Effect of Age on Sensory Gating of the Sleep State-Dependent P1/P50 Midlatency Auditory Evoked Potential

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The P1/P50 midlatency auditory evoked potential is a sleep state-dependent waveform present during waking and rapid eye movement (REM) sleep and absent during slow-wave sleep. The P50 potential was studied in normal male and female subjects of various ages including post-pubertal adolescents (12-19 yrs), young adults (24-39 yrs), middle-aged adults (40-55 yrs) and older adults (55-78 yrs). There were no statistically significant differences in the mean peak amplitude or mean peak latency of the P50 potential between males and females or between age groups. Using a paired stimulus paradigm, the degree of sensory gating of the P50 potential was tested at three different interstimulus intervals (ISIs), 250, 500 and 1000 msec. There were no statistically significant differences in the sensory gating of the P50 potential between males and females. However, there was a significant decrease in sensory gating of the P50 potential in the adolescent group compared to each of the other age groups at the 250 msec ISI, but not at the 500 or 1000 msec ISI. These results suggest the presence of decreased sensory gating in normal adolescents compared to normal, older age groups.

CURRENT CLAIM: The sleep state-dependent P1/P50 potential appears to show decreased sensory gating in normal adolescents compared to young and older normal adults.

The P1 or P50 potential is a midlatency auditory, click stimulus-evoked response recorded from the vertex that occurs at a latency of 40-70 msec in the human. The P50 potential has three main characteristics: 1) it is present during waking and REM sleep, but not during slow-wave sleep (Erwin and Buchwald, 1986a) (i.e., it is sleep state-dependent, occurring during cortical electroencephalographic (EEG) synchronization of fast oscillations, mainly 30-40 Hz, but not during cortical synchronization of slow oscillations (<15 Hz) (Steriade et al., 1996); 2) it is blocked by the cholinergic antagonist scopolamine (i.e., may be mediated, at least in part, by cholinergic neurons [Buchwald et al., 1991]); and 3) it undergoes rapid habituation at stimulation rates greater than 2 Hz (i.e., is not manifested by a primary afferent pathway, but perhaps by multi-synaptic, low security synaptic elements of the reticular activating system (RAS) [Buchwald et al., 1981; Erwin and Buchwald, 1986b; Hinman and Buchwald, 1983]). The P50 potential, but none of the earlier latency primary auditory potentials, thus diminishes and disappears with progressively deep stages of sleep and then reappears during REM sleep. This suggests that at least one generator of the P50 potential is functionally related to states of arousal, prompting the idea that the potential is generated, at least in part, by cholinergic mesopontine cell groups which are known to be preferentially active during waking and REM sleep, but inactive during slow-wave sleep (Buchwald et al., 1991; Erwin and Buchwald, 1986a, 1987; Garcia-Rill, 1997). Therefore, abnormalities in the manifestation of the P50 potential might indicate disturbances in the control of states of arousal.

The P50 potential has been shown to exhibit characteristic abnormalities, especially in sensory gating, in various psychiatric and neurological disorders, all of which are marked, and even presaged, by sleep disorders. A measure of sensory gating can be derived from the use of paired stimuli to test the level of habituation in the system being studied. Important seminal studies using the P50 potential in pathological conditions revealed that schizophrenic patients did not inhibit the response to the second click stimulus under conditions in which normal subjects do show such reduced responsiveness, i.e., there was a decrease in sensory gating (Adler et al., 1982; Freedman et al., 1983). Schizophrenic patients show reduced slow wave sleep, reduced REM sleep latency, exaggerated startle response and hallucinations (Braff et al., 1978; Caldwell and Domino, 1967; Feinberg et al., 1969; Jus et al., 1973; Zarcone et al., 1975). More recently, we reported the presence of decreased sensory gating of the P50 potential in a paired stimulus paradigm in another disorder marked by abnormalities of arousal and excitability, post-traumatic stress disorder (PTSD), in both male combat veterans and female rape victims (Gillette et al., 1995; Skinner et al., 1999). PTSD is also marked by such sleep abnormalities as increased REM sleep drive, hyperarousal, hallucinations and exaggerated startle response (Butler et al., 1990; Ross et al., 1989; Shalev et al., 1992). A similar decrease in sensory gating of the P50 potential was observed in patients in the late stages of Parkinson's disease (PD), suggesting that a sensory gating deficit can be present in these subjects (Teo et al., 1997). Interestingly, the decrease in sensory gating was normalized in
PD patients following bilateral pallidotomy for the relief of symptoms of the disease (Teo et al., 1998). The P50 potential also appears to undergo changes in amplitude as a result of other pathological states, being reduced in amplitude in patients with Alzheimer's disease (Buchwald et al., 1989), autism (Buchwald et al., 1988) and narcolepsy (Boop et al., 1994), which is characterized by daytime somnolence, cataplexy, sleep paralysis and hypnagogic hallucinations. In very general terms then, the P50 potential is upregulated (increased amplitude and/or decreased sensory gating) in disorders which are marked by upregulation of RAS output, and downregulated in disorders marked by decreased RAS output.

Significantly, the predominant age of onset of some of these disorders (schizophrenia, the anxiety disorder of panic attacks, narcolepsy, startle disease or hyperekplexia (Dooley and Andermann, 1989), etc., is post-pubertal, at a time during which sleep-wake cycle control is maturing (Roffwarg et al., 1966). Most of the research conducted on these populations, however, has utilized age-matched comparison groups of, on average, twenty years of age and older. Given that the P50 potential appears useful in assessing a number of pathological conditions, there is a surprising dearth of, and a great need for, normative data regarding its characteristics, especially soon after puberty. Previous studies targeting the development of the sleep state-dependent P50 potential described a decrease in sensory gating in adolescents (Freedman et al., 1987), a finding which later was not confirmed by the same group (Myles-Worsley et al., 1996). Other workers reported a gender difference in gating of the P50 potential in young subjects (Hetrick et al., 1996). All of these studies used a 500 msec interstimulus interval (ISI) in the paired stimulus paradigm. Our results suggest that a shorter ISI (250 msec) is more sensitive to differences in sensory gating of the P50 potential (Gillette et al., 1995; Skinner et al., 1999; Teo et al., 1997, 1998). The purpose of this study then, was to acquire such normative data on the P50 potential in various age groups using a cross-sectional design in order to assess whether there are characteristic differences in average peak amplitude, latency and/or degree of sensory gating (at a shorter ISI than previously studied) either between males and females or across age groups, as a function of maturational or developmental influences. Preliminary results have been presented (Rasco et al., 1998).

METHODS

Subjects

Male and female subjects, ages 12-78 yrs, were recruited either as age-matched controls for various projects under way in our laboratory or specifically for the present study. All were without history of neurological or psychiatric disorder and were medication free at the time of the recording, and for at least one month prior to recording. All subjects over the age of eighteen signed an informed consent, and those under the age of eighteen had their parents sign consent forms, which were approved by the institutional human research committee. Our final results included a total of fifty subjects. Twenty-five males (M) and twenty-five females (F) were divided into four different age groups: an adolescent population (CB-7 M, 6 F, 12-19 yrs), a young adult population (CC-6 M, 6 F, 24-39 yrs), a middle-aged adult population (CD-6 M, 7 F, 40-54 yrs), and an older adult population (CE-5 M, 5 F, 55+ yrs) for the purposes of the study, i.e., to assess possible maturational effects on the amplitude, latency and sensory gating of the P50 potential. All subjects were Caucasian.

We originally included a group (CA) of 7-10 year olds (5 M, 3 F) in our analysis. However, the data obtained from this age group were not used due to the fact that these children produced a large degree of high amplitude slow wave (theta and alpha-like) activity that obscured the P50 potential and made measurement unreliable or impossible. One possible explanation for such a phenomenon is that young people in this age range have been shown to produce a higher degree of slow wave activity (Gasser et al., 1988; Yordanova and Kolev, 1996) along with weakened inhibition of electrophysiological responses (Dustman et al., 1996), compared to adults. In addition, infants and children have a positivity of about 85-120 msec latency instead of the adult N100 (Courchesne, 1990). Since this potential does not habituate at low frequencies of stimulation, it is unlikely to be a developing P50 potential with a prolonged latency. Previous studies have included measures of positive polarity potentials with latencies of 100 msec in prepubertal subjects (Myles-Worsley et al., 1996), however, we could not be certain that such responses represented an incipient adult P50 potential and the data were discarded.

Recordings

Our techniques for recording and analyzing the P50 potential have been published previously (Skinner et al., 1999; Teo et al., 1997, 1998). Subjects were seated on a recliner in a well lit, sound-attenuating, shielded room with an observation window. Gold-plated surface electrodes were used with a water-soluble conducting paste, and electrode resistance was maintained at <5 Kohm. The P50 potential was recorded at the vertex (Cz) referenced to a frontal electrode (Fz). Eye movements (EOG) were detected using diagonally placed canthial electrodes, while jaw movements (EMG) were detected using a lead over the mentalis muscle referred to the chin. A subclavicular ground was used instead of mastoid or earlobe leads since the subjects wore headphones during the recording. Each channel was led to a Grass Instruments 5P11 amplifier with high resistance input stage. The gain and bandpass were as follows: P50 potential x100 K and 3 Hz-1 KHz; EOG x20 K and 3 Hz-1 KHz; and EMG x10 K and 30 Hz-1 KHz, with a 60 Hz notch filter on each amplifier. Fast Fourier Transform analysis showed that the P50 potential was not degraded by the notch filter.

Prior to the recording, headphones were placed on each subject and the hearing threshold for each ear determined using a Grass Instruments Audiostimulator STM10. The test stimulus was a rarefaction click of 0.1 msec duration set at least 50 dB
above threshold, usually 95-103 dB, as required. Testing consisted of three sessions presented in random order, each 5-7 min in duration, consisting of paired click stimuli at interstimulus intervals (ISI) of 250, 500 and 1000 msec. For each ISI, pairs of clicks were delivered once every 5 sec (previous studies have shown that stimulation at faster frequencies can lead to a decrement in the P50 potential amplitude) (Buchwald et al., 1991; Erwin and Buchwald, 1986a, 1986b, 1987) until 64 pairs of evoked potentials were acquired, averaged and stored by the computer. It should also be noted that recent studies strongly recommend the use of at least a 10 sec intertrial interval (Boutros and Belger, 1999). However, those studies employed a 4 msec duration stimulus instead of a 0.1 msec duration stimulus as in the present study. As will become evident below, the shorter duration stimulus we used allowed full response recovery in <2 sec intertrial interval (note slope of the sensory gating in all groups from 250 to 500 to 1000 msec in Figure 4, in which extrapolation indicated 100% response, i.e., full recovery, in <2 sec). Amplified signals were displayed on an oscilloscope for visual monitoring, digitized using a GW Instruments I/O module, averaged using Superscope software (GW Instruments) and stored on computer (Macintosh Quadra 650) disk and on magnetic tape using a Neurodata digitizer and a VHS tape recorder.

The subjects were studied between 10 a.m. and 1 p.m., with each recording session lasting approximately 45 min, including placement of electrodes. EEG signals which contained interference from EOG or EMG leads were excluded from the average. Every subject was recorded until 64 acceptable trials were averaged. If more than eight trials (12.5%) were excluded due to this criterion, in order to obtain 64 trials for the average, the subjects were removed from the study. The subjects were instructed to keep their eyes open and to count the number of trials presented as a means of maintaining vigilance. The counts of stimuli reported allowed comparison with those delivered, thereby enabling further assessment of the subject's alertness. Since the amplitude of the P50 potential is sleep state-dependent (Buchwald et al., 1991; Erwin and Buchwald, 1986a, 1986b, 1987), it was important to monitor vigilance with counts and by visual inspection through the observation window. Only subjects who reported >90% accuracy rate in stimulus counts were included in this study (n=50). No subject was actually eliminated from this study, since all of these normal individuals met our reporting criteria. However, this criterion remains standard in our lab and is essential when studying pathological populations with alertness problems, e.g., narcoleptic (Boop et al., 1994) or brainstem tumor patients (ongoing studies).

Data Analysis
The P50 potential, a midlatency auditory evoked potential, was identified as the largest amplitude positive wave occurring between 40 and 70 msec latency. The peak of the potential usually occurred between 45 and 60 msec latency. The P50 potential follows the brain stem auditory evoked responses (BAERs) occurring at <10 msec latency and the primary auditory cortical evoked potential (Pa) at 25-40 msec latency. Latency to peak and maximum amplitude were measured for each subject. The latency of the P50 potential induced by the first click stimulus of a pair was measured for each subject at each of the three ISIs tested. A mean latency for each subject was then calculated. The mean latency of each group was calculated as the mean of the mean latencies for all subjects in each group. Amplitude measurements were performed using the peak-to-peak method previously described (Erwin and Buchwald, 1986a, 1986b, 1987). Briefly, the amplitude from the preceding negativity (Nb), or from the preceding baseline if Nb were absent, to the peak of the P50 potential was measured. There were no obvious differences between groups in terms of the shape of the P50 potential or the presence or absence of Nb. The amplitude of the P50 potential induced by the first click stimulus of a pair was measured for each subject at each of the three ISIs tested. The mean amplitude for each subject was then calculated, and the mean of the mean amplitudes for each group was then derived. However, the criteria for measuring P50 potential amplitude could not be reliably applied to the pre-pubertal age group that was deleted from the study (CA, ages 7-11 yrs).

The degree of sensory gating was determined by calculating the amplitude of the P50 potential elicited by the second stimulus of a pair as a percent of the amplitude of the P50 potential elicited by the first stimulus of a pair. This takes advantage of the fact that the two stimuli are temporally proximate, such that changes in vigilance would affect both responses and their ratio, consequently, would remain constant. The percent sensory gating for each ISI was calculated for each subject and a mean for each gender and group of subjects then was determined. A higher percent is indicative of a decrease in sensory gating, i.e., there is a larger response to the second stimulus than normal.

One-way analysis of variance (ANOVA) was used to examine the possible effect of gender on the amplitude, latency and sensory gating of the P50 potential at each ISI across and within age groups. One-way ANOVA also was used to examine the effect of age on P50 potential amplitude, latency and sensory gating at each ISI between age groups. Post hoc analysis using a Scheffé test was performed on those variables found to be significant at p<0.05 level by the one-way ANOVA.

RESULTS

Subjects
One-way ANOVA showed that males and females did not differ significantly in age across or within the four age groups studied. Across age groups, the average age (mean ±SE) of the total number of male subjects (n=25), which was 39±4 yrs, was not statistically different from that of the total number of female subjects (n=25), which was 40±4 yrs. Within each age group, the average age of males (M) did not differ statistically from that of females (F), as follows: Group CB (M=16±1 yrs,
F=17±1 yrs); Group CC (M=29±2 yrs, F=30±2 yrs); Group CD (M=46±2 yrs, F=46±2 yrs); and Group CE (M=70±3 yrs, F=67±3 yrs). One-way ANOVA, as would be expected, indicated that there were statistically significant ($F_{3,45}=234.9$, $p<0.0001$) age differences between the four age groups studied. Mean ages of the four groups were as follows: Group CB=16±1 yrs; Group CC=30±2 yrs; Group CD=46±2 yrs; and Group CE=69±3 yrs. A Scheffé post hoc comparison showed that each age group was significantly different from the others at the $p<0.01$ level of significance.

**Gender Effects on Amplitude, Latency and Sensory Gating Measures**

There were no statistically significant differences in peak amplitude measures between males and females across age groups. The mean (±SE) peak amplitude of the twenty-five males was 1.8±0.2 µV, while that of the twenty-five females was 1.8±0.2 µV. One-way ANOVA also indicated that males and females did not differ significantly in terms of amplitude measures within age groups. Mean amplitude measures in µV for males and females within groups were as follows: Group CB (M=1.8±0.4, F=1.1±0.3); Group CC (M=1.3±0.3, F=1.6±0.3); Group CD (M=1.9±0.5, F=2.5±0.5); and Group CE (M=1.9±0.3, F=2.5±0.6). Figure 1A is a graph of the mean amplitudes of both males and females in each age group.

Similarly, one-way ANOVA showed no statistically significant differences between males and females in peak latency measures across age groups. The mean (±SE) peak latency for the males was 48±1 msec, while that of the females was 48±1 msec. ANOVA also indicated that latency did not vary as a function of gender within age groups. Mean latency measures in msec within age groups were as follows: Group CB (M=47±4, F=48±3); Group CC (M=51±2, F=48±1); Group CD (M=47±1, F=49±2); and CE (M=47±1, F=49±1). Figure 1B is a graph of the mean latencies of both males and females in each age group.

We found no statistically significant gender effects on sensory gating of the P50 potential at any of the three ISIs tested, either across or within age groups. Results in terms of percent sensory gating at each ISI for males versus females across all age groups were as follows: 250 msec ISI (M=28±13%, F=27±12%); 500 msec ISI (M=41±13%, F=39±15%); and 1000 msec ISI (M=66±16%, F=90±19%). Percent sensory gating was not statistically different in males versus females within age groups at the 250 msec ISI, as follows: Group CB (M=58±15%, F=55±15%); Group CC (M=11±11%, F=17±11%); Group CD (M=7±4%, F=22±7%); and Group CE (M=32±9%, F=15±4%). Percent sensory gating results were not statistically different across sex within age groups for the 500 msec ISI: Group CB (M=57±17%, F=38±22%); Group CC (M=40±11%, F=38±13%); Group CD (M=25±11%, F=48±7%); and Group CE (M=39±10%, F=31±16%). Finally, sensory gating results were not statistically different across sex for the 1000 msec ISI: Group CB (M=79±20%, F=99±25%); Group CC (M=52±10%, F=83±20%); Group CD (M=52±20%, F=90±16%); and Group CE (M=84±15%, F=89±17%). In summary, we found that none of the variables studied, namely peak amplitude, latency and sensory gating, varied as a function of gender either across or within age groups.

**Age Effects**

Using one-way ANOVA, we found that neither amplitude nor latency varied significantly across age groups. The mean (±SE) peak amplitudes for the four age groups (with combined male and female subjects) were: Group CB=1.5±0.4 µV; Group CC=1.4±0.3 µV; Group CD=2.2±0.5 µV; and Group CE=1.9±0.4 µV. One-way ANOVA, as would be expected, indicated that there were statistically significant ($F_{3,45}=234.9$, $p<0.0001$) age differences between the four age groups studied. Mean ages of the four groups were as follows: Group CB=16±1 yrs; Group CC=30±2 yrs; Group CD=46±2 yrs; and Group CE=69±3 yrs. A Scheffé post hoc comparison showed that each age group was significantly different from the others at the $p<0.01$ level of significance.
CE=1.9±0.4 µV. Mean (±SE) peak latencies for the groups were: Group CB=48±3 msec; Group CC=49±2 msec; Group CD=48±1 msec; and Group CE=48±1 msec. However, one-way ANOVA indicated that sensory gating varied significantly as a function of age at the 250 msec ISI (F^2_{3,46}=7.85, p<0.0002). The mean (±SE) percent sensory gating at the 250 msec ISI was 57±10% for the adolescent Group CB compared to 14±7% for Group CC, 15±5% for Group CD, and 24±6% for Group CE. Post hoc analysis using a Scheffé comparison indicated that Group CB (12-19 yrs) differed significantly from the CC and CD age groups at the p<0.01 level and from the CE group at the p<0.05 level. The latter three age groups did not differ significantly from each other. Figure 2 includes representative recordings from individuals in each age group showing the manifestation of the P50 potential following each stimulus of a pair at the 250 msec ISI. Note the marked decrease in amplitude of the P50 potential following the second stimulus in each of the older subjects (lower recordings), but not in the adolescent subject (top recording). One-way ANOVA showed no significant differences in P50 potential sensory gating between age groups at the two longer ISIs. At the 500 msec ISI, percent sensory gating was 48±13% for Group CB, 39±8% for Group CC, 36±7% for group CD, and 35±9% for Group CE. Percent sensory gating at the 1000 msec ISI was 91±15% for Group CB, 67±12% for Group CC, 72±13% for Group CD and 87±11% for Group CE. Figure 3 shows the grand averages of the 250 msec ISI paired stimulus paradigm of P50 potential recordings for the entire population of adolescents (12-19 yrs) and their closest age group, young adults (24-39 yrs), which were similar to the two older age groups. Figure 4 is a graph of the percent sensory gating of the P50 potential of each age group across the three ISIs tested. ** indicates a significant (p<0.0002) difference from the young adult group, while the group of older adults is significantly (p<0.0002) lower than the young adults. The graph also shows that the percent sensory gating is significantly higher in the adolescent group compared to the young adults at the 250 msec ISI.
group at each of the three ISIs tested. In summary, results showed a significant decrease in sensory gating at the 250 msec ISI for the adolescent group compared to each of the other age groups. No significant differences were evident at the 500 or 1000 msec ISIs. Table 1 summarizes these results and presents a breakdown of the mean and standard error of the percent sensory gating for each age group divided by sex for each ISI.

### DISCUSSION

The main findings reported herein suggest that the amplitude and latency of the sleep state-dependent P1/P50 midlatency auditory evoked potential are stable after puberty and into adulthood. However, sensory gating of the potential (using a paired stimulus paradigm and shorter ISI than previously tested) was significantly decreased in post-pubertal adolescent subjects compared to young, middle-aged and older adults. Since the P50 potential is sleep state-dependent, this finding suggests that there is a difference in the control of states of arousal in the adolescent group tested. Previous studies on the development of the P50 potential reported a delay in maturation of sensory gating in adolescents (Freedman et al., 1987), while a subsequent study failed to find a difference in sensory gating in children and adolescents compared to young adults (Myles-Worsley et al., 1996). Paradoxically, our findings are in agreement with both of these studies. On the one hand, we found a reliable decrease in sensory gating in adolescents, but only when we used a shorter ISI (250 msec) than that used in these two studies (500 msec) (Freedman et al., 1987; Myles-Worsley et al., 1996), therefore supporting the main conclusion of the earlier investigation. On the other hand, our results using the longer (500 msec) ISI showed that there was no statistical difference between adolescents and older age groups when assessing sensory gating of the P50 potential. Our previous results on patients with PTSD (Gillette et al., 1995; Skinner et al., 1999) and PD (Teo et al., 1997, 1998) had demonstrated that the shorter ISI was more sensitive in revealing decreased sensory gating of the P50 potential, while the present results suggest that the shorter ISI also may be more sensitive to developmental factors which may affect sensory gating.

One question that arises is, why does a difference in sensory gating arise at the 250 msec ISI and not at the longer ISIs? Previous studies have suggested that it is likely there are different neuronal mechanisms operating at various ISIs that contribute to sensory gating (Nagamoto et al., 1991). While effects at very short intervals (<150 msec) can be explained by membrane and synaptic mechanisms, sensory gating at longer intervals may be due to activation of multisynaptic afferents, possibly from areas such as the reticular formation and the nonspecific thalamic nuclei (Nagamoto et al., 1991). More recently, it has been suggested that sensory gating is a multistage operation and part of a complex multicomponent system (Boutros and Belger, 1999). These authors also suggest that deficits of different aspects of sensory gating could lead to different psychopathologic manifestations. The present findings, therefore, suggest that there is a difference in sensory gating in adolescents, but only in mid-range (250 msec vs. later) components, an effect which disappears in early adulthood. We do not know which neuronal mechanisms might be differentially active at this interval, but future research may be able to pinpoint which of these components is affected during adolescence.

Our present results do differ from those of Hetrick et al. (1996), in that we found no statistical gender difference in any of our measures, especially in P50 potential sensory gating. That study employed a single ISI (500 msec) and found percent sensory gating to be 34±34% in males and 51±42% in females, whereas our results using the same ISI were 41±32% for males and 39±35% for females of all age groups combined. If we consider male versus female sensory gating at the 500 msec ISI for the different age groups (Table 1), sensory gating was very similar (less than 10% difference in the means) in the young adult (CC) and older adult (CE) groups, but was numerically decreased (about 20% or more difference in the means) in males in the adolescent (CB) group and in females in the middle-aged adult (CD) group. Nevertheless, none of these differences reached statistical significance, probably due to the variability (standard deviations) in the populations. Perhaps, a larger population than that employed in our studies would yield a gender difference similar to that reported by Hetrick et al. (1996), especially in the middle-aged adult (CD) group at the 500 msec ISI. However, using the more sensitive 250 msec ISI, the mean percentages were very similar between genders in the younger groups (CB and CC), and tended to differ more in the older groups (CD and CE). The difference between the two studies may, therefore, have arisen as a result of differences in the subject population, perhaps in a more extensive representation of middle-aged adult females than in our study, or the presence of subjects with occult anxiety in the samples of previous studies.
Development

Recent work on electrophysiological measures of inhibition suggest that children do not inhibit or dampen responses to sensory stimuli as effectively as adults (Dustman et al., 1996). Studies of the startle response have shown that infants (6-24 weeks of age) (Graham et al., 1981) and preschool children (Ornitz et al., 1986, 1991) show decreased sensory gating to pre-stimulation-induced startle compared to adults. However, 8-year olds appear to have similar sensory gating of the startle response to young adults (Ornitz et al., 1986, 1991), but these groups were not compared to adolescents. In general, inhibition appears to exert an increasingly stronger role in children and adolescents as they mature to adulthood. This age-related increase in inhibition may be associated with frontal lobe maturation (Bjorklund and Harnishfeger, 1990; Dempster, 1992). The frontal lobes appear to exert inhibitory control over the RAS (Campbell et al., 1969; Skinner and Yingling, 1977) and they do not appear to fully mature until adolescence (Dempster, 1992; Lynn and Compton, 1966). This could account for the decreased sensory gating of the P50 potential, which is probably generated by elements of the RAS (Buchwald et al., 1981, 1991; Erwin and Buchwald, 1986a, 1986b) in adolescents compared to young, middle-aged and older adults. Given these findings, it is not surprising that developmental disturbances during adolescence could easily result in disorders which manifest sleep-wake abnormalities and deficits in arousal, sensory gating and the like later in life.

What could be the mechanisms at play behind such deficits? There is a reorganization of the sleep-wake cycle at this time, the proportion of slow wave sleep decreasing by 25-30% (Roffwarg et al., 1966) and a 75% decrease in delta amplitude (Feinberg et al., 1977). In addition, both PET and SPECT studies show a decrease in frontal blood flow between 15 and 19 years of age before reaching adult levels (Chiron et al., 1992; Chugani et al., 1987). It is during adolescence that a significant degree of synaptic pruning, especially in the frontal lobes, occurs after the exuberant growth of infancy (Huttenlocher, 1990). Disturbances in synaptic elimination during adolescence have been proposed to cause schizophrenia (Feinberg, 1982), a disease with mostly post-pubertal onset and marked by decreased sensory gating of the P50 potential (Adler et al., 1982; Freedman et al., 1983). Additionally, we have proposed that disorders which result in overactivity of the RAS should lead to decreased glucose utilization/blood flow in the frontal lobes, thereby inducing "hypofrontality" such as is evident in schizophrenia, anxiety disorders, PD, depression, etc. (Garcia-Rill, 1997; Reese et al., 1995). The evidence for this proposal includes animal studies which show that decreased glucose utilization is induced in frontal areas after prolonged activation of the RAS (Gonzalez-Lima and Scheich, 1985), and the fact that positron emission tomography studies have found that decreased blood flow in frontal lobes occurs normally during RAS-mediated REM sleep (Maquet et al., 1996). The P50 potential appears to be generated, at least in part, by cholinergic neurons of the posterior midbrain (Buchwald et al., 1981, 1991; Erwin and Buchwald, 1986a, 1986b; Garcia-Rill, 1997; Reese et al., 1995), which are known to generate REM sleep events (Steriade and McCarley, 1990; Steriade et al., 1991). Therefore, overactivity (or, more accurately, disinhibited activity) in the cholinergic arm of the RAS could produce such symptoms as a sensory gating deficit, hyperarousal, hypervigilance, increased REM sleep drive, and REM sleep intrusion into waking (i.e., hallucinations) (Garcia-Rill, 1997; Reese et al., 1995). While these symptoms are not characteristic of adolescence, the results reported herein suggest that there is an inclination towards decreased sensory gating during adolescence which, in the absence of appropriate maturational control or in the presence of insult or disturbance, could facilitate the onset of life-long arousal, attentional and sleep-wake disorders post-pubertally (e.g., schizophrenia, narcolepsy, panic attacks, startle disease, etc.). Much evidence is needed to substantiate the suggestions made above, especially further studies using the P1/P50 potential and, perhaps, a similar measure of arousal, the startle response.

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