Cortical auditory system maturational abnormalities in children with autism disorder: an MEG investigation

Nicole M. Gage\textsuperscript{a,}\textsuperscript{*}, Bryna Siegel\textsuperscript{b}, Timothy P.L. Roberts\textsuperscript{a}

\textsuperscript{a}Biomagnetic Imaging Laboratory, San Francisco, CA, USA
\textsuperscript{b}Pervasive Developmental Disorders Clinic, University of California, San Francisco, CA, USA

Abstract

Latency of electric (e.g., P1 and N1) and magnetic (e.g., M100) auditory evoked components depends on age in typically developing children, with longer latencies for younger (4–6 years) and shorter, adult-like latencies for older (14–16 years) children. Age-related changes in evoked components provide indirect measures of auditory system maturation and reflect changes that occur during development. We use magnetoencephalography (MEG) to investigate maturational changes in cortical auditory systems in left (LH) and right (RH) hemispheres in children with autism disorder (AD) and Controls. We recorded auditory evoked responses over left and right temporal lobes in 17 Control and 15 AD children in the age range 8–16 years and measured M100 latency as a function of age, subject group and hemisphere. Linear regression analyses of age and M100 latency provided an estimate of the rate of latency change (ms/year) by hemisphere and subject group. Controls: M100 latency for the group ranged from 100.8 to 166.1 ms and varied linearly in both hemispheres, decreasing at a rate of \(-2.4\) ms/year (LH) and \(-2.4.5\) ms/year (RH). AD: M100 latency ranged from 116.2 to 186.2 ms. Slopes of regression lines did not differ from zero in either LH or RH. M100 latency showed a tendency to vary with age in LH, decreasing at a rate of \(-4.6\) ms/year. M100 latency in RH increased slightly (at a rate of 0.8 ms/year) with age. Results provide evidence for a differential auditory system development in AD children which may reflect abnormalities in cortical maturational processes in AD.

\textsuperscript{*}Corresponding author. Department of Cognitive Sciences, Mail Code 5100, 3151 Social Sciences Plaza A, University of California, Irvine, CA 92697-5100, USA. Tel.: +1-949-824-1297; fax: +1-949-824-2307.
E-mail address: ngage@uci.edu (N.M. Gage).

\textsuperscript{©} 2003 Elsevier B.V. All rights reserved.

1. Introduction

Language impairment is a defining feature of autism disorder (AD) [16]. Delay in the development of speech and language function in infants and young children is an early indicator of AD [20]. In addition to severe deficits in aural language, individuals with AD frequently exhibit hypo- and hyper-reactivity to sensory stimulation, particularly in the auditory modality [27]. While the presence of language impairment and atypical sound sensitivity are well documented in the literature through clinical observations, their behavioral description is incomplete and the underlying neural basis or bases of the disorders are largely unknown. An important question to be addressed in autism research is to what degree development delays in speech and language and atypical sound sensitivity stem from maturational abnormalities in the sensory auditory system.

Neuronal networks in the auditory system encode, transmit, and evaluate the temporal structure of stimuli with submillisecond precision. Maturational changes in these systems have been estimated using electroencephalography (EEG) to record auditory evoked potentials (AEPs) [1,7,11,29,31,32]. In particular, the latency of the P1 and N1 components in the AEP has been demonstrated to depend on age in typically developing children, with a general finding of longer latencies for younger (4–6 years)
children, progressing to shorter latencies in older children, with adult-like latencies found for adolescents in the age range of 14–16 years [1,5,13,37,46]. While it is not known at present what P1 and N1 latency prolongation in children may mean in terms of neural system development or behavior, it has been suggested that it may reflect maturational changes related to synaptogenesis, myelinogenesis, dendritic pruning [5,11,14] or to laminar maturation in superficial layers (II and upper III) of auditory cortex that occurs between the ages of 5–12 [31,32], with the general notion that as neural systems mature, conduction rates increase, thereby decreasing the time to peak latency in evoked components.

Evidence that the latency of components in the AEP (such as the P1 and N1) may reflect delays or abnormalities in the maturation of cortical auditory systems in special populations of children has been provided in studies with children with severe language impairment (LI), phonological dyslexia, and auditory processing and hearing disorders [12,15,22,45]. For example, Eggermont et al. [12] measured the latency of the P1 component in deaf children with cochlear implants who had undergone prolonged auditory deprivation prior to implant. They reported that time-to-maturation of the P1 in the children with implants was delayed for a duration that was roughly equal to the duration of their deafness [12]. Tomquist-Uhlen et al. [45] measured N1 latencies in a group of severely LI children and reported prolonged latencies in this group as compared to age-matched controls, and no age dependency. Thus, the latency of the P1 and N1 components may provide a non-invasive and objective measure of cortical auditory system maturation in both typically developing children and children with auditory and/or language processing deficits.

Several studies have investigated age related effects of N1 peak latency in children with AD as compared to age matched, typically developing controls. Findings to date have been mixed, however. One study reported shorter N1 latencies for AD children aged 6–18 years [26], while a second study reported longer N1 latencies in very young (infancy–4 years) AD children with tuberous sclerosis complex [37]. Two studies with slightly older children reported no difference in N1 between AD children aged 7–14 and controls [18,19]. A third study of non-mentally retarded AD children aged 7–10 and controls reported longer (43–70 ms) N1 latencies in the AD group in response to individually presented words in a target detection paradigm [10]. Interestingly, Dunn et al. reported longer reaction time responses in their AD group and suggested that, in combination with the N1 prolongation, these results may reflect slower processing of linguistic stimuli in AD children. The widely varying ranges of age in these studies in addition to the high level of heterogeneity found in general in samples of children with autism spectrum disorder may underlie the mixed results reported to date in the literature. However, the variability of findings for children with AD may also be due in part to the differing maturational rates and time-to-maturity of subcomponents (such as the N1, N1) of the AEP [31]. While key results in studies investigating N1 latency in AD children have not replicated to date, they combine to provide at least partial evidence that cortical auditory systems may follow a different maturational path in AD.

The magnetic analog of the electric N1, the M100 (or N1m) detected by MEG, is primarily sensitive to sulcal neural activity and is generated mainly in supratemporal cortical fields with a source that localizes to auditory cortex [25,36] (for a review, see Ref. [33]). Relevant to the present investigation, MEG provides a measure with which to evaluate neural responses that are limited primarily to auditory cortex. In addition, MEG provides the ability to distinguish the two cerebral hemispheres and thus neural responses may be evaluated separately for left and right auditory cortices.

There have been a few studies to date using MEG to evaluate the age dependence of the M100 in typically developing children. In the first MEG study with children, Paetau et al. [28] recorded auditory evoked responses to speech and non-speech stimulus that were presented at interstimulus intervals (ISIs) that ranged from 0.9 to 2.4 s. Paetau et al. reported that M100 latency decreased with subject age for children ranging from 3 to 15 years and hypothesized that the effect was due to longer refractory periods in auditory cortex in young children as compared to older children and adults. Rojas et al. [34] extended this work and compared M100 latency for tones presented at ISIs that ranged from 2 to 12 s in order to quantify the refractoriness of auditory cortex in groups of younger (6–8 years) and older (15–17 years) typically developing children. While the results of Rojas et al. were in general agreement with those of Paetau et al., a key difference is that Rojas et al. reported refractory changes in children of differing ages in the right hemisphere but not in the left, whereas Paetau et al. did not report any hemispheric difference in their sample. Rojas et al. [34] suggested that longer refractory periods in younger children may be due to maturational processes occurring during development, such as synaptogenesis, dendritic arborization and pruning, however they did not address why these processes might be limited to right hemisphere sites.

In a third study, Takeshita et al. [41] compared latency of several electric (e.g., N1, N250) and magnetic (e.g., M100, M250) components and provided further evidence for an age dependence of M100 latency in children who ranged in age from 6 to 14 years. Takeshita et al. only recorded neuromagnetic fields over the right hemisphere, leaving open the question of whether there are hemispheric asymmetries in the latency of the M100 that depend on age which, by extension, may reflect asymmetries in the maturational paths of left and right cortical auditory systems in typically developing children.

In the present investigation, we use MEG to record...
auditory evoked neuromagnetic fields over left and right hemispheres in a group of typically developing children and AD children in order to evaluate the age dependence of the M100 component. Based on previous EEG and MEG investigations with typically developing children, we hypothesize that M100 latency will depend on age in our group of control children. Of key interest in this study is whether we will find evidence for hemispheric asymmetries in age dependence, which may reflect differences in the developmental path of left and right auditory cortices in typically developing children. Next, we evaluate age dependence in AD children. Motivated by the pervasive nature of language deficits in autism, coupled with evidence for abnormal development of temporal lobe areas that subserve auditory and speech sound processing \cite{3,8,17,30}, we hypothesize that M100 latency will show a weaker or reduced age dependence for AD children. Due to the lack of previous investigations using MEG to evaluate auditory evoked responses in AD children, this investigation must be exploratory in nature. Our dependent measure is M100 latency. Our design includes Hemisphere and Tone Frequency as within-subject factors, Group (Control, AD) as a between-subject factor, and age as a covariate.

2. Materials and methods

2.1. Participants

Participants consisted of 15 males (age 8–14, Mean 11.4, S.D. 2.0) with AD recruited from the Pervasive Developmental Disorders Clinic at the University of California, San Francisco, and 17 controls (five female, age 10–16, Mean 13.5, S.D. 1.7). All AD participants had normal hearing as confirmed by earlier clinical audiological assessment. All participants were native speakers of English. All participants were studied without the use of sedation.

Children with AD were diagnosed according to procedures outlined in the California DDS Diagnostic Best Practice for Autism Guidelines (2002) \cite{2}, including direct observation using a standardized autism-specific behavioral rating, a clinical history designed to rule in autism and rule out related disorders, an age-appropriate cognitive test against which to rate possible autism symptoms versus mental retardation, and finally use of the DSM-IV \cite{9} criteria based on an overall evaluation of these data. The children with AD were selected according to the following inclusion criteria: normal non-verbal or Performance IQ (IQ\textlesssim70 as assessed by a version of the Weschler Intelligence Scale for Children (WISC-R or WISC-III) and Verbal IQ at least 1 S.D. (15 points) below Performance IQ.

MEG scanning required that participants remain motionless for several minutes at a time. In order to increase the likelihood of successful MEG recording, AD children who met the above-mentioned inclusion criteria were pre-screened in an effort to select individuals who would be cooperative during the MEG scanning procedures. Stimulus presentation and MEG recording were performed with the approval of the institutional committee on human research. Informed written consent was obtained from each participant and parent or legally authorized representative.

2.2. Stimulus presentation and MEG recordings

Sinusoidal tones of frequency 200 and 1000 Hz (250 ms duration) were presented monaurally using Etymotic™ ER-3A earphones and air tubes designed for use with the MEG system (Etymotic, Oak Brook, IL). Stimuli were presented at 40 dB SL (sensation level, i.e., 40 dB above the perceptual detection threshold, which was individually determined for each stimulus and each participant). Neuromagnetic fields were recorded for each participant using a 37-channel biomagnetometer (MAGNES™, Bti, San Diego, CA.) in a magnetically shielded room. The sensor-array was placed over the temporal lobe contralateral to the ear of stimulus presentation. Evoked response to a reference 1000 Hz sinusoidal tone (400 ms duration) was evaluated to determine if the sensor array was positioned to effectively record the auditory evoked M100 field. Epochs of 600 ms duration (100 ms pre-stimulus onset and 500 ms post-stimulus onset) were acquired around each stimulus at a sampling rate of 1041.7 Hz with a bandwidth of 400 Hz and a 1.0-Hz high-pass filter. This procedure was repeated for each hemisphere. Presentation was blocked by stimulus condition. Each stimulus was presented 120 times per block in a passive listening paradigm. Block duration was 2–3 min. Blocks were presented in a pseudorandom order for each of the two stimulus conditions, for each hemisphere. MEG recording continued until each stimulus condition was presented in each hemisphere (for a total of four scanning blocks) or until the participant was no longer able to tolerate the procedure.

2.3. Data analysis

The data were inspected and individual epochs that contained motion-related artifacts (>2.5 pT, pT=10^{-12} T) were removed. Data were then selectively averaged by stimulus condition and hemisphere for each participant. Averaged waveforms were band-pass filtered using a high cut-off frequency of 40 Hz. The root mean square (RMS) of the field strength across all 37 channels was calculated for each sample point. The M100 peak was determined as the peak in RMS value across 37 channels in the interval 80–200 ms, subject to a single equivalent current dipole.
13 children with AD and all 17 Controls. See Fig. 1 for a characteristic waveform recorded from an AD participant.

3.1. General findings: M100 latency results

Age was a statistically significant covariate \( F(1,15)=7.96, P=0.037 \). Further analyses of M100 latency were evaluated at covariate age = 12.77. A main effect of Group was statistically significant \( F(1,15)=5.22, P=0.037 \). M100 latency differed by Group, with longer M100 latencies for the AD group (\( M=139.06 \), S.E.M. = 3.02) as compared to the Control group (\( M=129.15 \), S.E.M. = 2.65) (see Fig. 2). The effect of Hemisphere was not statistically significant \( F(1,15)=1.66, P=0.217 \); however, there was a trend for latencies in the left hemisphere to be somewhat longer than in the right. The effect of Tone frequency failed to reach statistical significance \( F(1,15)=2.77, P=0.117 \); however, M100 latency was longer for the low (200 Hz) frequency tone as compared to the high (1000 Hz) frequency tone for both groups and in each hemisphere (see Fig. 2). No interactions reached statistical significance.

3.2. Linear regression analyses

3.2.1. Control

Results of linear regression analyses indicated a significant relationship between M100 latency and age. M100 latency varied in a linear manner for the 200-Hz tone in LH \((-4.4 \text{ ms/year})\) and RH \((-5.4 \text{ ms/year})\), and for the 1000 Hz tone in LH \((-3.5 \text{ ms/year})\) and RH \((-3.7 \text{ ms/year})\) (see Table 1 for detailed intercept, slope, and correlation coefficient data by condition and subject group). Scatterplots of M100 latency as a function of age in the left (panel a) and the right (panel b) hemispheres for 17 Controls are presented in Fig. 3.

![Fig. 2. Mean M100 latency for Control (a) and AD (b) groups with y-scale representing M100 latency (in ms). Results are presented for 200- and 1000-Hz tones separately for the left and right hemispheres. Error bars represent one standard error of the mean (S.E.M.).](image)
Table 1
Intercept, slope, correlation coefficient, and P value from the regression analyses of M100 latency as a function of age performed separately for the Control and AD groups

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Slope</th>
<th>Correlation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 Hz tone</td>
<td>201.3</td>
<td>-4.4</td>
<td>0.54</td>
<td>0.04*</td>
</tr>
<tr>
<td>1000 Hz tone</td>
<td>174.4</td>
<td>-3.5</td>
<td>0.54</td>
<td>0.05*</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 Hz tone</td>
<td>205.3</td>
<td>-5.4</td>
<td>0.67</td>
<td>0.01*</td>
</tr>
<tr>
<td>1000 Hz tone</td>
<td>168.3</td>
<td>-3.7</td>
<td>0.76</td>
<td>0.001**</td>
</tr>
<tr>
<td><strong>AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 Hz tone</td>
<td>213.0</td>
<td>-4.8</td>
<td>0.50</td>
<td>0.12</td>
</tr>
<tr>
<td>1000 Hz tone</td>
<td>175.0</td>
<td>-3.8</td>
<td>0.51</td>
<td>0.07</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 Hz tone</td>
<td>144.7</td>
<td>0.2</td>
<td>0.03</td>
<td>0.94</td>
</tr>
<tr>
<td>1000 Hz tone</td>
<td>117.1</td>
<td>1.4</td>
<td>0.30</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Regression results are shown for the 200- and 1000-Hz tones and for each hemisphere. **P<0.01; *P<0.05.

3.2.2. AD

Scatterplots of M100 latency as a function of age in the left (panel a) and the right (panel b) hemispheres for 13 children with AD are shown in Fig. 4. Results of linear regression analyses indicated a relationship between M100 latency and age in the LH, however the slope of the regression lines did not statistically differ from zero for either the 200-Hz tone (−4.8 ms/year) or the 1000-Hz tone (−3.8 ms/year) (see Table 1). There was no statistically reliable relationship between age and M100 latency in the RH (see Fig. 4b), where the slopes of the regression lines were slightly positive for both the 200-Hz tone (0.2 ms/year) and the 1000-Hz tone (1.4 ms/year), indicating a trend towards an increase in M100 latency with age (see Table 1).

4. Discussion

4.1. M100 age-dependence: control children

In the present investigation, we measured M100 latency as a function of age and hemisphere in order to investigate maturational changes in cortical auditory systems in typically developing and AD children. First, we provide evidence that M100 latency varies in a linear manner with age in both the left and the right hemispheres in healthy children (see Fig. 3). The rate of change for this effect was similar in the two hemispheres, with an average rate of −4.0 ms/year found for the left hemisphere and −4.5 ms/year found for the right (see Table 1). Generators for the M100 localize to sources in supratemporal sites [25,33,36] and therefore our results represent neural activity that is generally restricted to auditory cortex. Our findings presented here for Controls indicate that there are maturational changes in cortical auditory systems in typically developing children between the ages of 10–16, and that these changes appear to develop in a similar manner in left and right auditory cortical fields.

Our findings of age-dependent changes in the latency of the M100 in typically developing children are in good accord with previous findings using MEG or EEG to estimate cortical maturational processes [1,5,13,29,31,46]. Our findings of a rate of change in M100 latency that is similar to results reported for the electric N1, where rates have been reported ranging from −2 to 4 ms/year in similarly aged children [13,38,46]. Our results here provide evidence that maturational patterns (as measured by rate of latency change by year) are similar in the
two hemispheres, a result that is similar to that of Paetau et al. [28], who found no hemispheric asymmetries in auditory cortical refractory periods in their sample of children. Our results differed somewhat from those of Rojas et al. [34], who reported age-related changes in refractory periods that were specific to the right hemisphere. However, there are many differences in the stimuli, stimulus presentation rates, and the ages of the children between the Rojas et al. study and the present investigation which may account, at least in part, for the differential findings.

4.2. M100 age-dependence: AD children

Second, we report a strikingly different pattern of effect in AD children: M100 latency had a tendency to vary linearly with age in left hemisphere sites (see Fig. 4a), with an average rate of change of $-4.3$ ms/year (see Table 1). While results for AD children were more variable and the slopes of the regression lines did not statistically differ from zero, nevertheless, the general finding of a rate of change of $-4$ ms/year found in the left hemisphere for AD children is quite similar to our findings for Controls. In the right hemisphere, however, M100 latency increased slightly with age (see Fig. 4b), an opposite pattern of the effects found in the Control group and in the left hemisphere of the AD group.

Previous reports of age-dependent latency changes in electric and magnetic evoked components have been interpreted as relating to maturational changes in cortical auditory system [1,5,7,11,13,14,31,32,38]. While the nature of the cortical mechanisms that produce latency changes in children are not known, it has been proposed that developmental processes such as myelination, axonal growth, and maturation of superficial cortical layers (e.g., II and upper III) may be responsible, in part, for the shortening of the latency of cortical auditory components as children grow older [5,7,11,31,32]. If this is the case, then our findings here provide evidence that these developmental processes produce latency effects that are similar in the two hemispheres by the age of 10 years in typically developing children. In contrast, our findings for AD children provide evidence for little or no age dependence in the M100 in right hemisphere auditory sites, and sharply differing responses in the two hemispheres. Cumulatively, our results for AD children may indicate that those neural developmental processes which produce age-dependent effects in evoked response latencies in typically developing children follow a different maturational path in AD children, and that this maturational path may be asymmetric in the two hemispheres.

4.3. M100 latency prolongation in AD

We report generally longer M100 latencies in our group of children with AD as compared to Controls (see Fig. 2). These findings are similar to those reported by Dunn et al. [10], who observed delayed N1 latencies, particularly over left hemisphere sites, for AD children aged 7–10 years as compared to age-matched controls. The authors suggested that latency prolongation may reflect delays in linguistic processing by AD children. Similar findings of latency delays in AD children have been reported in the EEG literature in response to non-linguistic stimuli, with results hypothesized to be due to abnormalities in myelination processes, resulting in slower transmission rates in central auditory pathways [4]. Evidence in support of this view is provided in a study by Mazia et al. [21] who recorded brainstem auditory evoked responses (BAER) in AD children and reported prolongation in BAER in AD children as compared to controls. These findings are similar to earlier reports of prolonged BAER transmission times in AD [23,39,40,42,44]. (It is important to note,
however, some studies have reported either no difference between AD and Controls, or differences that do not appear to be specific to AD [7,35]. Maziade et al. [21] interpreted their findings as reflecting a slowing in nerve conduction in the auditory system in AD and suggested that the slowing may be due to abnormalities in myelination processes during development. In the healthy brain, neural networks in the auditory system encode and transmit the fine structure of speech and non-speech sounds with submillisecond temporal resolution, which is critical to the accurate perception of speech. Impairments in temporal processing of the fine structure in sounds in clinical populations with speech perceptual disabilities (such as auditory neuropathy) have been related to the demyelination of auditory VIII nerve fibers [47]. If the general prolongation of M100 latency reported here for AD children reflects slowed conduction times in auditory cortical sites, then it may be the case that at least some of the language impairment observed in children with AD is due to poor synchronization within and between cortical language processing regions.

4.4. Cerebral hemisphere asymmetries in development

4.4.1. Controls

Evidence for asymmetries in the rate and age of development of the cerebral hemispheres in typically developing children has been provided by Thatcher et al. [43]. Thatcher et al. reported a steadily increasing development of EEG coherence and phase in frontal and temporal lobe sites in the right hemisphere in a large sample of children varying in age from 2 months to 15 years. A different pattern of development was reported for the left hemisphere, where a surge of development of coherence and phase was observed in the age range 5–10 years, with much higher levels of both coherence and phase observed for children in this age range in left hemisphere sites as compared to the right hemisphere. Coherence and phase measures achieved similar proportions in the two hemispheres after age 10. The Control children studied here ranged in age from 10 to 16. It may be the case that the similar pattern of MEG measures of age-dependency reported here for the two hemispheres for the Controls may reflect similar developmental processes in those hemispheres in this age range, in a manner similar to the findings of Thatcher et al. [43]. Future studies with younger children are needed in order to ascertain if there are hemispheric asymmetries in MEG age-dependence measures that occur early and persist throughout development in individuals with AD.

The present findings provide empirical evidence that the maturation of cortical auditory systems in children with AD may follow a differential path as compared to typically developing children, particularly in the right hemisphere. Results must be treated with caution due to the relatively small sample size, the cross-sectional nature of the study, and the high level of variability found in our sample of AD children and in the AD population in general. While future studies employing a longitudinal design are needed in order to verify the findings of abnormal auditory cortical maturation in children with AD, the present investigation provides evidence that language impairment and atypical sound sensitivity may be linked to abnormalities in cortical sensory auditory processing in AD children.

Acknowledgements

We are grateful to the children and their parents for participating in this investigation. This work is supported by a research fellowship from the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute (N.G.) and a research grant from the National Alliance of Autism Research (T.R.). We are grateful to David Poeppel and to our reviewers for providing thoughtful insights and helpful suggestions. We would like to thank Susanne Honma and Jeff Walker for their excellent technical assistance as well as Cathy Hayer and Melanie Callen for help with participant recruitment, screening, and preparation.
References


