

A Developmental Study of AEP N2 and Autonomic versus Controlled Processes in Normal Children

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Abstract

In the developmental investigations on event related potentials (ERPs), it is not well known whether the N2 elicited by startle stimuli changes at the same rate as the developmental P3b changes, or shows some different developmental course. The present research provided the data on the developmental and maturational changes of AEP (auditory evoked potential) N2 component elicited by the acoustic sudden stimuli. The results showed that the AEP N2 appeared to develop at different rates in the developmental curves of latencies and amplitudes, as compared with the P3a elicited by sudden stimuli and the P3b elicited by an oddball paradigm. The peak latency of electromyographic (EMG) responses in young children was longer than in adults, and decreased progressively as a function of age, reaching adult values by late adolescence or the early twenties. These findings suggest that the N2 elicited by sudden stimuli has a different developmental time table in children, and may reflect a bottom-up activity of the sensory processing taking place in the brainstem, as compared with the P3b component.

Introduction

About thirty years ago, H. L. Williams and his colleagues (Williams et al., 1962) reported that N2 amplitude of auditory evoked potentials (AEPs) elicited by click stimuli remarkably increased during sleep stages 2-3-4, and decreased during the REM sleep stage. These findings were confirmed by E. D. Weitzman and H. Kremen (Weitzman & Kremen, 1965) and other studies (Sugawara, 1976, 1988). The N2 wave is the most prominent negative component in AEPs, particularly influenced by the subject's arousal level (Starr & Don, 1988). Although the N2 amplitudes during sleep stages 2-3 are larger than during stage 4, this effect might be explained by assuming that each response peak latency of N2 to the acoustic stimuli is varied by the spontaneous δ -wave activities during stage 4. It is known that the N2 amplitude shows a considerable decrement during the REM stage in which the unit evoked activity is markedly reduced in the mesencephalic reticular formation, whereas spontaneous single unit activity is greatly increased (Huttenlocher,

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1960, 1961). E. V. Evarts (Evarts, 1962, 1963) also found an enhancement of spontaneous unit activity from the visual cortical cells in cats during REM sleep. These increased rates of spontaneous discharge in this specific physiological stage may occlude the input of afferent information, and produce the small amplitude of evoked potentials (EPs).

However, the N2 wave is clearly evoked not only during NREM stages, but also during the awake state. Moreover, just as the P3 is mainly composed of two (or more) different waves (P3a and P3b), the AEP N2 wave of event related potentials (ERPs) is composed of not only one component, but consists of several autonomically or voluntarily elicited negative components (Table 1).

Table 1. Classification of N2 kinds of ERP components.

Authors:	
Components, Stimuli, Subjects, Processing type, Modality & topography, Findings	
Williams et al. (1962)	
Component	---N2
Stimuli	---click (85 db, every 2 sec.)
Subjects	---3 normal adults (young male subjects)
Processing type	---autonomic
Modality & top.	---auditory, vertex
Findings	---arousal effects
Weitzman & Kremen (1965)	
Component	--- N2
Stimuli	---click (50-60 dB 0.5 msec pulse, every 4 sec)
Subjects	---10 normal young adults
Processing type	---autonomic
Modality & top.	---auditory, vertex-occipital recording
Findings	---arousal effects, N2 latencies and amplitudes were significantly greater in all stages of sleep, as compared with the awake and the rapid eye movement state.
Orinitz et al. (1968)	
Component	---N2
Stimuli	---click (1 msec pulse duration, 80-90 dB, every 2.2-2.4 sec)
Subjects	--- 26 normal children, age range 19 months-12 years, 23 autistic children, age range 22 months-8 years
Processing type	---autonomic
Modality & top.	---auditory, central-occipital recording
Findings	---the reduction on N2 amplitude recorded at the scalp during the REM burst sleep in normal subjects might be a centrally determined process independent of peripheral input control.
Picton et al. (1974)	
Component	--- N2
Stimuli	---click (50 μ sec square pulses) or tonebursts (50 msec duration)
Subjects	---12 normal adults, age range 20-30 years
Processing type	---autonomic
Modality & top.	---auditory, front-central scalp
Findings	---arousal effects
Simson et al. (1976, 1977)	
Component	---MSPs (missing stimulus potentials), NMSPs (negative MSPs), N2
Stimuli	---50 msec, 2000 Hz, 50-60 dB tone, 10 msec flash, every 1 sec
Subjects	---8 adults (1 female and 7 males), 21-45 years
Processing type	---controlled
Modality & top.	---auditory and visual, modality specific, intermodal differences
Findings	---memory readout, omission of a temporally predictable stimulus

Näätänen et al. (1978, 1983, 1986)

Components	--- MMN (mismatch negativity), orienting response (OR) wave, N2b
Stimuli	---standard vs signal (deviant) auditory stimuli, 70 vs 80 dB, 1000 vs 1140 Hz, constant interval 800 msec, left vs right ear
Subjects	---normal adults
Processing type	---autonomic
Modality & top.	---auditory, modality specific, vertex-frontal-temporal
Findings	---the MMN is a reflection of the activation (the elicitation of the change OR) of a comparison mechanism whereas the initial OR would be gene related without any comparison mechanism

Proryesz et al. (1987)

Component	---N2
Stimuli	---computer-generated display, 240 straight line stimuli rotated in three possible orientations with visual angle 5.46, /2-5sec
Subjects	---20 alcoholics (14 males and 6 females) and 20 controls
Processing type	---controlled, easy and difficult discriminations, RT paradigm
Modality & top.	---visual, occipital (Oz)
Findings	---N2 latencies were found to be significantly delayed in alcoholics compared to controls, especially for easy discrimination

Verleger et al. (1992)

Components	---N2b, N2
Stimuli	---auditory: 65 dB 1000 (86 %, non-target) & 2000 (14 %, target) Hz, 60 msec duration, /1.5 sec visual: the German words drucken or warten, 200 msec duration bright 26.3cd/m ² or dim 4.5cd/m ² , /2 sec, 4 different stimuli
Subjects	---20 elderly healthy adults (8 males, 12 females), ages ranged from 55 to 87 years (mean 67), and 7 mild dementia patients (1 male, 6 females), ages ranged from 64 to 75 years (mean 69)
Processing type	---controlled, oddball task, push/wait task
Modality & top.	---visual, auditory, Cz
Findings	---P3 did not differ between groups but the patients' N2b was delayed compared to controls, the patients had problems in deciding what to do with the perceived stimuli

Initially, S. Sutton and his colleagues (Sutton et al., 1965) proposed that EPs could be classified into exogenous and endogenous events which might be related to autonomic and controlled psychophysiological information processing. The large negative N2 wave with a peak latency of 220-500 msec is equivalent to the vertex sharp wave that can be distinctly seen in the EEG during all stages of sleep. Although the nature of the N2 wave is not well known, it is interesting that this sharp wave is particularly prominent at the first cycle as compared with the second or third cycle (Ornitz et al., 1967). Pressman et al. (1982) reported that the amplitudes of the AEP P2 and N2 component were enhanced following sleep deprivation. It might represent either the prevention of general arousal or the initiation of arousal change, involved with the activities of diencephalic or mesencephalic reticular formation. The N2-P3a complex wave may be associated with an orienting response to the unexpected change, while the P3b may appear after a target stimulus is identified by the more detailed processing within the attended channel.

Näätänen et al. (1982) suggested that the MMN or N2a wave is an automatic process, occurring without conscious recognition of the stimulus change. They (1980) also reported that the N2 wave increased in amplitude as the infrequent-oddball stimulus became easier to discriminate from the

frequent-standard stimuli. However other investigation (Ford et al., 1976) found no significant change in the N2 component with regard to the discriminability. Moreover, Fitzgerald and Picton (1983) showed that the N2 amplitude in the ERP to an oddball stimulus increased in amplitude as the stimulus became more difficult to discriminate from the standard stimuli. The effects of changing the discriminability of the target stimuli on the N2 wave have varied among different experiments. Thus disagreement in the results of N2 behavior might be due to there being additional underlying cortical and subcortical components that are superimposed, which create the scale-recorded N2 wave. Renault and his colleagues (Renault and Lesever 1987; Renault et al. 1982) described two N2 components with different scalp distribution in the ERP along with an unpredictable detected omission of a visual stimulus from a regular train. It suggested that the N2a might reflect sensory processing with maximum amplitude over parieto-occipital regions, while the N2b wave of the second negativity with a maximum amplitude at the vertex might reflect the orienting response to the detected omission occurring as a mismatch informative event. The P3 is usually preceded by the N2 wave peaking at 220-270 msec (except during sleep stages 3-4) which would be related to the momentary shift of attention toward an unexpected perturbation in the environment. Thus, the amplitude of N2-P3 complex growing with the magnitude of the deviation could be useful in research of human information processing. Particularly, the P3 component in response to an infrequent target tone occurring in a sequence of standard tones has been widely investigated for developmental brain and clinical application of diagnosis. Goodin et al. (1978) found that the P2, N2 and P3 latencies (not N1) increase progressively as a function of age, although the younger children have a remarkably longer P3 latency than do the younger adolescents. These ERP latency changes may parallel the development of information processing speed and memory span (Howard & Polich, 1985).

The majority of developmental or clinical researches on the ERPs has focussed on the changes of the P3 component with respect to aging or neuropathology, not on the prominent negative peak (N2). The purpose of the present research is to provide data on the developmental and maturational changes of AEP N2 latencies and amplitudes to unattended tones and eyelid reflexes elicited by startle acoustic stimuli in normal children (of ages 3-8 years) as compared to young adults. It is not yet known whether the N2 elicited by startle stimuli develops at the same rate as the developmental course of P3b activity changes, because there was no systematic developmental investigation of the startle N2 components.

Method

Subjects

Seventy-six normal children (40 males and 36 females) whose ages ranged from 3 to 8 years, and 17 normal adults (7 males and 10 females) were screened for good health, normal development, and absence of any symptoms suggesting neurological pathology. None had any history of neurological or middle inner ear pathology.

Stimuli

White noise burst tones (50 msec duration, 104 dB SPL, zero rise-fall time) were presented binaurally to the right and left ear through TDH-49 circumaural earphones applied to the subject's head with a random schedule of intertrial interval (ITI) every 25-45 seconds, during which the subjects watched silent color TV cartoons (for the children) or movies (for the adults) sitting in a comfortable chair.

Procedure and Recording

Before beginning the experimental session, practical trials were carried out to familiarize the subjects with the experimental situation, and were made as enjoyable as possible. One week after the preliminary training session, each subject returned for the second 20-min laboratory session. The subjects were seated comfortably in a reclining chair in a sound-attenuated, electrically-shielded room, where they were instructed to watch the TV and to remain quiet throughout the period of unexpected acoustic stimulus presentation.

Electroencephalographic (EEG) potentials recorded monopolarly from midline placements over central (Cz) and parietal (Pz) scalp electrode locations in the international 10-20 system with linked mastoides (A1-A2) as reference using standard chlorided silver disc electrodes. Electrodes were also placed on the lateral canthus and above the supercilium of the left eye in order to measure the amplitude and latency of the eyelid reflex. The Fpz was the earth electrode. Electrode impedances were less than 5 kOM. The amplifiers were set to a high-frequency cutoff of 100 Hz and a lowcut of 0.1 Hz. All mean peak latencies and amplitude measures of AEP components were quantified with a baseline-to-peak measurement by subtracting the average activity in the 100 msec prestimulus base line from the amplitude of the peak in the search epoch with an analysis time of 1.2 sec (giving a resolution of 1 msec/point). EEG responses and AEP N2 waves contaminated by large electrooculographic (EOG) and electromyographic (EMG) responses were rejected from the analyzing data. All single-trial and average data were recorded on a floppy disk for further analysis. The statistical significance of the AEP differences on the amplitude and latency values among different age groups was evaluated by the repeated measure analysis of variance (ANOVA) (This method was previously mentioned in a paper "A developmental study of the relationship between ERP P3a latencies and eyelid reflexes by startle acoustic stimuli in normal children", by the author (1993)).

Results

The typical AEP N2 wave-forms of a subject elicited by the infrequent-startle acoustic stimuli are shown in Fig. 1. The means and standard deviations of the rise-time latencies of eyelid reflexes (EMG) for binaural sudden stimulation are presented for each different-aged children and adult groups in Table 2 and Fig. 2. The rise-time result showed that these latencies decreased progressively as a function of age (3 year-old subjects: $n=11$, 46.3 ± 8.56 msec; adults: $n=17$, 31.8 ± 3.28 msec). The amplitude and latency measurements for the peak EMG are presented for the

subjects at ages 3, 4, 5, 8 and 18-24 in Table 3 and Fig. 3. As can be seen in Table 3 and Fig. 3, the younger children displayed significantly longer latencies of the EMG peak to startle stimuli as compared to the elder subjects (3 years: $n=11$, 81.8 ± 10.9 msec; adults: $n=17$, 62.0 ± 6.6 msec), but the amplitudes increased as a function of age.

It was also clear that the amplitudes of developmental N2 progressively increased as a function of age (3 years: $n=11$, -34.2 ± 18.8 μ V; 4 years: $n=17$, -47.6 ± 27.3 μ V; adults: $n=17$, 6.9 ± 4.5 μ V), but the latencies showed a U-shape function of age (Table 4. and Fig. 4). The variabilities of EMG and AEP N2 amplitudes were greater in the younger subjects and steadily decreased with age. It was not shown that the N2 latency steadily decreased with age, which differs from the developmental changes of P3b. There were apparent amplitude differences of the ERP components elicited by the click stimuli as compared with the normal (or oddball) experimental paradigm. The N2 did not generally overlap with the peak of P3a and P3b, and it is known that the N2 has no effect on task. The clearest evidence was the longest latencies of the EMG rise-time, peak and the AEP N2 component in the 3 year-old group, when compared to these latencies of 8 years and adult subjects. The adult subjects displayed smaller amplitudes of the N2 components than the children's negative amplitudes, though the amplitude differences among each children group were relatively very few and did not reach statistical significance for large deviations. The EMG and AEP data were statistically analyzed using the ANOVA among each group planned comparisons.

Table 2.

The means and standard deviations of the rise latencies of eyelid reflexes (EMG) for binaural acoustic stimulation in different-aged children and adult subjects.

	Latencies (msec) **	
3 years	46.3	(± 8.56)
4 years	38.7	(± 7.19)
5 years	40.8	(± 9.18)
8 years	35.9	(± 7.80)
Adults	31.8	(± 3.28)

**significant $P < .01$; ANOVA (the analysis of variance).

Table 3.

The means and standard deviations of the peak latencies and amplitudes of eyelid reflexes (EMG) for binaural acoustic stimulation in different-aged children and adult subject.

	Latencies (msec) **	Amplitudes (μ V) **
3 years	81.8 (± 10.9)	113.4 (± 102.5)
4 years	74.5 (± 10.5)	105.4 (± 58.9)
5 years	72.2 (± 10.6)	137.9 (± 108.2)
8 years	68.7 (± 7.1)	142.1 (± 71.8)
18-24 adults	62.0 (± 6.6)	182.1 (± 81.8)

**significant $P < .01$; ANOVA (the analysis of variance).

Table 4.

The means and standard deviations of AEP N2 latencies and amplitudes for binaural acoustic stimulation in different-aged children and adult subjects.

	Latencies (msec) ns	Amplitudes (μV) **
3 years	249.3 (± 18.1)	-32.0 (± 18.8)
4 years	237.5 (± 25.5)	-47.6 (± 27.3)
5 years	237.3 (± 19.8)	-29.2 (± 23.4)
8 years	231.7 (± 26.7)	-19.6 (± 16.4)
18-24 adults	248.5 (± 23.6)	6.9 (± 4.5)

ns: not significant ($P < .1$) ** significant $P < .01$

ANOVA (the analysis of variance).

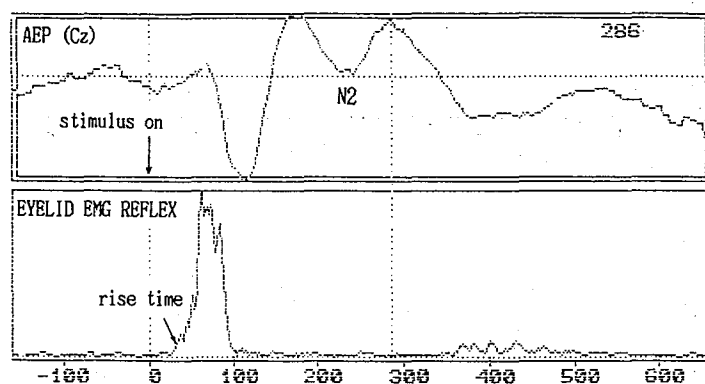


Fig. 1 The AEP wave form at Cz and eyelid EMG reflex elicited by startle acoustic stimuli.

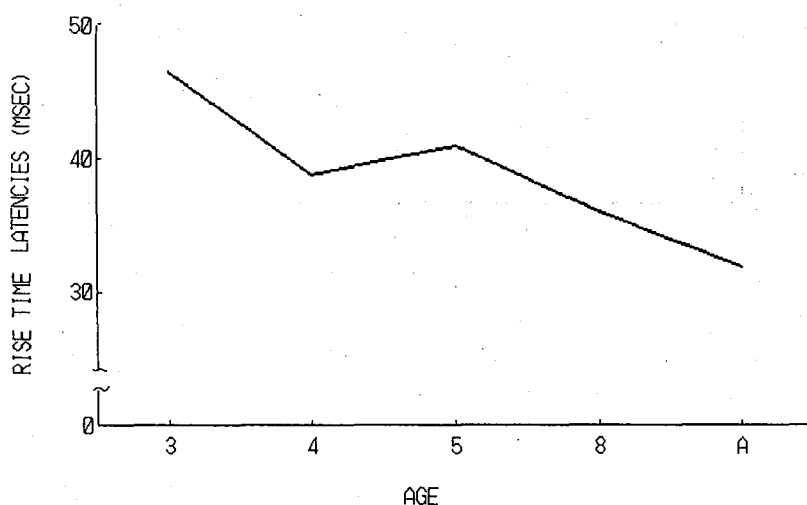


Fig. 2 The mean rise latencies of eyelid EMG reflexes for each age group.

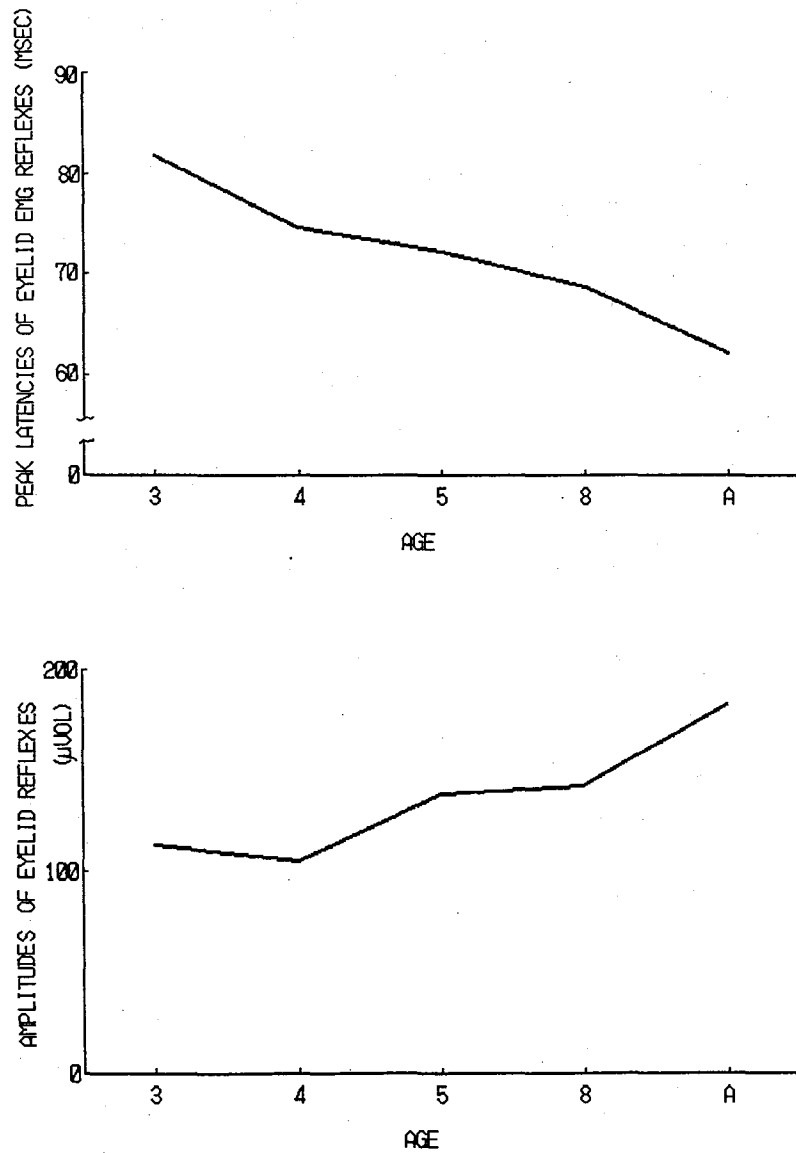


Fig. 3 The group averaged latencies and amplitudes of eyelid EMG reflexes for binaural auditory stimulation in children and adult subjects of different ages.

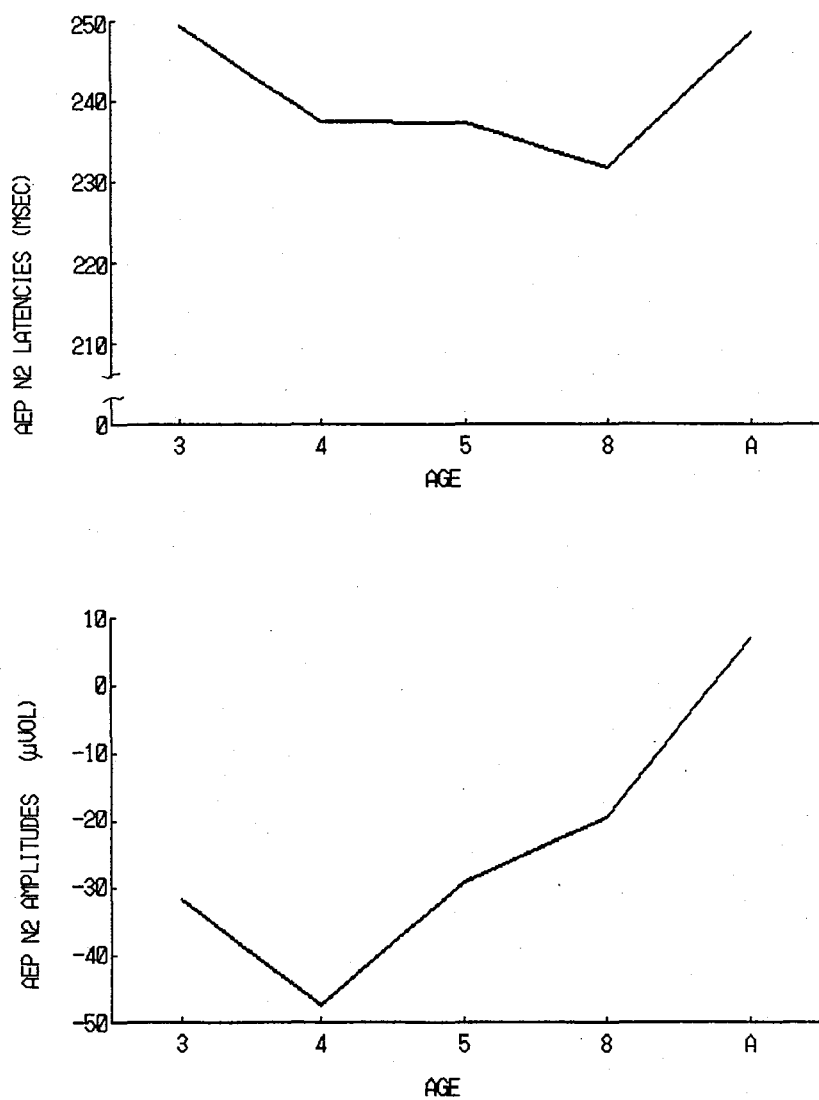


Fig. 4 The mean latencies and amplitudes of AEP N2 elicited by startle acoustic stimuli in children and adult subjects of different ages.

Discussion

This research investigated the developmental changes of AEP N2 elicited by startle acoustic stimuli in normal children as compared to normal young adults. Unfortunately, the neural generator and nature of this prominent negative component is not well known; nevertheless, this large electrical event must be important to cerebral function. Neural sources of the N2 have been proposed in cortical, limbic, diencephalic, and mesencephalic regions based on scalp topographic analysis, intracranial recording, and neuro-magnetic studies. The general assumption is that the multiple generators may contribute to the N2, as with the P3. Moreover, we do not as yet have a clear understanding of either the generators of EP late components or the physiological, psychological significance of N2 component, although the sources of early brainstem components have been elucidated by correlative investigations between animal experiments (Jewett, 1970; Buchwald & Huang, 1975; Caird et al., 1985; Legatt et al., 1986) and clinicopathological data in human patients (Starr & Hamilton, 1976; Stockard & Rossiter, 1977).

Recently, intracranial electrodes are sometimes inserted in the subthalamus, thalamus, and midbrain regions for stimulation in patients. Velasco and his colleagues (1986) recorded the surface and intracranially subcortical responses which included ventral (subthalamo-thalamic, orbitofronto-hippocampal) and dorsal (dorsothalamic striatal) structures simultaneously in the surface responses in parkinsonian and epileptic patients. Polarity of component C was inverted between dorsothalamic structures in parkinsonian patients and orbitofronto-hippocampal regions in epileptic patients. The results showed that the component C of subcortical response correlated to the N2 of vertex response. Yingling and Hosobuchi (1984) found the reversal polarity between subthalamic and dorsal thalamic sites for potentials correlating with surface N2, P3, and SW ERP, and suggested a deep midline thalamic, subthalamic, or midbrain source for N2, P3, and the SW. It would not be surprising to find that deep midline subthalamamic or thalamic sites contribute to surface ERPs (Dila, 1971; Skinner and Yingling, 1977; Yingling and Skinner, 1977; Knight, 1990). The P3 component does not seem to be generated by a serial sequential process linked to N2 generation, because several patients with an abnormal N2 show normal P3 latency and amplitude. R. T. Knight (1990) reported that temporoparietal lesions leave N2 intact, but abolish P3b and reduce P3a by more than 70%. This suggests that the cognitive processes engaged during P3 generation might occur in parallel to those involved in N2 generation. Based on known anatomical connections, it is conceivable that the temporoparietal junction region could modulate a subcortical P3 generator residing in the hippocampal or associative thalamic nuclei (Knight, 1990). In this regard, recent PET scan data have confirmed that focal cortical lesions can produce profound hypometabolism in distant anatomically connected subcortical or cortical structures (Metter et al., 1986; Knight, 1990). Two important investigations have recently been provided by both the UCLA and Yale University groups (Halgren et al., 1986; McCarthy et al., 1987). E. Halgren and his colleagues (Halgren et al., 1980) observed that the most prominent cognitive component, P3b, might result from activity in medial temporal lobes, especially hippocampal formation and amygdala. On the other hand, R. T. Knight et al. (1989) recorded P3s in subjects with discrete unilateral lesions of human posterior

association cortex, to assess the contribution of the temporal-parietal junction to auditory P3 generation. They suggested that auditory association cortex in the human temporal-parietal junction is critical for auditory P3 generation. The N2 may reflect the activity of neural circuit engaged during P3 generation in auditory association cortex in the temporal-parietal junction. However no consensus has emerged about either the behavioral process or the brain mechanism underlying N2 generation.

Since initial clinical ERP studies, some investigators have hopefully hypothesized that the ERP technique might become helpful in the characterization of different forms of diagnosis and developmental evaluation. The amplitude of the P3 wave in an auditory or visual target-detection task often remains smaller in amplitude in psychiatric patients, especially in schizophrenics even when they are attending to the stimuli. The ERP abnormalities in prolonged latencies and amplitudes were observed in patients with various kinds of dementia illnesses and in association with other neurological syndromes, beyond the age-dependent normal range, which might indicate the memory deficits due to posterior association cortex or limbic pathology (Pfefferbaum et al., 1984; Knight et al., 1989).

In the diagnosis and evaluation of patients with Alzheimer's disease, Parkinson's disease (Hansch et al., 1982), depression (Brown et al., 1982), schizophrenia and chronic alcoholism (Pfefferbaum et al., 1979, 1984), several laboratories have tried to confirm general reductions in ERP amplitudes and prolonged ERP latencies as compared with those of age-matched control subjects. However, these effects of the ERP abnormalities are not specific to the patients of each diagnosis group. In more sophisticated analysis to detect neuropathology, the P3 components did not significantly show a difference in the latency between the patients and controls (e.g. Slaets & Fortgens, 1984; Verleger, 1992). Moreover, other findings suggest that the ERP is generated by a neural system involved in orientation or encoding of environmental events. The most serious problem in using the ERP latency and amplitude for the developmental evaluation and diagnosis is the wide range of normal ERP latencies, and the variability unrelated to age is generally greater than the variability related to age within any age range, although the P3b latency consistently decreases or increases with increasing age. Another difficulty is that the ERP correlated more with the degree of global dysfunction on a sensory or cognitive biological basis than with any specific diagnosis. Thus, the ERP may correlate more closely with the degree of deviant electrophysiological responses of the global sensory or cognitive dysfunction. More specific sophisticated experiments (not an oddball paradigm) should be designed for any specific diagnosis.

R. Näätänen has proposed that the MMN represents a basic auditory sensory neural mechanism generated in the modality-specific auditory cortex. The distributions of N2 and negative missing stimulus potential may reflect the cortical activity within the secondary auditory and visual regions which is mediated by a bottom-up mode of sensory processing from the brain stem, whereas the late positive component (positive missing stimulus potential or P3b) is considered to derive principally from inferior-parietal association cortex. The scalp topograph of the P3 becomes more frontal in distribution, which may be related more to sensory processes than cognitive processes in infants. It is possible that this effect might be explained by assuming that the P3p is only gener-

ated in elderly subjects after a revision or update of information provided by the sensory evaluation. The latency of AEP P3b component decreases progressively as a function of age to reach adult values by about 18 years, and gradually increased in the study of normal subjects between 18 and 90 years (Ford et al., 1979a, 1979b; Goodin et al., 1978; Pfefferbaum et al., 1980). The developmental EMGs and ERPs elicited by startle acoustic stimuli did not show the same developmental courses. It suggests that these activities are organized by apparently different neural systems. Although a cogent reason for the ERP latency changes as a function of age remains unknown, these changes may show that the speed of information processing changes respectively with age (Courchesne, 1978; Bashore, 1990a, 1990b).

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