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Research report

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

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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 -4 ms/year (LH) and -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.

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Theme: Development and regeneration

Topic: Sensory systems

Keywords: Autism; Magnetoencephalography; Maturation; Auditory cortex; Language

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 observa-

tions, 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)

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65 children, progressing to shorter latencies in older children,
 66 with adult-like latencies found for adolescents in the age
 67 range of 14–16 years [1,5,13,37,46]. While it is not known
 68 at present what P1 and N1 latency prolongation in children
 69 may mean in terms of neural system development or
 70 behavior, it has been suggested that it may reflect maturation
 71 changes related to synaptogenesis, myelinogenesis,
 72 dendritic pruning [5,11,14] or to laminar maturation in
 73 superficial layers (II and upper III) of auditory cortex that
 74 occurs between the ages of 5–12 [31,32], with the general
 75 notion that as neural systems mature, conduction rates
 76 increase, thereby decreasing the time to peak latency in
 77 evoked components.

78 Evidence that the latency of components in the AEP
 79 (such as the P1 and N1) may reflect delays or abnormal-
 80 ities in the maturation of cortical auditory systems in
 81 special populations of children has been provided in
 82 studies with children with severe language impairment
 83 (LI), phonological dyslexia, and auditory processing and
 84 hearing disorders [12,15,22,45]. For example, Eggermont
 85 et al. [12] measured the latency of the P1 component in
 86 deaf children with cochlear implants who had undergone
 87 prolonged auditory deprivation prior to implant. They
 88 reported that time-to-maturation of the P1 in the children
 89 with implants was delayed for a duration that was roughly
 90 equal to the duration of their deafness [12]. Tonnquist-
 91 Uhlen et al. [45] measured N1 latencies in a group of
 92 severely LI children and reported prolonged latencies in
 93 this group as compared to age-matched controls, and no
 94 age dependency. Thus, the latency of the P1 and
 95 N1 components may provide a non-invasive and objective
 96 measure of cortical auditory system maturation in both
 97 typically developing children and children with auditory
 98 and/or language processing deficits.

99 Several studies have investigated age related effects of
 100 N1 peak latency in children with AD as compared to age
 101 matched, typically developing controls. Findings to date
 102 have been mixed, however. One study reported *shorter* N1
 103 latencies for AD children aged 6–18 years [26], while a
 104 second study reported *longer* N1 latencies in very young
 105 (infancy–4 years) AD children with tuberous sclerosis
 106 complex [37]. Two studies with slightly older children
 107 reported no difference in N1 between AD children aged
 108 7–14 and controls [18,19]. A third study of non-mentally
 109 retarded AD children aged 7–10 and controls reported
 110 longer (43–70 ms) N1 latencies in the AD group in
 111 response to individually presented words in a target
 112 detection paradigm [10]. Interestingly, Dunn et al. reported
 113 longer reaction time responses in their AD group and
 114 suggested that, in combination with the N1 prolongation,
 115 these results may reflect slower processing of linguistic
 116 stimuli in AD children. The widely varying ranges of age
 117 in these studies in addition to the high level of hetero-
 118 geneity found in general in samples of children with
 119 autism spectrum disorder may underlie the mixed results
 120 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_p, N1_c) 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 chil-
 dren. 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

178 auditory evoked neuromagnetic fields over left and right
 179 hemispheres in a group of typically developing children
 180 and AD children in order to evaluate the age dependence
 181 of the M100 component. Based on previous EEG and
 182 MEG investigations with typically developing children, we
 183 hypothesize that M100 latency will depend on age in our
 184 group of control children. Of key interest in this study is
 185 whether we will find evidence for hemispheric asymmet-
 186 ries in age dependence, which may reflect differences in
 187 the developmental path of left and right auditory cortices
 188 in typically developing children. Next, we evaluate age
 189 dependence in AD children. Motivated by the pervasive
 190 nature of language deficits in autism, coupled with evi-
 191 dence for abnormal development of temporal lobe areas
 192 that subservise auditory and speech sound processing
 193 [3,8,17,30], we hypothesize that M100 latency will show a
 194 weaker or reduced age dependence for AD children. Due
 195 to the lack of previous investigations using MEG to
 196 evaluate auditory evoked responses in AD children, this
 197 investigation must be exploratory in nature. Our dependent
 198 measure is M100 latency. Our design includes Hemisphere
 199 and Tone Frequency as within-subject factors, Group
 200 (Control, AD) as a between-subject factor, and age as a
 201 covariate.

202 2. Materials and methods

203 2.1. Participants

204 Participants consisted of 15 males (age 8–14, Mean
 205 11.4, S.D. 2.0) with AD recruited from the Pervasive
 206 Developmental Disorders Clinic at the University of
 207 California, San Francisco, and 17 controls (five female,
 208 age 10–16, Mean 13.5, S.D. 1.7). All AD participants had
 209 normal hearing as confirmed by earlier clinical audiologi-
 210 cal assessments available for review in patient charts.

211 Control children were free of known neurological
 212 disease and had normal hearing as reported by the parent
 213 and based on previous clinical audiological assessment. All
 214 participants were native speakers of English. All partici-
 215 pants were studied without the use of sedation.

216 Children with AD were diagnosed by according to
 217 procedures outlined in the California DDS Diagnostic Best
 218 Practice for Autism Guidelines (2002) [2], including direct
 219 observation using a standardized autism-specific behavioral
 220 rating, a clinical history designed to rule in autism and rule
 221 out related disorders, an age-appropriate cognitive test
 222 against which to rate possible autism symptoms versus
 223 mental retardation, and finally use of the DSM-IV [9]
 224 criteria based on an overall evaluation of these data. The
 225 children with AD were selected according to the following
 226 inclusion criteria: normal non-verbal or Performance IQ
 227 ($IQ \geq 70$ as assessed by a version of the Weschler In-
 228 telligence Scale for Children (WISC-R or WISC-III) and

Verbal IQ at least 1 S.D. (15 points) below Performance
 IQ. 229

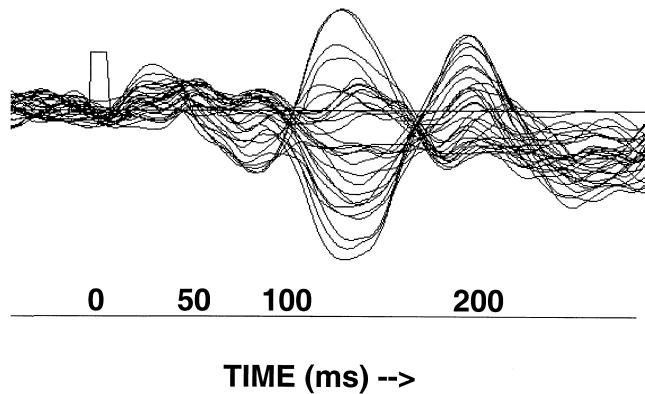
230
 231 MEG scanning required that participants remain motion-
 232 less for several minutes at a time. In order to increase the
 233 likelihood of successful MEG recording, AD children who
 234 met the above-mentioned inclusion criteria were pre-
 235 screened in an effort to select individuals who would be
 236 cooperative during the MEG scanning procedures.
 237 Stimulus presentation and MEG recording were performed
 238 with the approval of the institutional committee on human
 239 research. Informed written consent was obtained from each
 240 participant and parent or legally authorized representative.

241 2.2. Stimulus presentation and MEG recordings

242 Sinusoidal tones of frequency 200 and 1000 Hz (250 ms
 243 duration) were presented monaurally using Etymotic™ ER-
 244 3A earphones and air tubes designed for use with the MEG
 245 system (Etymotic, Oak Brook, IL). Stimuli were presented
 246 at 40 dB SL (sensation level, i.e., 40 dB above the
 247 perceptual detection threshold, which was individually
 248 determined for each stimulus and each participant). Neuro-
 249 magnetic fields were recorded for each participant using a
 250 37-channel biomagnetometer (MAGNES™, Bti, San
 251 Diego, CA.) in a magnetically shielded room. The sensor-
 252 array was placed over the temporal lobe contralateral to the
 253 ear of stimulus presentation. Evoked response to a refer-
 254 ence 1000 Hz sinusoidal tone (400 ms duration) was
 255 evaluated to determine if the sensor array was positioned
 256 to effectively record the auditory evoked M100 field.
 257 Epochs of 600 ms duration (100 ms pre-stimulus onset and
 258 500 ms post-stimulus onset) were acquired around each
 259 stimulus at a sampling rate of 1041.7 Hz with a bandwidth
 260 of 400 Hz and a 1.0-Hz high-pass filter. This procedure
 261 was repeated for each hemisphere. Presentation was
 262 blocked by stimulus condition. Each stimulus was pre-
 263 sented 120 times per block in a passive listening paradigm.
 264 Block duration was 2–3 min. Blocks were presented in a
 265 pseudorandom order for each of the two stimulus con-
 266 ditions, for each hemisphere. MEG recording continued
 267 until each stimulus condition was presented in each
 268 hemisphere (for a total of four scanning blocks) or until the
 269 participant was no longer able to tolerate the procedure.

270 2.3. Data analysis

271 The data were inspected and individual epochs that
 272 contained motion-related artifacts (>2.5 pT, $pT = 10^{-12}$ T)
 273 were removed. Data were then selectively averaged by
 274 stimulus condition and hemisphere for each participant.
 275 Averaged waveforms were band-pass filtered using a high
 276 cut-off frequency of 40 Hz. The root mean square (RMS)
 277 of the field strength across all 37 channels was calculated
 278 for each sample point. The M100 peak was determined as
 279 the peak in RMS value across 37 channels in the interval
 280 80–200 ms, subject to a single equivalent current dipole



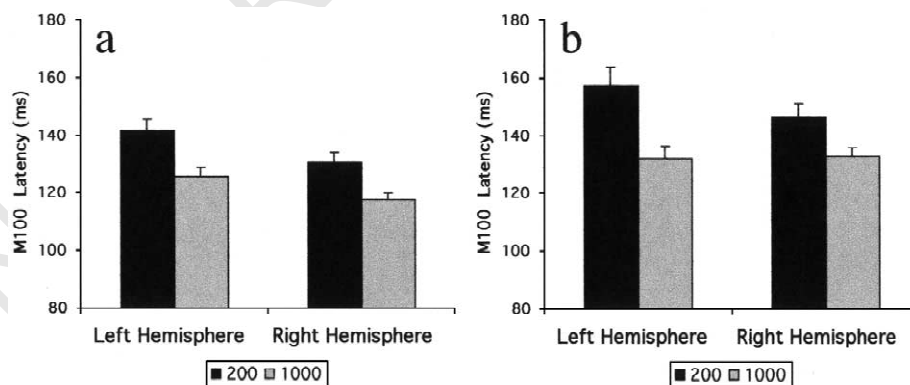
284 Fig. 1. Auditory evoked neuromagnetic field (AENF) recorded over the
 285 left hemisphere of one characteristic Control subject (time in milliseconds
 286 is depicted along the horizontal axis.); 37 channels (sensors) with y-scale
 287 representing evoked response magnitude in units of fT are shown
 288 collapsed on the same horizontal time axis. The M100 component,
 289 occurring ~100 ms post stimulus onset, has a source that localizes to
 290 auditory cortex, as modeled by a single equivalent current dipole (SECD).

296 (SECD) model/data correlation $r > 0.95$, with $Q < 50.0$ nA,
 297 and a signal-to-noise ratio that met or exceeded a factor of
 298 6:1.

299 The latency of the M100 component served as the
 300 dependent measure. Subject group was entered into a
 301 General Linear Model (GLM) as a between subjects factor,
 302 hemisphere and tone frequency were between subject
 303 factors, age served as a covariate. Linear regression
 304 analyses of M100 latency and age were conducted in order
 305 to evaluate the rate of change (ms/year) by group, hemi-
 306 sphere, and tone. An α level of 0.05 was used for all
 307 statistical tests.

308 3. Results

309 Two children with AD were unable to tolerate any
 310 portion of the recording process. Auditory evoked neuro-



293 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
 294 tones separately for the left (black filled columns) and right (gray shaded columns) hemispheres. Error bars represent one standard error of the mean
 295 (S.E.M.).

magnetic fields were acquired from each of the remaining 311
 13 children with AD and all 17 Controls. See Fig. 1 for a 312
 characteristic waveform recorded from an AD participant. 313

314 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 315
 evaluated at covariate age = 12.77. A main effect of Group 316
 was statistically significant ($F(1,15) = 5.22$, $P = 0.037$). 317
 M100 latency differed by Group, with longer M100 318
 latencies for the AD group ($M = 139.06$, S.E.M. = 3.02) as 319
 compared to the Control group ($M = 129.15$, S.E.M. = 2.65) 320
 (see Fig. 2). The effect of Hemisphere was not statistically 321
 significant ($F(1,15) = 1.66$, $P = 0.217$); however, there was 322
 a trend for latencies in the left hemisphere to be somewhat 323
 longer than in the right. The effect of Tone frequency 324
 failed to reach statistical significance ($F(1,15) = 2.77$, $P = 325$
 0.117), however M100 latency was longer for the low (200 326
 Hz) frequency tone as compared to the high (1000 Hz) 327
 frequency tone for both groups and in each hemisphere 328
 (see Fig. 2). No interactions reached statistical signifi- 329
 cance. 330
 331

332 3.2. Linear regression analyses

333 3.2.1. Control

Results of linear regression analyses indicated a signifi- 334
 cant relationship between M100 latency and age. M100 335
 latency varied in a linear manner for the 200-Hz tone in 336
 LH (-4.4 ms/year) and RH (-5.4 ms/year), and for the 337
 1000 Hz tone in LH (-3.5 ms/year) and RH (-3.7 338
 ms/year) (see Table 1 for detailed intercept, slope, and 339
 correlation coefficient data by condition and subject 340
 group). Scatterplots of M100 latency as a function of age 341
 in the left (panel a) and the right (panel b) hemispheres for 342
 17 Controls are presented in Fig. 3. 343

345 Table 1
346 Intercept, slope, correlation coefficient, and *P* value from the regression
347 analyses of M100 latency as a function of age performed separately for
348 the Control and AD groups
349

	Intercept	Slope	Correlation	<i>P</i>
Control				
<i>Left hemisphere</i>				
354	201.3	−4.4	0.54	0.04*
355	174.4	−3.5	0.54	0.05*
<i>Right hemisphere</i>				
357	205.3	−5.4	0.67	0.01*
358	168.3	−3.7	0.76	0.001**
AD				
<i>Left hemisphere</i>				
361	213.0	−4.8	0.50	0.12
362	175.0	−3.8	0.51	0.07
<i>Right hemisphere</i>				
364	144.7	0.2	0.03	0.94
365	117.1	1.4	0.30	0.37

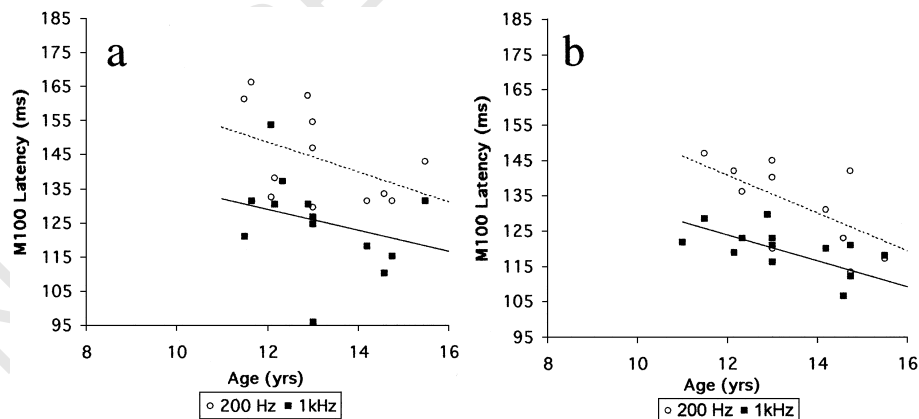
367 Regression results are shown for the 200- and 1000-Hz tones and for each
368 hemisphere.

369 ***P*<0.01; **P*<0.05.

376 3.2.2. AD

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

370



371

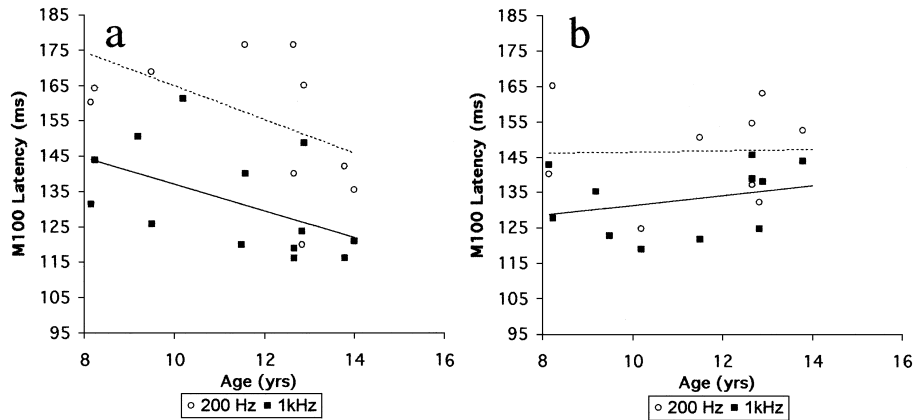
372 Fig. 3. M100 latency plotted as function of age for Controls in the left hemisphere (a) and the right hemisphere (b). The y-scale represents M100 latency
373 (in ms) and x-scale represents subject age (in years). Trend lines indicate that M100 latency varied in a linear manner with slopes indicating a −4.4
374 ms/year for the 200-Hz tone and −3.5 rate of change for the 1000-Hz tone in the left hemisphere (a); and a −5.4 ms/year for the 200-Hz tone and a −3.7
375 rate of change for the 1000-Hz tone in the right hemisphere (b).

391 4. Discussion

392 4.1. M100 age-dependence: control children

393 In the present investigation, we measured M100 latency
394 as a function of age and hemisphere in order to investigate
395 maturational changes in cortical auditory systems in typi-
396 cally developing and AD children. First, we provide
397 evidence that M100 latency varies in a linear manner with
398 age in both the left and the right hemispheres in healthy
399 children (see Fig. 3). The rate of change for this effect was
400 similar in the two hemispheres, with an average rate of
401 −4.0 ms/year found for the left hemisphere and −4.5
402 ms/year found for the right (see Table 1). Generators for
403 the M100 localize to sources in supratemporal sites
404 [25,33,36] and therefore our results represent neural activi-
405 ty that is generally restricted to auditory cortex. Our
406 findings presented here for Controls indicate that there are
407 maturational changes in cortical auditory systems in typi-
408 cally developing children between the ages of 10–16, and
409 that these changes appear to develop in a similar manner in
410 left and right auditory cortical fields.

411 Our findings of age-dependent changes in the latency of
412 the M100 in typically developing children are in good
413 accord with previous findings using MEG or EEG to
414 estimate cortical maturational processes [1,5,13,29,31,46].
415 Our findings of a rate of change in M100 latency that is
416 ~−4 ms/year are similar to results reported for the electric
417 N1, where rates have been reported ranging from −2 to 4
418 ms/year in similarly aged children [13,38,46]. Our results
419 here provide evidence that maturational patterns (as mea-
420 sured by rate of latency change by year) are similar in the
421 two hemispheres, a result that is similar to that of Paetau et
422 al. [28], who found no hemispheric asymmetries in audito-
423 ry cortical refractory periods in their sample of children.
424 Our results differed somewhat from those of Rojas et al.
425 [34], who reported age-related changes in refractory



429 Fig. 4. M100 latency plotted as function of age for AD in the left hemisphere (a) and the right hemisphere (b). The y-scale represents M100 latency (in ms)
 430 and x-scale represents subject age (in years). Trend lines were non-significant from zero, however there was a general tendency for M100 latency to vary
 431 linearly with slopes indicating a rate of change of -4.8 ms/year for the 200-Hz tone and -3.8 ms/year for the 1000-Hz tone in the left hemisphere (a).
 432 Slopes in the right hemisphere (b), while not statistically different from zero, indicated a slightly positive rate of change as a function of age, with rates of
 433 change of 0.2 ms/year for the 200-Hz tone and 1.4 ms/year for the 1000-Hz tone.

434 periods that were specific to the right hemisphere. How-
 435 ever there are many differences in the stimuli, stimulus
 436 presentation rates, and the ages of the children between the
 437 Rojas et al. study and the present investigation which may
 438 account, at least in part, for the differential findings.

439 4.2. M100 age-dependence: AD children

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

453 Previous reports of age-dependent latency changes in
 454 electric and magnetic evoked components have been
 455 interpreted as relating to maturational changes in cortical
 456 auditory system [1,5,7,11,13,14,31,32,38]. While the nature
 457 of the cortical mechanisms that produce latency changes in
 458 children are not known, it has been proposed that de-
 459 velopmental processes such as myelination, axonal growth,
 460 and maturation of superficial cortical layers (e.g., II and
 461 upper III) may be responsible, in part, for the shortening of
 462 the latency of cortical auditory components as children
 463 grow older [5,7,11,31,32]. If this is the case, then our
 464 findings here provide evidence that these developmental
 465 processes produce latency effects that are similar in the
 466 two hemispheres by the age of 10 years in typically
 467 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 asymmet-
 ric in the two hemispheres.

477 4.3. M100 latency prolongation in AD

478 We report generally longer M100 latencies in our group
 479 of children with AD as compared to Controls (see Fig. 2).
 480 These findings are similar to those reported by Dunn et al.
 481 [10], who observed delayed N1 latencies, particularly over
 482 left hemisphere sites, for AD children aged 7–10 years as
 483 compared to age-matched controls. The authors suggested
 484 that latency prolongation may reflect delays in linguistic
 485 processing by AD children. Similar findings of latency
 486 delays in AD children have been reported in the EEG
 487 literature in response to non-linguistic stimuli, with results
 488 hypothesized to be due to abnormalities in myelination
 489 processes, resulting in slower transmission rates in central
 490 auditory pathways [4]. Evidence in support of this view is
 491 provided in a study by Mazziade et al. [21] who recorded
 492 brainstem auditory evoked responses (BAER) in AD
 493 children and reported prolongation in BAER in AD
 494 children as compared to controls. These findings are
 495 similar to earlier reports of prolonged BAER transmission
 496 times in AD [23,39,40,42,44]. (It is important to note,
 497 however, some studies have reported either no difference
 498 between AD and Controls, or differences that do not
 499 appear to be specific to AD [7,35].) Mazziade et al. [21]
 500 interpreted their findings as reflecting a slowing in nerve
 501 conduction in the auditory system in AD and suggested

503 that the slowing may be due to abnormalities in myelination
 504 processes during development. In the healthy brain,
 505 neural networks in the auditory system encode and transmit
 506 the fine structure of speech and non-speech sounds
 507 with submillisecond temporal resolution, which is critical
 508 to the accurate perception of speech. Impairments in
 509 temporal processing of the fine structure in sounds in
 510 clinical populations with speech perceptual disabilities
 511 (such as auditory neuropathy) have been related to the
 512 demyelination of auditory VIII nerve fibers [47]. If the
 513 general prolongation of M100 latency reported here for
 514 AD children reflects slowed conduction times in auditory
 515 cortical sites, then it may be the case that at least some of
 516 the language impairment observed in children with AD is
 517 due to poor synchronization within and between cortical
 518 language processing regions.

519 4.4. Cerebral hemisphere asymmetries in development

520 4.4.1. Controls

521 Evidence for asymmetries in the rate and age of
 522 development of the cerebral hemispheres in typically
 523 developing children has been provided by Thatcher et al.
 524 [43]. Thatcher et al. reported a steadily increasing develop-
 525 ment of EEG coherence and phase in frontal and temporal
 526 lobe sites in the right hemisphere in a large sample of
 527 children varying in age from 2 months to 15 years. A
 528 different pattern of development was reported for the left
 529 hemisphere, where a surge of development of coherence
 530 and phase was observed in the age range 5–10 years, with
 531 much higher levels of both coherence and phase observed
 532 for children in this age range in left hemisphere sites as
 533 compared to the right hemisphere. Coherence and phase
 534 measures achieved similar proportions in the two hemi-
 535 spheres after age 10. The Control children studied here
 536 ranged in age from 10 to 16: it may be the case that the
 537 similar pattern of MEG measures of age-dependency
 538 reported here for the two hemispheres for the Controls may
 539 reflect similar developmental processes in those hemi-
 540 spheres in this age range, in a manner similar to the
 541 findings of Thatcher et al. [43]. Future studies with
 542 younger children are needed in order to ascertain if there
 543 are hemispheric asymmetries in MEG age-dependence
 544 measures in typically developing children in the age range
 545 of 5–10 years.

546 4.4.2. AD

547 While our effects here await replication, it may be the
 548 case that the general prolongation in M100 latency found
 549 in both hemispheres for the AD children combined with
 550 the lack of age dependence in right hemisphere sites may
 551 reflect a general development delay in auditory cortical
 552 systems. The present findings leave open the questions of:
 553 (i) are there differences in auditory cortical maturation in
 554 the two hemispheres *throughout* early development, and
 555 (ii) do these auditory cortical hemispheric asymmetries

556 *persist* beyond the age range tested here? While answers to
 557 these questions await future investigations, the work of
 558 Thatcher et al. [43] may be relevant to the present
 559 investigation: the authors' findings of hemispheric
 560 asymmetries in development were focused in the age range
 561 of 5–10 years in typically developing children. While our
 562 AD sample was somewhat older in chronological age (at
 563 8–14 years), they were younger as measured by mental age
 564 evaluation, reflecting some developmentally delays. Thus it
 565 could be the case that our AD children were in a
 566 developmental stage that was similar to the 5–10-year-olds
 567 tested by Thatcher et al. The hemispheric asymmetries
 568 with lack of age dependence in the right hemisphere that
 569 we report here may potentially reflect a finding similar to
 570 that of Thatcher et al., where they reported a surge of
 571 developmental maturation between the ages of 5–10 years
 572 in the left hemisphere that was not observed in the right.
 573 Future studies with both younger children and older
 574 adolescents are needed in order to ascertain if there are
 575 hemispheric asymmetries in MEG age-dependence mea-
 576 sures that occur early and persist throughout development
 577 in individuals with AD.

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

592 5. Uncited references

593 [6]; [24]

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