changes in complex non-speech sounds. Four variants of each stimulus were employed: a) *long* (190 ms, 5 ms rise and fall times) stimulus with *low* pitch (fundamental frequency (F0) 113 Hz), b) *short* (104 ms) with *low* pitch, c) *long* with *high* pitch (125 Hz), and d) *short* with *high* pitch. Each long stimulus served as a standard in one block and as a deviant in the other speech or non-speech blocks. The SOA was 700 ms.

Study V was designed to determine whether the central auditory system of children with autism is able to abstract invariant features from speech-like variable input. There were altogether 36 stimulus tokens. These were 6 vowels (/a/, /e/, /i/, /o/, /u/, and /y/), each presented with 6 different frequencies (100, 112, 123, 135, 149, and 166 Hz). Each token was equiprobably presented as a standard and as a deviant stimulus across the conditions. The experiment consisted of four separate conditions (Fig 1.). There were two oddball conditions (in here called *constant-feature conditions*), one with pitch, the other one with phoneme deviants, and two *varying-feature conditions*, one with pitch, and the other one with phoneme deviants. The *constant-feature* conditions had one repeatedly presented standard stimulus that was occasionally replaced by one of the 5 infrequent deviant stimuli (total p = .15). In the *varying-feature* conditions, both standard and deviant stimuli were constantly varying in pitch in the sequences with phoneme-category deviants or in phoneme identity in the sequences with pitch deviants. That is, in the varying-feature condition, there were 6 different stimulus tokens that together served as a standard (total p = .85) and 30 different deviant stimulus tokens (total p = .15). The duration of the stimuli was 190 ms and the SOA was 702 ms.

During all the experiments, subjects watched self-chosen silent videos and were instructed to ignore the sound stimuli. Breaks were given when needed, and children were accompanied by a parent if necessary. The stimuli were presented through loudspeakers located in front of the subject at 55 dB SPL (**Study I**), at 56 dB SPL (**Studies II-IV**), or at 45 dB SPL (**Study V**).

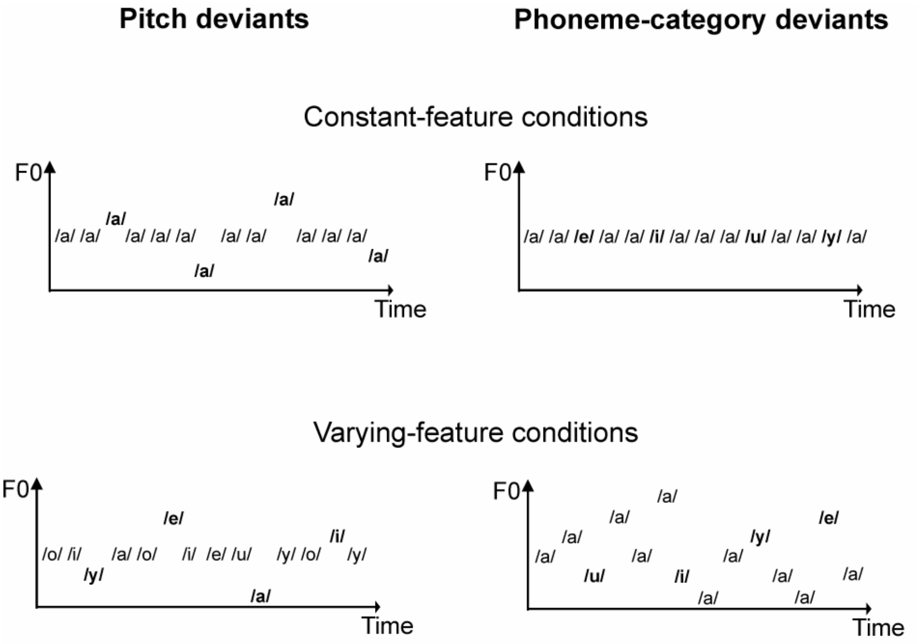

Figure 1. A schematic illustration showing examples of the experimental conditions used in Study V. Note that 5 different stimulus blocks were created for each condition, and that every pitch and vowel token was presented equiprobably as a standard and as a deviant stimulus across the conditions (Reprinted from Lepistö et al., 2008, with the permission of Elsevier).

3.2.2. Data acquisition and analysis

The electroencephalogram (EEG) was recorded with NeuroScan system and SynAmps amplifier using Ag/AgCl electrodes placed according to the International 10-20 system (Jasper, 1958). In **Study I**, electrodes were placed at F3, F4, C3, and C4, and in **Studies II-IV**, at F3, Fz, F4, C3, Cz, C4, T3, T4, TP3, TP4, and Pz scalp sites. In **Study V**, recording sites F3, Fz, F4, C3, Cz, C4, TP3, TP4, and Pz were used. In all the studies, electrodes were also placed at the mastoids, and eye movements were monitored with electrodes placed below and at the outer corner of the right eye.

ERPs were separately averaged for each standard and deviant type, filtered, and baseline-corrected with respect to a 100 ms pre-stimulus period. Right mastoid served as a reference during the experiment; the data were off-line re-referenced to the average of the mastoid recordings. For further details of the data acquisition and analysis, see Table 3.

Table 3. The details of the data acquisition and analysis.

	Study I	**Studies II-V**
Sampling rate	250 Hz	500 Hz
EEG recording bandpass	DC–30 Hz	0.1–100 Hz
Artefact rejection	± 150 µV	± 100 µV
Epoch duration	-100–600 ms	-100–700 ms
Filtering bandpass	1–15 Hz	1–20 Hz

The standard sounds elicited a P1-N2-N4 –complex in children (**Studies I-III**), and a P1-N1-N2 –complex in adults (**Study IV**). In **Study I**, the P1 peak latency was identified at 50–150 ms and the N2 peak latency at 150–300 ms from stimulus onset. The peak amplitudes were measured at the latencies of the maximal amplitudes, which were identified from the grand-average waveforms separately for each group, each stimulus type, and each electrode (the P1 range 120–128 ms; the N2 range 260–272 ms). In **Studies II-IV**, the individual peak latencies of the standard responses were identified from latency windows as follows: Children: P1 50–150 ms; N2 150–300 ms; N4 300–500 ms; Adults: P1 50–120 ms; N1 70–170 ms; N2 220–500 ms. The peak amplitudes were measured at the individual peak latencies (integrated over 10 ms).

The MMN and P3a responses were quantified from difference waveforms obtained by subtracting the ERPs elicited by standard stimuli from those elicited by deviants. These difference waveforms were separately created for each stimulus class and deviant type combination. In **Study I**, the MMN peak latency was identified at 100–350 ms and that of the P3a at 250–450 ms from stimulus onset. The MMN and P3a peak amplitudes (integrated over 50 ms) were measured at the latencies of their maximal amplitudes, which were identified from the grand-average waveforms separately for both groups, each stimulus type and each electrode (the MMN range 176–268 ms; the P3a range 304–368 ms). In **Studies II-IV**, the individual peak latencies of the MMN were measured from latency windows as follows: 100–300 ms for pitch, phoneme, and non-speech phoneme-counterpart deviants, and 200–400 ms for duration deviants. For the P3a, the corresponding windows were 200–500 ms and 300–600 ms. In **Study V**, the individual peak latencies of the MMN were measured from the 100–

300 ms latency window. In **Studies II-V**, the peak amplitudes were measured at the individual peak latencies (integrated over 50 ms).

The significance of each component was assessed with *t*-tests against zero. Differences in the ERP amplitudes and latencies between the groups were analysed with the analysis of variance (ANOVA) for repeated measures. The Greenhouse-Geisser correction was applied when appropriate. Post-hoc tests were applied to determine the sources of the significant main effects and interactions. In the Results section, all results are significant with *p*-values less than .05, unless otherwise mentioned.

3.3. Sound-identification task

Behavioural sound-discrimination task was carried out after the ERP session in studies including participants with AS (**Studies III & IV**). Subjects were presented with sound pairs of which 50% were the same and 50% different to each other and were instructed to press one button if the sounds were the same and another button if they were different. The stimuli and sound contrasts were the same as in the corresponding ERP studies. The within-pair SOA was 700 ms, and the between-pair SOA was 2800 ms. Stimuli were presented via headphones at 63 dB SPL. Button presses occurring within 150–2200 ms after the onset of the second sound of a pair were analysed and the between-group differences in hit rates and reaction times were tested with ANOVAs.

4 RESULTS AND DISCUSSION

4.1. Auditory sensory processing in autism and Asperger syndrome

In **Study I**, the children with autism did not differ significantly from their controls in responses to standard sounds, although their P1 amplitude tended to be diminished (Fig 2). However, in **Study II** the children with autism had smaller obligatory ERPs than their controls particularly frontocentrally for both speech and non-speech standard sounds (Fig 2). Significant group differences were found for the P1 to speech and non-speech stimuli, for the N2 to non-speech stimuli, and for the N4 to speech stimuli. These results suggest that the encoding of physical features of both speech and non-speech sounds is impaired in children with autism, and conform to earlier studies showing altered obligatory brain responses to sounds in individuals with autism (for a review, see Bomba & Pang, 2004).

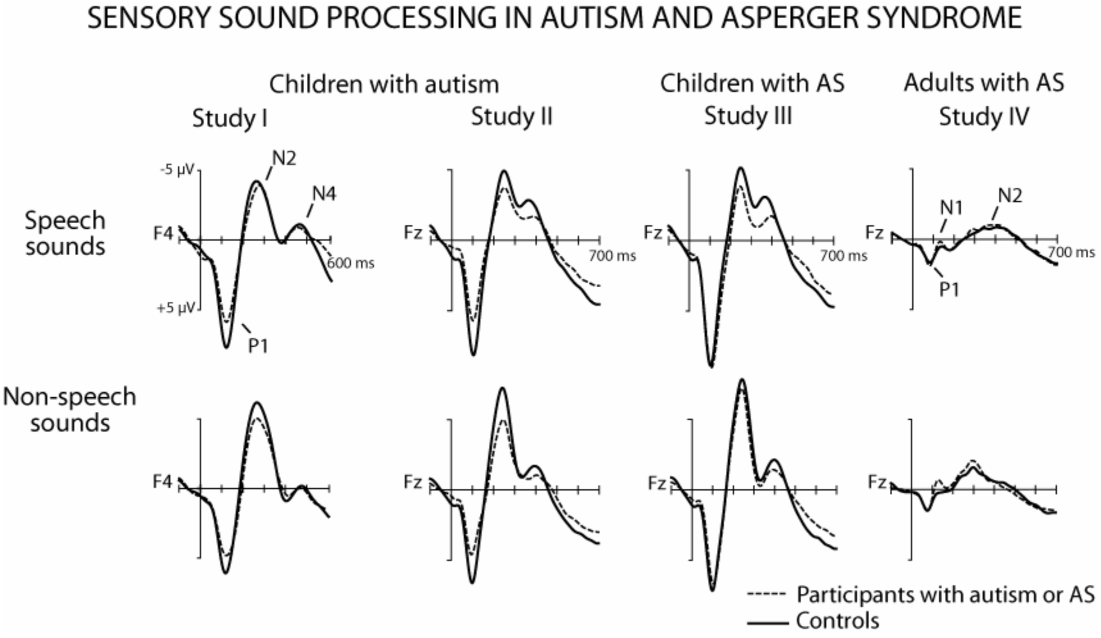

Figure 2. ERPs elicited by phoneme (top row) and complex non-speech (bottom row) standard sounds in children with autism (Studies I & II), children with AS (Study III), and adults with AS (Study IV).

The pattern of the results in individuals with AS differed from that in children with autism. Both the children (**Study III**) and the adults with AS (**Study IV**) had rather similar standard-sound ERPs as their controls, except for the frontocentrally diminished N4 amplitude for speech stimuli in children with AS (Fig 2). These results suggest that early sensory sound processing is considerably less affected in individuals with AS than in those with autism.

4.2. Cortical sound discrimination and identification in autism and Asperger syndrome

Auditory cortical discrimination in individuals with ASD was more affected by the physical sound feature to be discriminated than by whether the stimulus was a speech or a non-speech sound. The children with autism had either typical (**Study I**) or enhanced (**Studies II & V**) MMN responses to pitch changes (Figs 3, 4, & 7). Also changes in phonemes elicited typical (**Study II**) or enhanced (**Study V**) MMN responses in oddball conditions in the children with autism (Figs 5 & 7). Furthermore, these children had shorter MMN latencies for non-speech phoneme counterpart changes than their controls (**Study II**). In contrast, the MMN for duration changes was diminished in amplitude in the children with autism, although significantly only for the non-speech stimuli (**Study II**; Fig 6).

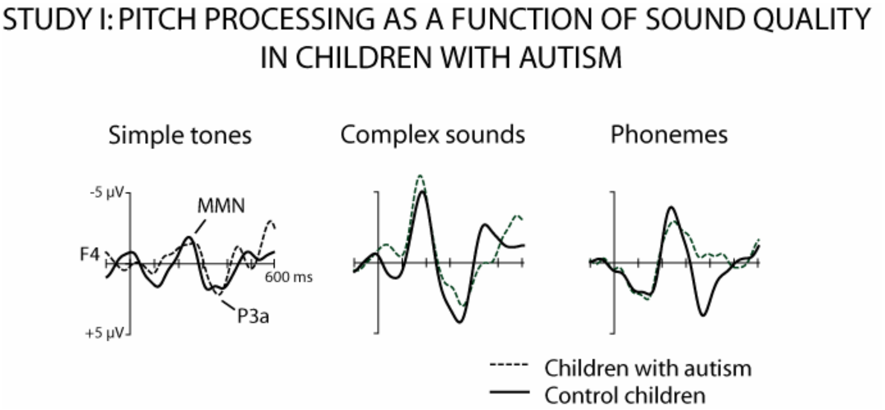

Figure 3. Deviant-minus-standard difference waveforms showing the MMN and P3a responses elicited by pitch changes in simple tones, complex sounds, and phonemes in children with autism and their controls (Study I).

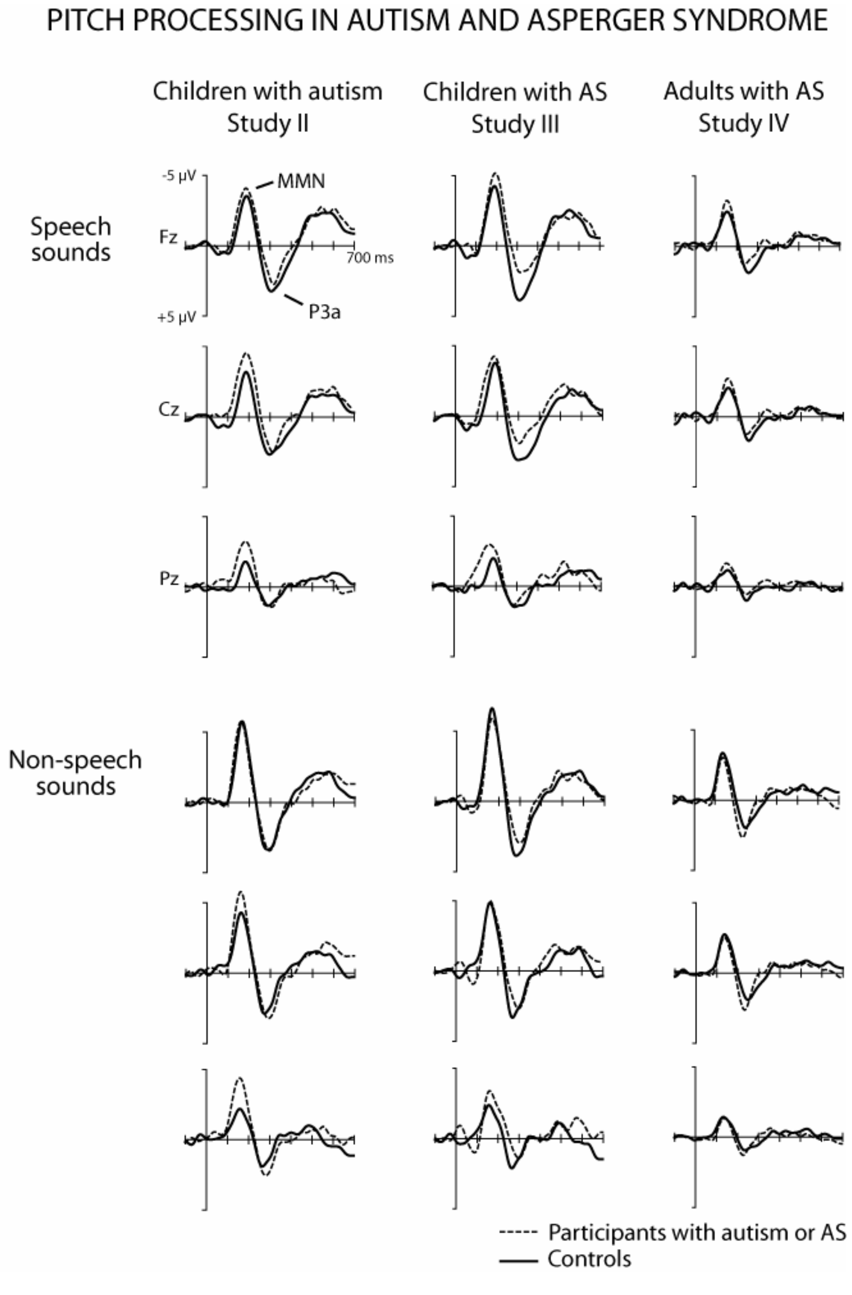

Figure 4. Deviant-minus-standard difference waveforms showing the MMN and P3a responses elicited by pitch changes in phonemes (top) and in complex non-speech sounds (bottom) in children with autism (Study II), children with AS (Study III), and adults with AS (Study IV).

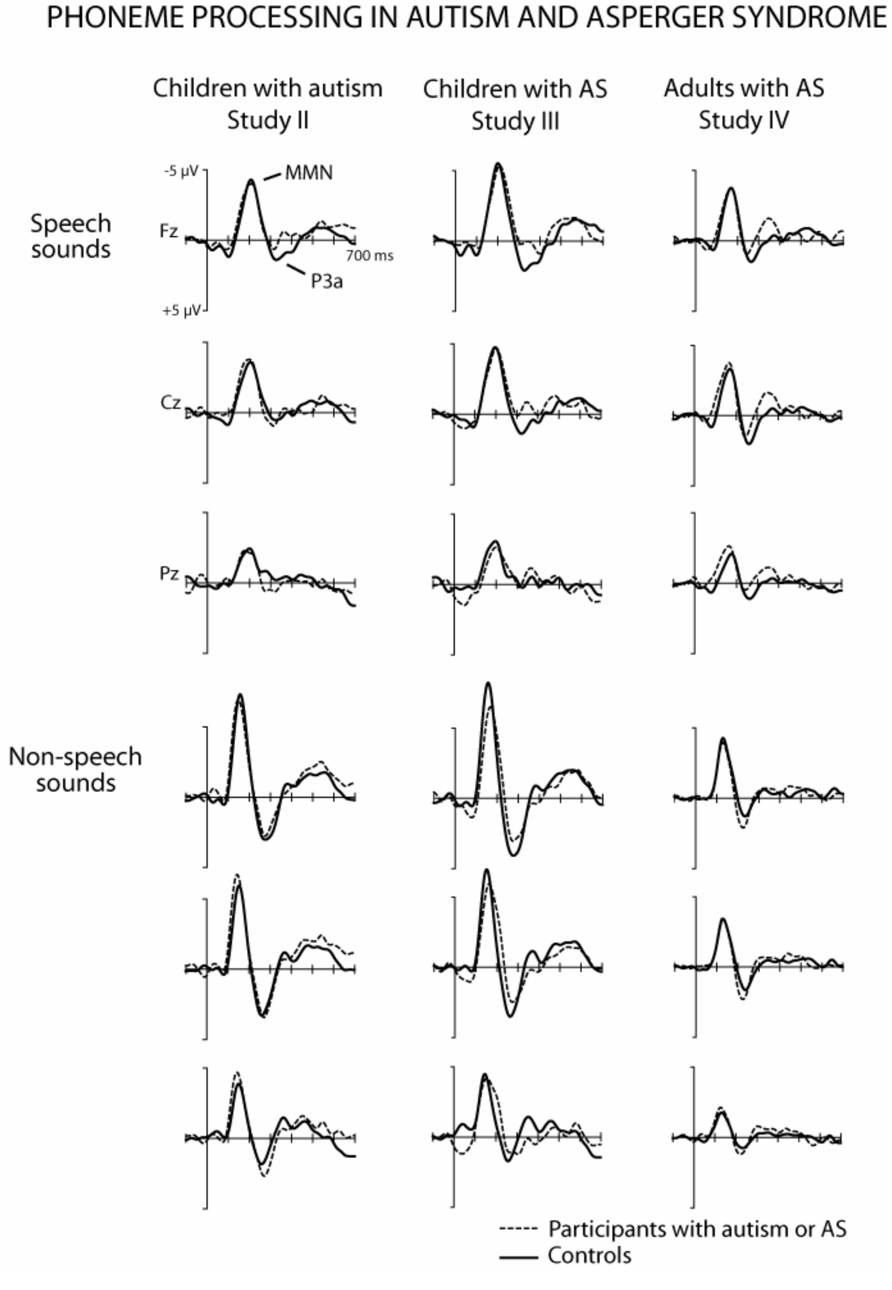

Figure 5. Deviant-minus-standard difference waveforms showing the MMN and P3a responses elicited by phoneme-category changes (top) and their non-speech counterpart changes (bottom) in children with autism (Study II), children with AS (Study III), and adults with AS (Study IV).

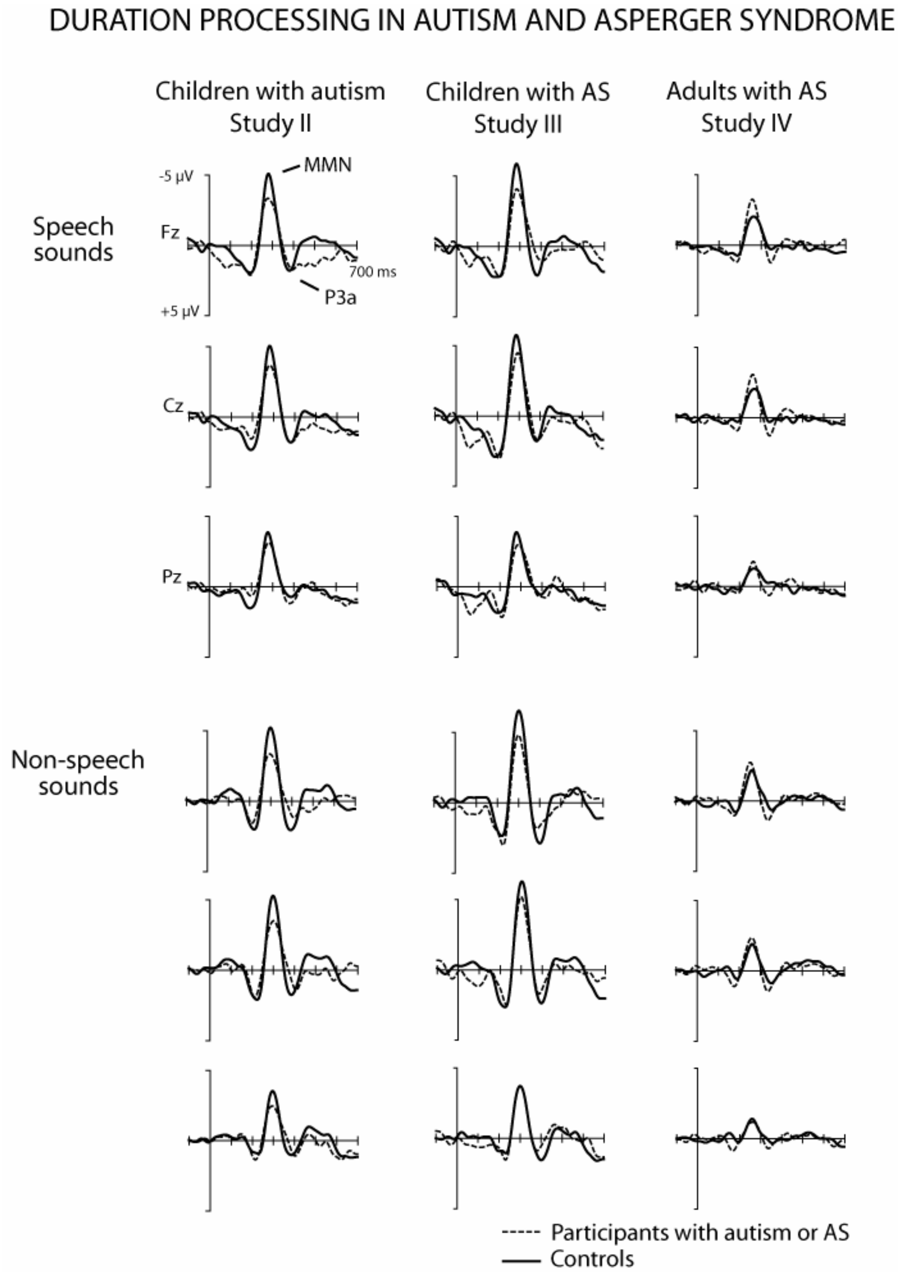

Figure 6. Deviant-minus-standard difference waveforms showing the MMN and P3a responses elicited by duration changes in phonemes (top) and in complex non-speech sounds (bottom) in children with autism (Study II), children with AS (Study III), and adults with AS (Study IV).

Both in the children and adults with AS (**Studies III & IV**), the MMN was in general larger in amplitude over the right hemisphere and at the midline than over the left hemisphere, whereas no hemispheric differences were found in controls, or in children with autism (**Studies I, II, & V**). These findings suggest an altered balance in interhemispheric information processing in individuals with AS.

Similarly to the children with autism, the children with AS (**Study III**) also had enhanced MMN amplitudes for pitch changes (significant only for speech stimuli parietally), but diminished MMN amplitudes for duration changes particularly over the left hemisphere. They also had a lower hit rate in the sound-identification task for both speech and non-speech duration changes as compared with the controls, and tended to have prolonged reaction times for speech-duration changes. Furthermore, the MMN latency for phoneme changes was prolonged in children with AS as compared with controls. In contrast with these results, the adults with AS had enhanced MMN amplitudes for all the stimulus contrasts, including duration changes (**Study IV**). However, in the sound-identification task the adults with AS had longer reaction times than their controls. As their MMN latencies were similar, the longer reaction times probably resulted from a different response strategy of the adults with AS.

In summary, children with autism and AS show enhanced processing of pitch changes, whereas they are impaired in discriminating changes in sound durations. Furthermore, the children with autism have enhanced MMN amplitudes for phonemes, too, which could result from the fact that the discrimination of both pitch and vowel sounds is based on spectral differences.

4.3. The extraction of invariant sound features in autism

In **Study V**, the MMN was recorded for pitch and phoneme-category changes in constant-feature and varying-feature conditions. Consistent with **Studies I & II**, the MMN was enhanced in amplitude in the children with autism for both pitch and phoneme-category changes in the constant-feature conditions (Fig 7). In the varying-feature conditions, which required abstracting invariant sound features, the children with autism still had enhanced MMN responses for pitch changes, whereas no significant differences were found for MMNs to phoneme changes (Fig 7). Furthermore, whereas in the varying-feature conditions the children with autism had frontocentrally larger MMN amplitudes for pitch than phoneme changes, the control children had frontally larger MMN amplitudes for phoneme than pitch changes. In conclusion, when the context of the stimuli is speech-like and requires abstracting invariant features from varying input, children with autism maintain their superiority in pitch processing but lose their advantage in phoneme processing.

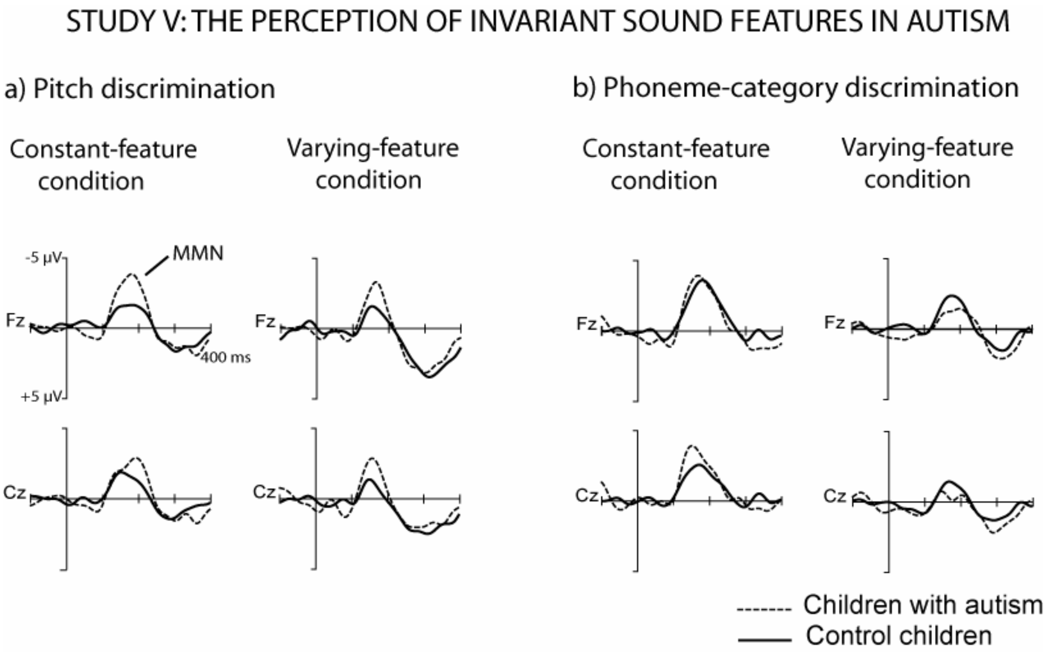

Figure 7. Deviant-minus-standard difference waveforms in children with autism and controls for a) pitch changes in the constant-feature and varying-feature conditions, and for b) phoneme-category changes in the constant-feature and varying-feature conditions (Study V).

4.4. Involuntary orienting to speech and non-speech sounds in autism and Asperger syndrome

In **Study I**, children with autism had significantly diminished P3a amplitudes for pitch changes in phonemes, but not for the corresponding changes in simple or complex non-speech sounds (Fig 3). Consistent with this, in **Study II**, children with autism had diminished P3a amplitudes for speech-pitch and phoneme changes, but not for either speech or non-speech duration changes, or for non-speech pitch changes (Figs 4–6). However, they also had diminished P3a amplitudes for the non-speech phoneme counterpart changes. These results suggest that although children with autism are impaired in their involuntary orienting for both speech and non-speech changes, their impairment is more severe in orienting to speech than non-speech sounds.

Similarly as children with autism, children with AS (**Study III**; Figs 4–6) had diminished P3a amplitudes for phoneme changes and tended to have diminished P3a amplitudes for speech-pitch changes (p = .073). They also had prolonged P3a latencies for speech-duration changes. The P3a responses for non-speech changes were similar in children with AS and controls. Further, the adults with AS (**Study IV**; Figs 4–6) had diminished P3a amplitudes for speech changes, but had enhanced amplitudes for non-speech changes. In sum, individuals with AS have similar deficits in orienting to speech sounds as children with autism. In the course of development, this deficit seems to become associated with an atypically enhanced orienting for non-speech sounds.

5. GENERAL DISCUSSION

5.1. Auditory cortical processing of speech and non-speech in autism and Asperger syndrome

5.1.1. Early sensory sound processing is deficient in autism, but fairly unimpaired in Asperger syndrome

As indicated by diminished obligatory ERPs, the processing of auditory information in children with autism diverged from the typical path already at the early stages of sound feature extraction and encoding. However, in the individuals with AS, in turn, the obligatory ERPs were fairly unimpaired. As autism and AS differ from each other primarily with respect to the language development, it could be assumed that the deficient sensory sound processing contributes to the language impairment in children with autism. However, the precise nature and consequences of deficient sensory sound processing in autism are difficult to define as the functional significance of the obligatory ERPs in childhood is not yet well understood (Čeponienė et al., 2001; Cunningham et al., 2000; Wunderlich & Cone-Wesson, 2006). In any case, children with autism appear to encode the sound features well enough to be able to discriminate sounds accurately (see the next section).

5.1.2. Sound-discrimination processes are altered in autism and Asperger syndrome

As indicated by enhanced MMN amplitudes, the children with autism and AS were more sensitive to pitch differences than their controls. However, these children had deficits in discriminating sound durations, as reflected by diminished MMN amplitudes for duration changes. Furthermore, the children with AS had lower hit rates and tended to have prolonged reaction times for duration changes in the behavioural sound-identification task. Converging evidence for deficient temporal processing in autism was reported by Kuhl et al. (2004). They found diminished MMN amplitudes in preschoolers with ASD for consonant changes in syllables (/wa/ vs. /ba/) that were acoustically identical except for the duration of the initial formant transitions. Furthermore, deficits in rapid temporal processing were identified in autistic children (Oram Cardy et al., 2005a). These results are of interest, because temporal processing is highly relevant for speech perception (Shannon et al., 1995). However, in contrast with children, the adults with AS showed enhanced processing even with respect to duration changes. This result was recently replicated in the same group of adults with a different paradigm (Kujala et al., 2007a).

The dissociation between pitch and duration discrimination in children with ASD may derive from differences in the cortical processing of these sound features. Studies in patients with brain damage (Harrington et al., 1998; Ilvonen et al., 2003), in individuals with amusia (Peretz & Hyde, 2003), and in normal subjects (Schön & Besson, 2002) suggest that pitch- and duration-related information are processed at least partly independently of each other. Whereas pitch discrimination takes place quite locally because of the tonotopic cortical organization, duration discrimination is based on a complex neural network (Belin et al., 2002; Ivry & Spencer, 2004). This network also involves the cerebellum, which is abnormal in individuals with autism (Courchesne, 1997). It might be this complexity of cortical temporal processing (c.f., Samson et al., 2006) that causes the initial delay in the development of duration-discrimination abilities in AS. As a result of brain maturation, however, duration-processing skills improve, so that in adulthood these individuals are processing duration in an enhanced manner similarly to other sound features.

The present results showing enhanced pitch processing in individuals with ASD are in agreement with other behavioural (Bonnel et al., 2003; Heaton, 2003, 2005; Heaton et al., 2001; Mottron et al., 2000; O'Riordan & Passetti, 2006) and MMN studies (Ferri et al., 2003; Gomot et al., 2002; Kujala et al., 2007a). Together with those on visual modality (Dakin & Frith, 2005; Happé & Frith, 2006), these studies confirm that the low-level perceptual functions are enhanced in ASD (Happé & Frith, 2006; Mottron et al., 2006). The enhanced low-level processing might be partly explained by altered minicolumnar organization recently reported in ASD. Minicolums, narrow chains of about 80-100 neurons that extend vertically across the cellular layers II-VI, are considered to be the fundamental units of cortical information processing (Buxhoeveden & Casanova, 2002; Mountcastle, 1997). In autism and AS, the minicolumns were reduced in width, but increased in numbers (Casanova et al., 2002a, 2002b; 2006). This was suggested to bias the cortical connectivity in ASD in favour of local rather than global information processing, which facilitates stimulus discrimination (Casanova et al., 2002c, 2006; see also Gustafsson, 1997).

Although enhanced pitch-discrimination skill at least partly explains the musical abilities often observed in individuals with autism (Rimland & Fein, 1988), it may also have adverse effects. It is likely to contribute to the auditory hypersensitivity (Dahlgren & Gillberg, 1989; Dunn et al., 2002; Gillberg & Coleman, 2000), as well as to the deficient speech perception in noisy environments (Alcantara et al, 2004), reported in ASD. Furthermore, it may compromise the filtering of relevant auditory information from irrelevant information, and fundamentally alter the quality and nature of the information the individual receives from the environment (O'Riordan & Passetti, 2006). As the consequence of aberrant low-level sensory information, higher-level integrative cognitive functions guided by this information may become abnormal (Baron-Cohen & Belmonte, 2005; Bertone et al., 2005; Just et al., 2004). With respect to speech perception, enhanced discrimination skills might result in the development of an auditory processing style that is biased towards perceptual, low-level information at the cost of higher-level speech and language processing.

5.1.3. The perception of invariant sound features is challenging for children with autism

Study V wished to determine whether the enhanced low-level processing of spectral sound features evident in autism has negative consequences for speech perception. Specifically, it was hypothesised that enhanced discrimination abilities might make auditory processing in autism too centred on the acoustical differences between the stimuli belonging to the same phoneme category, and therefore disrupt the extraction of the common, invariant features characterising all exemplars of a given phoneme (Gustafsson, 1997; O'Riordan & Passetti, 2006).

As expected, when sound discrimination did not require the extraction of invariant features, then the children with autism had enhanced MMN responses for both pitch and phoneme-category changes. However, when the stimuli constantly varied with respect to either pitch in the phoneme-discrimination sequences, or phoneme in the pitch-discrimination sequences, then the children with autism continued to have enhanced MMN responses for pitch changes, but not for phoneme-category changes. That is, children with autism lost their advantage in the phoneme discrimination when the context of the stimuli required abstracting invariant speech features from varying input. These results suggest that it was challenging for the central auditory system of the children with autism to ignore the irrelevant pitch changes. Furthermore, in the varying-feature conditions, the control children had larger-amplitude MMN responses for phoneme-category than pitch changes, whereas the children with autism showed the opposite pattern. These results suggest that as a consequence of learning, typically developing children may be more adept in abstracting invariant, linguistically relevant features (such as phoneme category) than linguistically irrelevant features (such as pitch). In contrast, as children with autism have enhanced low-level perceptual skills, their ability to abstract invariance from varying auditory input might be more governed by the saliency of the acoustical characteristics rather than by the linguistic relevance of these features.

It would be worth studying, whether the ability to abstract invariant speech features is more compromised earlier in the development in children with autism, and, furthermore, whether it is related to a child's speech perception and language abilities. It is likely that the abstraction of invariant speech features would be the most compromised in non-verbal children with autism. Consistent with this, Bishop et al. (2004) found that the impairment in phonological processing in children with ASD was substantially correlated with the VIQ, so that children with an average-VIQ had no deficits, whereas those with a lower-than-normal VIQ did. Furthermore, Constantino et al. (2007) reported that children with high-functioning ASD (mean FIQ 110) performed similarly to control children in tasks requiring the subjects to determine whether the phonemes spoken by different speakers were the same or different. However, verbal children with autism, too, may have difficulties in extracting invariant sound features in real-life listening conditions, which include considerably more acoustic variation than the present experimental paradigm.

5.1.4. Orienting to speech sounds is deficient in autism and Asperger syndrome

Based on the present studies, the first stage where the processing of speech and non-speech appears to differ from each other in ASD is the involuntary orienting of attention. Although the children with autism showed deficient involuntary orienting to both speech and non-speech sound changes, their impairment was more severe with respect to speech sounds. Furthermore, both the children and adults with AS had a diminished P3a to speech deviants only, suggesting specific deficits in orienting to speech. The adults with AS in fact additionally had enhanced P3a responses to non-speech changes. These results are in agreement with behavioural studies, which have also indicated impaired orienting to speech sounds in individuals with ASD (Blackstock, 1978; Dawson et al. 1998, 2004; Klin, 1991; Kuhl et al., 2005). As also the visual orienting and attention in ASD is more impaired for social (such as faces and people) than non-social stimuli (Klin et al., 2003; Maestro et al., 2002; Swettenham et al., 1998), it can be concluded that ASD are characterized by a general impairment in social orienting.

Impaired social orienting has been proposed to be one of the first symptoms of autism to emerge (Dawson et al., 2004; Maestro et al., 2002; Mundy & Neal, 2001). It is considered to reflect a difficulty in forming representations of the significance and reward value of social stimuli, perhaps because of their complex and rapidly changing nature (Dawson & Levy, 1989; Dawson et al., 2005). As a consequence, attention of children with autism is less drawn towards social than other stimuli, which is likely to have adverse consequences on their social and communication development by reducing social input and limiting their opportunities for social interaction and learning (Dawson et al., 2004, 2005; Mundy & Neal, 2001). For instance, in typically developing infants, early preference for speech guides attention and perception by granting speech a special status in relation to other sounds, and facilitates language learning by aiding in separating and selecting acoustic signals relevant for communication (Jusczyk & Bertoncini, 1988; Vouloumanos & Werker, 2004, 2007). If such a bias is absent or weakened in ASD, then the language development is rather likely to be affected. Supporting this, recent studies (Kuhl et al., 2005; Roberts et al. 2007) have shown that attention to social stimuli and the severity of the social-communication symptoms in young children with autism are related to each other. However, whereas social stimuli are easily ignored by individuals with ASD, other types of information may be attended to and processed more intensively (Heaton, 2003; Mundy & Neal, 2001) – this processing bias may be reflected in the enhanced orienting to non-speech sounds that was evident in adults with AS.

5.2. Comparison of auditory processing in individuals with autism and in those with Asperger syndrome

Because children with autism differ significantly from those with AS with respect to their language skills, auditory cortical processing was expected to be more affected in children with autism than in those with AS. However, although the early stages of sound encoding and feature extraction were more affected in autism than in AS, the groups otherwise had rather similar auditory discrimination and orienting profiles. In both groups, the cortical processing of pitch changes was enhanced, and that of duration changes deficient. However, in children and adults with AS, the MMN showed a right-hemisphere dominant distribution pattern, whereas in children with autism and in control children, no hemispheric differences were observed. Jansson-Verkasalo et al. (2003), too, reported a tendency toward a right-hemisphere dominant MMN in children with AS. Although preliminary, these results suggest an altered balance in interhemispheric information processing in individuals with AS. Furthermore, both groups had similar deficits in involuntary orienting to speech sounds. However, the children with autism also had deficits in orienting to non-speech changes, suggesting that their deficits in auditory orienting are more widespread than those of children with AS.

Generally speaking, these results support the notion (Wing, 1981, 1997) that autism and AS belong to the same continuum. Both of these ASD groups, irrespective of whether they had language impairment or not, showed enhanced pitch discrimination abilities and deficient orienting to speech sounds. Therefore, these characteristics may constitute a part of the broader phenotype of ASD, and thus be evident in the parents and siblings of the affected individuals, also. Supporting this, recent studies have shown partly similar detail-focused processing (Bölte & Poustka, 2006) and ERP-findings (Jansson-Verkasalo et al., 2005) in first-degree relatives of children with ASD as in these children. Alternatively, it is possible that the ERP paradigm employed in the studies of this thesis was not sensitive enough to separate groups in terms of auditory processing from each other. The possible differences in auditory processing between individuals with autism and AS might be better uncovered with paradigms tapping more complex auditory functions. Future studies should aim at exploring links between the ERP findings and the severity of symptoms, the level of cognitive development and other clinically relevant characteristics of ASD.

As the present studies indicated only mild ERP differences between children with autism and AS, it appears that their distinct language development cannot be sufficiently explained by differences in their cortical auditory processing. Rather, the language development in ASD is likely to be also influenced by the degree of the primary socio-cognitive impairment – After all, language evolved to address a need for social communication (Kuhl, 2004, 2007). Consistent with this, deficits in several socio-cognitive skills (such as imitation, symbolic play, and joint attention), closely linked with speech and language development, are characteristic for children with autism (Bruinsma et al., 2004; Landa 2007). Furthermore, interventions focusing on these socio-cognitive precursors of language have a positive effect on the language development in children with autism (Bono et al., 2004; Ingersoll & Schreibman, 2006; Landa 2007).

5.3. Clinical implications

As a consequence of enhanced auditory low-level perceptual processing and deficient orienting to speech sounds, as well as corresponding deficits in the visual domain (Dakin & Frith, 2006; Klin et al., 2003), the quality and nature of the information that a child with ASD receives from the environment is considerably atypical. Importantly, this is likely to affect the experience-dependent neural specialisation of the brain areas processing social stimuli. Therefore, the altered perceptual and attentional processes are continuously reinforcing themselves and, depending on the severity of the underlying primary socio-cognitive impairment, may even reinforce autistic behaviour. These concerns highlight the importance of early intensive intervention, as well as an active role of the parents and professionals carrying out the intervention. As a part of the intervention, these children have to be motivated to orient and attend to other people and their actions by specifically teaching them that these stimuli are rewarding and significant. As the language impairment in ASD appears to derive from a socio-cognitive impairment in addition to a “pure” language impairment, these children have to be taught basic social skills such as imitation and joint attention alongside traditional language training in order to increase their communication abilities. Finally, because of auditory hypersensitivity, these children benefit from a quiet environment that helps them to extract the relevant auditory information from irrelevant.

6 CONCLUSIONS

The present thesis investigated cortical processing of speech and non-speech sounds in individuals with autism and AS. The results suggest that individuals with ASD perceive and attend to the auditory world in a markedly atypical manner. In children with autism, auditory processing diverges from the typical path as early as at the initial stages of sound feature extraction and encoding. In addition, these children have altered sound-discrimination processes characterised by enhanced spectral but deficient temporal sound discrimination. However, the children with autism lose their advantage in vowel processing when the context of the stimuli is speech-like and requires abstracting invariant features from varying input. Finally, their involuntary orienting to sound changes is deficient in particular with respect to speech sounds.

Sound discrimination and orienting are rather similarly altered in children with AS and autism, suggesting correspondences in the auditory phenotype in these two disorders which belong to the same continuum. In contrast to children, however, adults with AS show enhanced processing of both spectral and duration changes, suggesting developmental changes in auditory processing in these individuals.

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