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Authors
Hetrick, William P
Sandman, Curt A
Bunney, William E
et al.

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Gender Differences in Gating of the Auditory Evoked Potential in Normal Subjects

William P. Hetrick, Curt A. Sandman, William E. Bunney, Jr., Yi Jin, Steven G. Potkin, and Margaret H. White

Central nervous system (CNS) inhibitory mechanisms hypothesized to "gate" repetitive sensory inputs have been implicated in the pathology of schizophrenia. The present study investigated gender differences in inhibitory gating of evoked brain responses to repeated stimuli in normal subjects (30 women and 30 men) using an auditory conditioning–testing paradigm. Pairs of click stimuli (S1 and S2) were presented with a 0.5 s intrapair and a 10 s interpair interval. The amplitudes and latencies of the P50, N100, P180 components of the auditory evoked response to the conditioning (S1) and test response (S2) were measured, and the gating ratios were computed (T/C ratio = S2/S1 * 100). The amplitudes to S1 were not significantly different between men and women at P50, N100, or P180. However, women had significantly higher amplitudes to S2 at P50 (p = 0.03) and N100 (p = 0.04). The T/C ratios for women were higher (i.e., less suppression of response to S2) for P50 (p = 0.08) and N100 (p = 0.04) compared to men. The results suggested that differences in auditory gating between men and women were not due to biological differences in the P50 and N100 generators but possibly to differential influence of inhibitory mechanisms acting on the generator substrates of these evoked responses.

Key Words: Auditory gating, gender, P50, event-related potentials

Introduction

The strength of inhibitory pathways in the central nervous systems (CNS) has been measured by the reduction in neuronal responsiveness to repeated stimulation (Eccles 1969; Sokolov 1963). Electroencephalographic (EEG) re-

sponses to repeated auditory stimulation are typically reduced and have been used to characterize inhibitory mechanisms acting on neuronal systems that give rise to evoked potentials (EPs; Davis et al 1966; Fruhstorfer et al 1970; Papanicolaou et al 1984; Roth and Kopell 1968). In a dual-click ("conditioning"–"test") paradigm, the relative decrease of the auditory P50 EP (also named P1) to repeated stimulation has been used as a measure of sensory gating (Adler et al 1982). "Both the first [conditioning] and the second [test] stimuli elicit responses, but the test response is the evidence, or 'test,' of the action of inhibitory or other gating mechanisms activated or 'con

From the Department of Psychiatry and Human Behavior University of California, Irvine, CA (WPH, CAS, WEB, YJ, SGP); and the Department of Psychology, California State University, Fullerton, CA (WPH, MHW).
Address reprint requests to: William Hetrick, Research 5A, 2501 Harbor Boulevard, Costa Mesa, CA 92626

ditioned' by the first stimulus" (Nagamoto et al 1989, p. 550).

Several reports have described gating of the midlatency, P50 auditory evoked brain response among normal subjects using the conditioning–testing paradigm (e.g., Freedman et al 1987a; Guterman et al 1992; Jerger et al 1992; Nagamoto et al 1989; Perlstein et al 1993; Schwartzkopf et al 1993; Waldo and Freedman 1986). However, it is the clinical application of this paradigm that has generated the most interest. An increasing number of clinical studies have described P50 gating abnormalities among schizophrenic individuals (Adler et al 1982; Baker et al 1987, 1990; Freedman et al 1983; Nagamoto et al 1989; Siegel et al 1984). In fact, abnormal auditory gating had been described as a "fixed trait" in schizophrenia (Freedman et al 1987b, p. 674) and is familially associated (Seigel et al 1984; Waldo et al 1991). Schizophrenics have higher conditioning–testing (C-T) ratios (e.g., amplitude of test response, S2, divided by the amplitude of the conditioning response, S1) compared to unaffected control subjects, indicating diminished auditory gating. It has been speculated that the inability to filter (or gate) sensory inputs underlies problems of perception and attention observed in schizophrenia, such as hyperalertness and poor selective attention (Venables 1964).

There are scattered reports in the literature suggesting the possibility of gender differences in the auditory P50 response. A comparison of P50 gating in manic, schizophrenic, and normal individuals indicated that women ($n = 22$; collapsed across patient groups and controls) showed significantly ($p = 0.01$) less suppression of the P50 wave compared to men ($n = 21$; Franks et al 1983). It was not clear in this study if the gender differences existed between the normal men ($n = 12$) and women ($n = 10$). In a life span study, it was reported that women ($n = 73$) had a higher mean amplitude response of the P50 to the first stimulus ($p = 0.05$) than men ($n = 90$), but there were no gender differences in P50 suppression (Freedman et al 1987a). A recent study of gating deficits in schizophrenia (Judd et al 1992) found that among younger subjects, "males had slightly larger P50 area [under the wave] responses than females" (p. 491) whereas "among older subjects, females had larger P50 area response than males" (p. 492). Gender differences also have been observed in sensorimotor gating of the acoustic startle reflex (Swerdlow et al 1993) and are related to differences in hormonal substrates (Swerdlow et al 1994). However, the source of gender differences in P50 gating is not clear. For example, hormonal fluctuations in menstruation ($n = 12$) do not appear to influence gating of the auditory evoked response (Waldo et al 1987).

The presence of gender differences in auditory gating has obvious implications for subject selection and gender matching between patient and comparison groups. The present paper investigated gender differences in CNS gating of the P50, N100, and P180 auditory evoked potentials in normal adults.

Methods

Subjects

Sixty subjects (30 men, 30 women) recruited from students and staff of University of California, Irvine, and the California State Developmental Research Institutes, Fairview, consented and completed the protocol. Female subjects were not tested at any particular time during their menstrual cycle and none of the subjects reported a history of psychiatric illness, substance abuse, neurological or audiological problems on a screening questionnaire. Ages ranged from 18 to 38 with a mean of 22.4 (SD 4.26) years for the men and 23.17 (5.64) for the women, and were not significantly different (pooled t test $= -0.59$, df $= 58$, $p = $ NS).

Conditioning–Testing Paradigm

The conditioning–testing paradigm consisted of a series of paired clicks ($n = 128$). The conditioning (S1) and testing (S2) stimuli were separated by 0.5 s with a fixed interpair interval (S1–S1) of 10 s. Click stimuli were 0.1 msec square-wave pulses generated by a Grass Click Tone Control Module (Model S10CTCM; Grass Instrument Co. Quincy, MA) and amplified to 84 dB SPL peak intensity as measured at the headphone cone (Bruel & Kjaer Precision Sound Level Meter, Copenhagen, Denmark type 2203 in linear, fast response mode). The clicks were presented through binaural headphones (Grass Instrument Co., Model 10H2S). White noise (62 dB SPL) generated by the Grass Click Tone Control Module was presented through a floor speaker in the test chamber to mask possible ambient noise. Testing sessions lasted approximately 22–25 min.

Electroencephalographic Recording Procedure

Testing was conducted in a dimly lit, electrically shielded, and sound-attenuating chamber while subjects reclined in a comfortable chair. The subjects were monitored continuously with an audiovisual system and were asked to keep their eyes closed during testing.

Monopolar recordings were made from gold cup electrodes filled with EC-2 creme (Grass Instrument Co., Quincy, MA) and placed according to the international 10–20 system at Cz and referenced to linked mastoids.

Eye movement artifacts were collected from monopolar leads placed at the left lateral canthus and suborbit. Subjects were grounded by a midforehead electrode. Electrode impedances were all below 5 kΩ before testing. Recordings were made by a modified NeuroComp electroencephalograph (EEG) (Newport Beach, CA) with analog filters at 0.8 and 200 Hz and gain of 20 K. Data were digitized at 400 Hz and stored off-line on a Intel 486 based IBM compatible computer. The EEG was collected in 1500 ms epochs from each channel, beginning 500 msec before S1, continuing for 500 msec to S2, and terminating 500 msec after S2. Each sweep consisted of 600 data points with 2.5 msec resolution.

Evoked Potential Reduction and Analysis

The single trial EEGs and electrooculogram (EOG) for each subject were digitally low-pass filtered at 100 Hz for the measurement of the P50 component of the auditory evoked potential (AEP) and bandpass filtered at 1–20 Hz for the measurement of N100 and P180. The filtered EEG records were then corrected for vertical and horizontal EOG (Gratton et al 1983, Miller et al 1988) and averaged within subject for each electrode site. This correction procedure has been used in previous investigations of AEP gating (Naber et al 1992; Perlstein et al 1993).

The amplitudes and latencies of the AEPs were collected with a computer assisted waveform scoring program. The averaged AEPs to S1 and S2 were simultaneously displayed to a computer monitor and scored by marking the component peaks. The algorithm used to define the peak of a component selected the most negative/positive point within the following latencies for the following peaks: P50 = 45–85, N100 = 70–120, P180 = 130–235. For the selection of S2 responses, additional constraints were that the P50, N100, and P180 latencies lie within 10, 25, and 40 msec, respectively, of the S1 peak latency. The amplitude (in μV) of the P50 peak was measured relative to the point of maximum deflection on the preceding negative peak, termed N40 here (Erwin and Buchwald 1986; Erwin et al 1991; Nagamoto et al 1989). N100 and P180 amplitudes were measured relative to the 50 msec prestimulus baseline average preceding each click (Jerger et al 1992). In some cases, no peaks were observed in response to S2, despite their obvious appearance at S1; this was interpreted as complete suppression and a peak amplitude of 0.01 μV was recorded to facilitate analysis (Jerger et al 1992; Schwartzkopf et al 1993). The waveforms (n = 60) were scored independently by two raters according to the preceding rules. Disagreements on the scoring of one P50, two N100, and two P180 responses were resolved by a third rater. Because peaks could not be
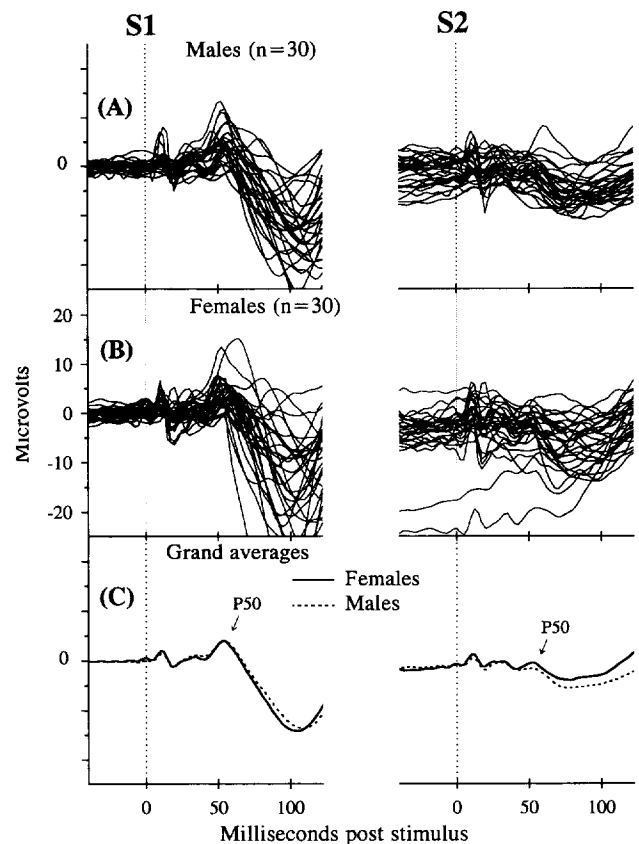

Figure 1. Averaged auditory EP waveforms (Cz) elicited by paired clicks (S1 and S2) for each (A) man and (B) woman, and (C) the grand averaged EPs. The mean reduction of the amplitude of the P50 response to S2 was significantly ($p = 0.03$) greater for men. (ISI = 500 msec, interpair interval = 10 sec; bandpass filter = 0.8–100 Hz for measurement of P50).

identified, N100 data for five subjects and P180 data for three were missing. For each AEP component, the peak amplitudes, latencies, and conditioning–testing ratios (C-T ratio = S2/S1 × 100) were calculated from averaged waveforms and stored for analysis.

Statistics

Analysis of gender differences among normals were conducted for P50, N100, and P180 amplitudes, latencies, and C-T ratios using the BMDP Statistical Software (Los Angeles, CA) unpaired t test program (3D). Welch's separate variances t test was used to test group differences when variances were not equal. If data distributions were skewed (as determined by Shapiro and Wilk's [1965] W statistic) and/or failed to meet the assumption of homogeniety of variance (as determined by Levene's [1960] test), the Mann-Whitney rank sum test was used.

Table 1. Amplitudes, Latencies, and T/C Ratios of P50, N100, and P180 for Men and Women

| | | S1 | | S2 | | T/C Ratio (S2/ |
		Latency	Amplitude	Latency	Amplitude	S1 × 100)
P50	M	58.25 ± 4.56	4.16 ± 2.52	55.85 ± 5.09	1.30 ± 1.46[a]	33.79 ± 33.55[b]
	F	57.51 ± 4.91	4.95 ± 3.00	55.52 ± 5.59	2.12 ± 1.37[a]	51.05 ± 41.87[b]
N100	M	107.63 ± 10.89	17.48 ± 6.97	88.13 ± 11.03	8.47 ± 4.04[c]	53.48 ± 31.47[d]
	F	105.63 ± 10.01	17.86 ± 8.76	93.00 ± 18.85	11.03 ± 5.11[c]	72.99 ± 38.68[d]
P180	M	190.03 ± 21.90	17.03 ± 7.22	179.08 ± 27.83	2.37 ± 3.09	15.90 ± 20.95
	F	189.47 ± 17.72	20.38 ± 9.63	169.11 ± 25.40	2.53 ± 5.00	14.42 ± 28.64

[a]Significantly different by Welch's separate variances t test, $t = -2.24$, df $= 57.8$, $p = 0.03$.
[b]Approached significant difference by Mann-Whitney rank sum test, $p = 0.08$.
[c]Significantly different by Student's t test, $t = -2.11$, df $= 55$, $p = 0.04$.
[d]Significantly different by Student's t test, $t = -2.05$, df $= 53$, $p = 0.04$.

Results

P50

The EOG corrected and averaged auditory evoked potentials for all men and women, and the grand averages are presented in Figure 1. The mean latencies (S1, $t = 0.61$, df $= 58$, $p = $ NS; S2, $t = 0.24$, df $= 58$, $p = $ NS, two-tailed) and amplitudes of the P50 responses to S1 ($t = -1.11$, df $= 58$, $p = $ NS) did not significantly differ between women and men (see Table 1). However, the
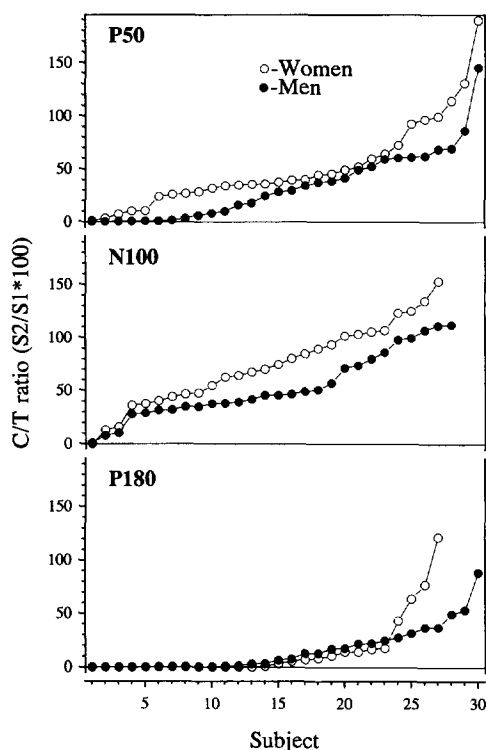

Figure 2. Testing/conditioning ratios of the P50, N100, and P180 responses for men and women plotted separately in ascending order. Ratio differences approached significance at P50 ($p = 0.08$) and were significantly different at N100 ($p = 0.04$).

mean P50 amplitude response to S2 was significantly larger for women ($M = 2.12 \pm 1.37$ SD) than men (1.30 $\pm$ 1.46; $t = -2.24$, df $= 57.8$, $p = 0.03$). The distribution and means of the T/C ratios (S1/S2 * 100) are presented in Figure 2 and show smaller ratios (i.e., greater gating) among men (33.79 $\pm$ 33.55) compared to women (51.05 $\pm$ 41.87). For example, seven of the eight subjects who had T/C ratios near zero (i.e., complete gating) and 13 of the 18 who had T/C ratios under 20 were men. Conversely, six of the seven subjects with ratios above 90 (i.e., very little gating or even augmentation of the S2 response) were women. A Mann-Whitney rank sum test determined that the T/C ratio differences between groups approached statistical significance ($p = 0.08$).

N100 and P180

The EOG corrected and averaged vertex waveforms for men and women are presented in Figure 3. There were no significant differences between men and women in the mean N100 latencies (S1, $t = 0.60$, df $= 56$, $p = $ NS; S2, $t \pm -1.21$, df $= 56$, $p = $ NS) or the mean N100 amplitudes to S1 (see Table 1; $t = -0.18$, df $= 53$, $p = $ NS). However, the mean N100 amplitude response to S2 was significantly larger for women (11.03 $\pm$ 5.11) than men (8.47 $\pm$ 4.04; $t = -2.11$, df $= 55$, $p = 0.04$). Women also had a significantly higher N100 T/C ratio (73.00 $\pm$ 38.68) than men (53.48 $\pm$ 31.47, $t = -2.05$, df $= 53$, $p = 0.04$; Fig. 2). No statistically significant differences were found at P180.

Discussion

The major finding of this study is that gender influenced gating of the auditory evoked potential in healthy, relatively young adults. Women had significantly higher mean amplitude responses of the P50 and N100 AEPs to the second (testing) click, and significantly higher N100 T/C ratios compared to men, indicating less gating (or neuronal
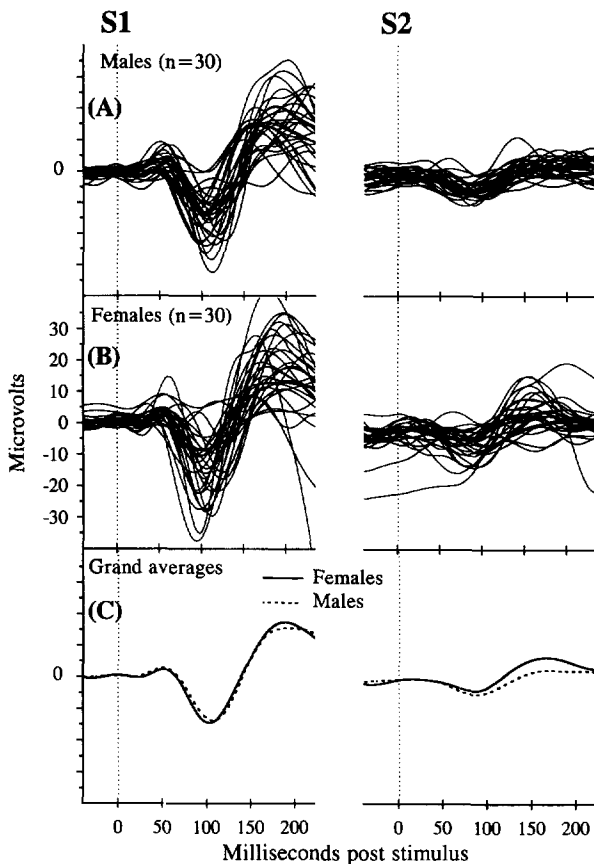
S1   S2

Figure 3. Averaged auditory EP waveforms (Cz) for each (A) man and (B) woman, and (C) the grand averaged EPs. The mean reduction of the amplitude of the N100 response to S2 was significantly ($p = 0.04$) greater for men. (Bandpass filter = 1–20 Hz for measurement of N100 and P180.)

inhibition to repeated stimulation). Because the averaged P50, N100, and P180 responses to the conditioning (S1) click were not significantly different between men and women, it appears that the gating differences are not related to neurophysiological differences in the generator substrates for these components. However, the significantly greater reduction of the P50 and N100 AEP components to repeated stimulation (i.e., S2) exhibited by men (and lower T/C ratios) suggested that the inhibitory mechanisms activated by the conditioning click are different in men and women.

The findings of the present investigation are consistent with the incidental findings of gender differences in P50 gating reported by Franks et al (1983). However, Freedman and colleagues (1987a) found that women had a higher mean P50 response to the conditioning stimulus (S1), but did not differ in suppression of the testing stimulus (S2). Judd et al (1992) reported that among "younger" adult subjects, men had slightly larger P50

responses, but among "older" adult subjects, women had larger P50 responses than men. Waldo et al (1987) did not find any gender effects on P50 gating. In contrast to the present P50 investigation, these studies had relatively small and/or heterogeneous samples (including schizophrenic subjects), which may have contributed to these equivocal findings. Aside from these select sampling differences and the focus on gender differences in the present study, the methods implemented in this investigation were consistent with those of previous studies of auditory gating. Furthermore Table 2 shows that the P50 data presented here are within the range, and are generally comparable to those reported in previous studies of auditory gating in normal subjects.

Nagamoto et al (1989) stated that a likely mechanism for inhibition, or suppression, of the P50 test response "is the activation of inhibitory neurons, such as the GABAergic neurons of the cerebral cortex, by the first stimulus" (p. 550). Excessive catecholamines (i.e., dopamine, epinephrine and norepinephrine) may mediate diminished suppression (Adler et al 1986, 1988). For example, administration of amphetamines (norepinephrine agonists) is associated with a loss of suppression in animals and was reversible by haloperidol, a dopamine blocker (Adler et al 1986; Bickford-Wimer et al 1990). A preliminary pharmacological intervention supported the hypothesis that nicotinic cholinergic neurotransmission is involved in auditory gating (Adler et al 1992). Attempts to define the neuroanatomical origins of the auditory P50 response have implicated the auditory cortex (Vaughan et al 1983; Wood and Wolpaw 1982; Reite et al 1988a, b), hippocampus (Bickford-Wimer et al 1990), and thalamus (Buchwald et al 1981; Hinman and Buchwald 1983; Erwin and Buchwald 1986, 1987). However, there are no known differences between men and women in these neuroanatomical structures or neuronal systems.

Gender has been shown to influence a variety of electrophysiological measures. It has been widely reported that adult women have larger brainstem and cortical evoked responses (e.g., Beaumont and Mayes, 1977; Buchsbaum et al 1974; Fein and Brown 1987; Halliday 1982; Michalewski et al 1980; Shagass et al 1972; Shearer et al 1992) and shorter EP latencies than men (e.g., Allison et al 1983; Fein and Brown 1987; Ikuta and Furuta 1982; Shagass et al 1972; Stockard et al 1979; Taylor et al 1990; Trune et al 1988). However, the factors that mediate electrophysiological differences between men and women are not well understood. Anatomical differences between men and women may underlie shorter EP latencies (Allison et al 1983; Houston and McClelland 1985; Trune et al 1988) as well as smaller EPs (Trune et al 1988), and it has been suggested that the functional organization of the cortex may underlie differences in EP source origins

Table 2. Studies of Auditory P50 Gating: Summary of Data Collected from Normal Subjects[a]

Authors	Year	No. subjects, gender	Mean age (years)	P50 AMP (S1; μV)	Mean T/C ratio (S2/S1 × 100)
Adler et al	1982	15 M	33.7	8.9	13.9
Franks et al	1983	12 M, 10 F	41.4	8.7	20.2
Siegel et al	1984	21 M, 14 F	36.5	~7.0	18.6
Waldo and Freedman	1986	21 M	na	5.6	24.6
Freedman et al	1987	90 M, 73 F	Men: 20.5	8.9	M&F: 35.8
			Women: 20.9	7.4	
Waldo et al	1987	12 M, 12 F	Men: ~26.0	5.0	34.0
			Women: 26.3	5.4	32.5
Kathmann and Engel	1990	9 M, 15 F	25.6	3.0	73.0
Boutros et al	1991	6 M, 4 F	28.5	4.1	~109.0
Naber et al[b]	1992	10 M, 10 F	27.4	7.6	57.4
Lamberti et al	1993	18 M, 10 F	26.7	3.4	~74.6
Schwarzkopf et al	1993	12 M, 8 F	26.7	2.5	48.4

[a]All studies used the C-T paradigm with 500 msec between S1 and S2, and 10 sec between pairs; P50 measured at Cz.
[b]Data reported are from session 1, block 1 (85 dB SPL).

(Baumann et al 1991). The extent to which anatomical and cortical orginizational differences between the genders contributed to the observed differences in auditory gating is not known. The effect of menstruation on the ERP has not been extensively investigated, but existing evidence suggests that P50 gating is not influenced by menstruation (Waldo et al 1987) and that reproductive hormones and steroids are not sole determinants of observed gender differences in the ERP (Buchsbaum et al 1974).

There are scattered studies of the effects of gender on phenomena conceptually linked to auditory gating (e.g., EP recovery cycle, distractability, vigilance, EP augmenting–reducing, etc.) but the experimental methods are varied, complicating clear interpretation. In contrast to the present aural findings, it has been reported that women, compared to men, have a reduced recovery amplitude to repeated visual stimuli (Lolas 1979) and showed less decline in cognitive efficiency when irrelevant visual cues were introduced (Guttentag 1973). Giambra and Quilter (1989) observed in a sensory vigilance task that women had slower reaction times to target stimuli and, among younger subjects (18–29 years), detected fewer targets than men. These effects may have been mediated by the differential arousal levels observed in the men and women (Giambra and Quilter 1989). Women may be more distractable than men in competing aural message paradigms (Halley 1975) and have less tolerance for loud tones than men (McGuinness 1974). Greater augmenting of the ERP

amplitudes to increasing intensity has been reported in women for auditory stimuli (Bruneau et al 1986), whereas no differences between the genders were found for visual stimuli (Cohn et al 1985).

The present findings of gender differences in the gating of the auditory EP warrant replication and further investigation. Concurrent assessment of conceptually related variables such as auditory gating, selective attention, vigilance, and/or arousal may further specify the nature of these differences. The present data indicate that the influence of gender, in addition to chronological age (Freedman et al 1987a; Papanicolaou et al 1984), must be considered in studies of auditory gating. However, the relevance of the observed gender differences to psychopathology is unclear because of reports that psychiatric illness appears to modify normal gender influences on cortical evoked potentials (Josiassen et al 1990; Shagass et al 1972).

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