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Stability of P50 auditory sensory gating during sleep from infancy to 4 years of age

Sharon K. Hunter[a], **Sabreena J. Gillow**[b,1], and **Randal G. Ross**[a,*]

Randal G. Ross: randy.ross@UCDenver.edu

[a]Department of Psychiatry, University of Colorado Denver, Aurora, CO, USA

[b]School of Medicine, University of Colorado Denver, Aurora, CO, USA

Abstract

The stability of cerebral inhibition was assessed across early childhood using a paired-click auditory sensory gating paradigm. The P50 ERP was measured during REM (or its infant analogue, active sleep) and NREM sleep in 14 children at approximately 3 months of age and again at approximately 4 years of age. Evoked response amplitudes, latencies, and the S2/S1 ratio of the amplitudes of the evoked responses were compared between the two visits. Significant reliability was found for the S2/S1 ratio (r = .73, p = .003) during REM but not non REM sleep (r = −.05, p = .88). A significant stimulus number by sleep stage interaction (F (1,12) = 17.1, p = .001) demonstrated that the response to the second stimulus decreased during REM but not NREM sleep. These findings suggest that this measure is stable during REM sleep across early childhood, is not affected by age, and is sleep-state dependent. P50 sensory gating is a biomarker which, if used properly, may provide a mechanism to further explore changes in the developing brain or may help with early screening for psychiatric illness vulnerability.

Keywords

Infant; Sleep; Auditory sensory gating; P50

1. Introduction

Infant and early child brain development and functioning are reflected in event-related potentials (ERPs), brain responses generated to incoming sensory stimuli. This approach is especially effective for use with infants and young children since data can be acquired passively and can be used to study the subtle capacities and functional differences often before behavioral measures can be utilized (Ceponiene et al., 2012; Hunter, Corral, Ponicsan, & Ross, 2008) and before the onset of clinical symptomology (Kisley, Olincy, & Freedman, 2001; Molfese, 2000; Sharma, Purdy, Newall, Wheldall, & Beaman, 2007).

*Corresponding author at: Department of Psychiatry, School of Medicine, University of Colorado Denver, 13001 E. 17th Place, Campus Box F546, Aurora, CO 80045, USA. Fax: +1 303 724 6207.
[1]Present address: Department of Neurology, Rush University Medical Center, Chicago, IL, USA.

Appendix A. Supplementary material: Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandc.2014.12.004.

However, for an ERP measured in early childhood to be an effective biomarker for later outcome, one must demonstrate that the measure is present and reliable across early development, the effects of state-dependency and age are either not present or can be accounted for, and the parameter is associated with the particular psychopathology of interest (Freedman et al., 2002; Lewis & Levitt, 2002; Ross, Kisley, & Tregellas, 2005).

One potential biomarker of cognitive is the inhibition of the mid-latency auditory ERP, P50. When evoked in response to repetitive pairs of auditory stimuli, while there is not universal agreement (Jin et al., 1998), this measure of cerebral inhibition is often conceptualized as reflective of an individual's ability to filter out irrelevant information (Kisley, Noecker, & Guinther, 2004). In adults, the P50 is a positive-going wave peaking at approximately 50 ms after stimulus presentation; in infants the latency is closer to 65–70 ms (Kisley, Polk, Ross, Levisohn, & Freedman, 2003). Despite the difference in latency, the evoked wave retains the term P50 to maintain consistency with adult reports. The amplitude of the P50 wave following the second click (S2) is divided by that of the P50 wave to the first click (S1), producing a S2/S1 ratio. Lower ratios are evidence of sensory gating; higher ratios reflect of diminished sensory gating. Approximately 80% of healthy adults have an S2/S1 ratio of less than 0.40 (Adler et al., 1982).

Diminished auditory sensory gating has been identified in a number of disorders in which patients have difficulty ignoring irrelevant sensory stimuli, such as schizophrenia (Siegel, Waldo, Mizner, Adler, & Freedman, 1984), bipolar disorder (Olincy & Martin, 2005), attention deficit-hyperactivity disorder (Freedman et al., 2002; Olincy, Ross, Harris, & Freedman, 1999), lower IQ aut-ism (Orekhova et al., 2008) post-traumatic stress disorder, panic disorder (Ghisolfi et al., 2006; Gillette et al., 1997) and Parkinson's disease (Teo et al., 1997). For schizophrenia, approximately half of an affected individual's unaffected relatives also exhibit deficits in sensory gating, suggesting P50 sensory gating as not only a marker of disease but also a marker of heritable vulnerability to disease (Siegel et al., 1984). Diminished P50 auditory sensory gating has also been identified in infants with a parent with psychosis, a mother with an anxiety disorder, or with prenatal exposure to tobacco, supporting the potential of P50 sensory gating to act as a biomarker of more general risk for psychopathology that extends into infancy (Freedman et al., 2002; Hunter, Kisley, McCarthy, Freedman, & Ross, 2011).

One obstacle to measuring P50 sensory gating is its state dependency. Diminished sensory gating has been demonstrated in individuals under acute stress (Freedman et al., 2002; Johnson & Adler, 1993; White & Yee, 2006) even if they have previously demonstrated intact sensory gating. This loss appears to be due to the increase in central norepinephrine release in response to the stressor (Adler et al., 1990; Kisley et al., 2001; Stevens, Meltzer, & Rose, 1993; White & Yee, 2006). State dependency may be particularly problematic for studies involving infants and children who often experience stress in new settings.

One potential method for standardizing state is to measure P50 gating during sleep. Kisley et al. (2001) demonstrated that P50 and related components were identifiable in most adults during all stages of sleep. Correlations were strong between sensory gating ratios obtained during wakefulness and REM sleep; however, sensory gating recorded during NREM sleep

was not correlated with results from either wakefulness or REM sleep. Subsequent research (Milner, Cuthbert, Kertesz, & Cote, 2009) similarly reported the presence of the P50 and associated waveforms in all stages of sleep, but suggested that inhibition of the evoked response to the second stimulus during Stage 2 NREM sleep may be absent. Amplitudes of the evoked responses during NREM also may be age dependent although the data are conflicting as to whether the result is an increase or decrease with age (Erwin & Buchwald, 1986; Shucard, Shucard, & Thomas, 1987). These results suggest that, in adults, wakefulness and REM sleep are the optimal states to assess P50 sensory gating, providing similar results. Little is known about the effect of sleep state or age on P50 sensory gating in young children.

Previous work has verified that, like adults, REM sleep is a favorable state in which to measure P50 sensory gating in infants: movement artifacts are reduced (Kisley et al., 2003), and ratios measured during REM sleep are stable when reassessed weeks later. This report expands on the effort to evaluate P50 sensory gating as a biomarker useable in young children by (a) examining its stability across early childhood development and (b) determining the state-dependency of P50 sensory gating during different stages of sleep.

2. Method

2.1. Participants

Fourteen preschool children (64% female, 79% Caucasian Non-hispanic) from a large metropolitan area and who were between 45 and 48 months (approximately 4 years) of age were studied. This sample followed to 4 years of age is a subset of larger sample examining the relationship of P50 sensory gating during REM sleep in infants to maternal psychiatric illness and nicotine use; the original sample was recruited via a mailing through a state vital statistics birth registry as described elsewhere (Hunter et al., 2008; Hunter et al., 2011). The fourteen participating children included an initial child born in June 2005 plus all children born between July 1 and September 1, 2005; thirteen of eighteen children within this birth range (72%) agreed to participate. While not a criteria for recruitment, maternal psychiatric history had assessed when the child was an infant and is a best estimate after completion of a structured interview (First, Spitzer, Gibbon, & Williams, 2002); diagnoses were divided into lifetime and those active during pregnancy. Nicotine use was based on self-report. Lifetime diagnoses which effected more than one mother included major depression (n = 6, 43%), an anxiety disorder (n = 6, 43%), alcohol or cannabis abuse (n = 3, 21%), and an eating disorder (n = 3, 21%); four mothers (29%) had no lifetime history of an Axis I psychiatric disorder (the percentages add up to greater than 100% because psychiatric comorbidity, particularly between anxiety and depression, is common). The rates for anxiety disorders or depression may appear high, but are consistent with what is found in general population female samples of childbearing age when structured diagnostic interviews are utilized (Moffitt et al., 2007). Anxiety is commonly chronic and all 6 women with a lifetime history of anxiety experienced at least some anxiety symptoms during pregnancy; only 1 woman (7%) experienced a major depression during pregnancy, this woman also experienced anxiety symptoms. No substance use disorders were active during pregnancy and none of the women reported pre-pregnancy or pregnancy tobacco use. The mean gestational duration

was 278 days (range 260–288 days). No child was born premature (less than 37 weeks gestational age). All children were medically healthy. No information about maternal mental health or tobacco use was obtained at the 4-year-old visit. The P50 sensory gating paradigm had been completed on all participants when the children were approximately 3 months post-conceptual age (mean_s.d. 14.4 ± 3.8 weeks).

2.2. Procedure

A local institutional review board approved all procedures involving human subjects, and parents gave written informed consent.

2.2.1. Infant visit—Parents were asked to bring their infant into the laboratory at a time when they would normally nap. After feeding and electrode placement, infants were encouraged to sleep by whatever method the parent felt was most likely to succeed (e.g. laid quietly in bed, rocked in mother's lap, swung in a motorized swing, etc.). If an infant was unable to fall asleep or did not sustain sleep long enough for successful recording, the parent and infant were asked to return on another day for an additional attempt.

2.2.2. Preschool visit—Many preschoolers reduce or eliminate daytime sleeping around the age of four, therefore participants were admitted for an overnight stay to a pediatric clinical research center at a local children's hospital. In addition to the researcher, one parent remained in the room with the child overnight. Because the longest period of REM sleep occurs in the early morning hours, data collection began at approximately 1 a.m. and continued until 6 a.m.

2.2.3. Electroencephalographic recordings—Ag/AgCl electrodes (Grass; West Warwick, Rhode Island, USA) filled with Ten20 conductive paste (DO Weaver; Aurora, Colorado, USA) were attached to the sleeping child with adhesive medical tape. Electroencephalogram (EEG) and auditory evoked potentials were recorded from the vertex of the scalp (Cz) referenced to the right mastoid. For aid in sleep staging, bipolar electrooculogram (EOG) was recorded from electrodes directly superior and lateral to either the left or right eye; submental electromyogram (EMG) was also recorded. Times of movement, changes in breathing and environmental events were also noted. Signals were recorded using NuAmps (Neuroscan Labs, Sterling, Virginia, USA). EEG signals were filtered between 0.05 and 100 Hz; EOG signals were filtered between 1 and 200 Hz; and EMG signals were filtered between 1 and 200 Hz. Sampling rate occurred at 1000 Hz. Stimulus presentation and recording began when the electrode impedances were below 10 kΩ. Paired 50 ms clicks with a 500 ms interstimulus interval were presented every 10 s in an otherwise quiet room through two speakers positioned on either side of the bed at a distance of .50 m from each ear. Volume was adjusted so that each click was at 85-dB sound pressure level at the ear. Recording continued while the child remained asleep, yielding 45–90 min of recorded data for infants and several hours of recorded data at 4 years of age. Methods for infant P50 sensory gating assessment have been previously described (Hunter et al., 2008; Kisley et al., 2003).

Sleep state was identified offline by visual inspection of the continuous recording in 20-s epochs. REM sleep or active sleep (the infant equivalent of REM) was identified by the presence of rapid eye movements obtained by the EOG, low amplitude in the EMG, and low amplitude high frequency in the EEG. NREM sleep was identified by the absence of rapid eye movements as obtained by EOG, increased amplitude in the EMG, and the presence of sleep spindles normally found during Stage 2 sleep. The amplitude of the EEG during Stage 3 and Stage 4 sleep make identification of the P50 difficult; therefore, data from these stages were not analyzed.

For the preschoolers, 20-min periods of identified REM and NREM sleep were identified and used in analyses. The REM period consisted of the first 20 min of the longest recorded REM cycle. Twenty minutes of NREM sleep immediately preceding the selected REM cycle and an additional 20 min immediately following the end of the selected REM cycle were also retained. Because the data collection period for infants was during nap time and much shorter, 20 min of NREM sleep immediately preceding the onset of the REM period selected for analysis were retained. This length of time was selected because it yields an adequate number of stimuli for analysis and reduces variability caused by individual differences in sleep (Hunter et al., 2008).

The data were converted from the Scan 4.1 software (Neuroscan Labs; Sterling, Virginia, USA) format to ASCII format so that further analysis using MatLab (Mathworks; Natick, Massachusetts, USA) software could be conducted. Single-trial-evoked potentials were extracted from 100 ms before each click to 200 ms following each click. Trials were excluded in which the signal on the recording of identified periods exceeded ±75 μV. The average waveforms from single trials were band pass filtered between 10 and 50 Hz in order to improve the signal to noise ratio (Adler et al., 1982; Chang, Gavin, & Davies, 2012) and to accentuate middle latency components of interest. For each subject, the largest positive peak between 50 and 100 ms after an auditory click (P50) preceded by a negative trough was identified and measured, peak to trough, by a computer algorithm.

One infant recording did not have sufficient NREM sleep for assessment. The average number of S1 and S2 stimuli during REM sleep was 72 (range 44–84) and 72 (range 44–85) respectively, for each visit during infancy (Visit 1) and 103 (range 79–149) and 103 (range 82–134), respectively, for the visit occurring around 4 years of age (Visit 2). During NREM sleep, the average numbers of S1 and S2 stimuli were 82 (range 62–104) and 80 (range 65–100), respectively, for Visit 1 and 194 (range 156–222) and 165 (range 144–197), respectively, for Visit 2.

For each child, a mean response latency and amplitude to each stimulus (S1 and S2) were calculated for both REM and NREM periods for each visit. In addition, their ratio was calculated by dividing the evoked response to S2 by the amplitude of the response evoked by S1. An S2/S1 ratio closer to 0 is indicative of robust sensory gating, while a ratio closer to 1 is indicative of diminished sensory gating. Fig. 1 shows examples of evoked-potential waveforms from a participant at 15 weeks of age (Visit 1) and 48 months of age (Visit 2) for one of the study participants.

2.2.4. Statistical approach—All variables were normally distributed. To assess the stability of P50 sensory gating parameters, Pearson correlations were used to compare results in infancy and at 4 years of age. Correlations were computed separately for results obtained during REM and NREM sleep. Correlations for measures taken during REM are based on 14 subjects; correlations during NREM and ANOVAs are based on 13 subjects. In order to assess the effects of age, sleep state, and stimulus number on P50 measures, repeated measures ANOVA with sleep state (REM vs. NREM), age (infancy vs. 4 years) and stimulus number (response to the first stimulus, S1, compared to response to the second stimulus, S2) as within-subjects variables were performed. For P50 sensory gating ratios, responses to the two stimuli are combined into a single variable; thus analyses only include sleep stage and age as within-subjects factors. To address the question of whether the sleep state immediately preceding the recorded state had an impact, for the preschool time point, the selected REM period was divided into two 10-min segments: one preceded by a period of NREM and one preceded by REM. In a similar fashion, preschool NREM recordings were divided into two 20-min segments, one preceded by NREM and one preceded by REM. Separate repeated measures ANOVAS, using sleep state and the number of stimuli as independent variables, were run for each of measures.

3. Results

In infancy, there was no significant effect of age or the number of averaged trials analyzed on P50 amplitude or latency in response to either stimuli or in the P50 sensory gating ratios (all p's > .29). At 4 years of age, there was no significant effect of age or the number of averaged trials analyzed on P50 amplitude or latency in response to either stimuli or in the P50 sensory gating ratios (all p's >.21). Mean amplitude and latency of P50 evoked responses are summarized in Table 1.

Effect of age, sleep stage, and stimulus number on the P50 evoked response. There was a significant interaction between sleep stage and stimulus number on the amplitude of the evoked response (Fig. 2 and Table 1). For both infants and 4-year-olds, during REM sleep, sensory gating ratios are significantly less than 1. This is due to a significant reduction in the amplitude of the response to the second sound relative to amplitude of response to the first sound. While the amplitude of P50 waves were not significantly correlated across age, P50 sensory gating ratios were strongly correlated with each other (Fig. 3).

In contrast, during NREM sleep, there was no significant reduction in response amplitude to the second vs. the first sound; thus, sensory gating ratios do not significantly differ from 1 (Fig. 2). During NREM sleep, there was no correlation across age for evoked P50 amplitudes or for P50 sensory gating (Table 1).

For latency of P50 response, there was a strong trend for an age by sleep interaction (p = . 053; Table 1 and Supplemental Fig. 1). In 4-year-olds, P50 latencies were between 63 and 65 ms in response to both the first and second stimuli. In infants, a similar P50 latency was seen during REM sleep, but during NREM sleep, latency was about 10 ms longer. No significant effect of stimulus number was identified.

Effect of the previous sleep stage on P50 evoked response. The amplitude of the P50 response is larger during a period of REM sleep that follows NREM than it is later in a REM cycle (Supplemental Table 1); however, the effect is proportionally similar for the response to the first sound (24% reduction) as it is for response to the second sound (21% reduction). Thus, no effect of recent sleep stage on P50 sensory gating is identified.

The latency of the P50 response is longer during a period of NREM sleep that follows a REM period than it is later in the NREM cycle (Supplemental Table 1). There is no significant effect of recent sleep stage on amplitude or gating ratios evaluated during a NREM period.

4. Discussion

A necessary step for establishing P50 auditory sensory gating as a useful biomarker for the early detection of abnormalities in cerebral inhibition is to demonstrate the stability of this measure of brain function over time. A second is to evaluate the effect of various sleep states on these measures since sleep is the optimal recording state for infants and young children. This study assessed the stability of P50 auditory sensory gating in early childhood by comparing measures gathered at 3 months and again at 4 years of age.

Previous studies have reported difficulty in establishing the stability of S2/S1 ratios (Freedman et al., 2002; Siegel et al., 1984; Smith, Boutros, & Schwarzkopf, 1994). One likely explanation for the intra- and inter-individual variability of this measure is the effect of arousal. This is supported by an early study by Adler et al. (1994) in which oral yohimbine, a presynaptic alpha-2 antagonist that increases neuronal transmission of noradrenaline, was used to test suppression of the S2 response. Compared to placebo administration, auditory sensory gating was significantly decreased in individuals without previous auditory gating deficits following yohimbine administration. With that in mind, subsequent studies demonstrated the stability of the evoked responses and auditory gating during non-stressed wakefulness and REM sleep in adults, and the stability of S2/S1 ratio between visits that occurred weeks apart by recording infants and assessing responses obtained during REM sleep (Hunter et al., 2008). It has been suggested that sensory gating is not fully developed in young children and improves as children age (Brinkman & Stauder, 2007; Marshall, Bar-Haim, & Fox, 2004). Slow decreases in arousal rather than actual improvement in the underlying cerebral inhibition circuit may also explain the generally poor performance of children. The stability of P50 auditory sensory gating over an almost 4-year period, when assessed during REM sleep when adrenergic tone is suppressed, suggests P50 sensory gating may be fairly well developed and therefore of use in infancy and early childhood.

The poor stability of auditory sensory gating during NREM sleep found in this study is in line with that reported in studies with adults and suggests that during this period of sleep the mechanisms involved with auditory sensory gating are operating differently. In this study, the S2/S1 ratios obtained during NREM sleep were not only greater than those measured during REM sleep, but they were very close to 1, suggesting that inhibition of the response to the test stimulus did not occur during NREM sleep. Other studies support this finding in

that even though the P50 waveform was visible in all stages of sleep, inhibition to S2 during Stage 2 sleep was poor. In this study, the waveform was present, and it is the increase in the S2 amplitude (inhibition failure) that appears responsible for the increased ratio. This may be indicative of the adrenergic tone that persists during the NREM stage as animal research has shown that norepinephrine neurons of the locus coeruleus are tonically active during NREM sleep, but become inactive during REM sleep (Kisley et al., 2001; Siegel & Rogawski, 1988).

During REM sleep and wakefulness, the thalamus shows a sustained tonic firing, which changes during NREM sleep as the outgoing spikes from the thalamus are reduced and the incoming spikes are filtered (van Luijtelaar, Miller, Coenen, Drinkenburg, & Ellenbroek, 1998). In a study that looked at the firing patterns of thalamocortical neurons in monkeys during different stages of sleep, researchers found that neurons fired with less frequency in NREM sleep when compared to REM sleep, indicating decreased responsiveness (Gottesmann & Gottesman, 2007). However, before progression to the REM stage, the neurons prematurely seemed to increase their firing. This raises the possibility that (a) the boundary between NREM and REM sleep may not be abrupt and may be difficult to discern and (b) there may be a residual effect of the previous sleep stage on sensory gating. This study identified an effect of recent sleep stages, with the shift from NREM to REM associated with higher amplitudes and from REM to NREM associated with longer latencies of the P50 response. However, P50 sensory gating ratios, the primary biomarker, were not significantly impacted by recent sleep stage changes, suggesting the gating ratio may be obtained during any portion of a REM cycle.

As psychiatric disorders are not generally diagnosable in infants, risk status is often inferred from parental psychopathology. The relatively high incidence of pregnancy-associated depression and anxiety in these infants' mothers suggests these results may be generalizable; however, these infants were not recruited based on parental psychopathology and, combined with the small sample size, it is possible that the findings may not be universally applicable.

In summary, during NREM sleep, P50 sensory gating is minimal to non-existent, and thus its ratings are not stable of time. Conversely, P50 sensory gating is prominent during REM sleep, is unaffected by recent changes in sleep stage, and is stable across early childhood. P50 sensory gating is a biomarker which, if used properly, may provide a mechanism to further explore changes in the developing brain or may help with early screening for psychiatric illness vulnerability. REM sleep appears to be the optimal state in which to asses P50 sensory gating in young children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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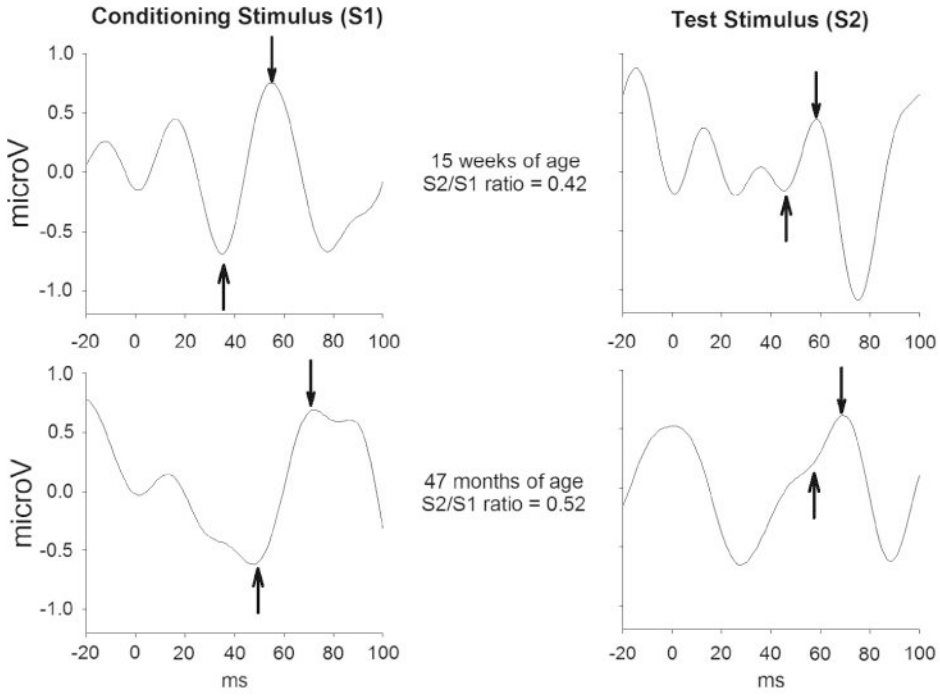

Fig. 1.

Averaged auditory event related potentials from the same infant at 15 weeks of age (top row) and 47 months of age (bottom row). Stimulus onset occurred at 0. P50 evoked response amplitude is measured between the arrows.

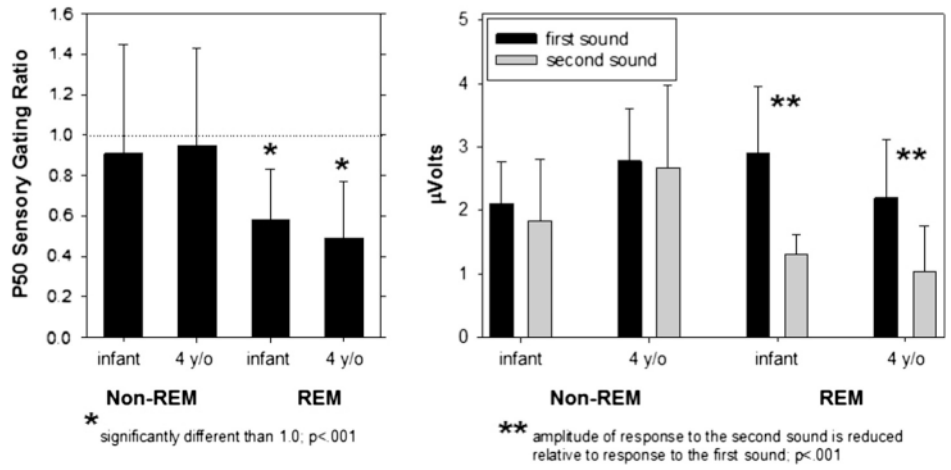

Fig. 2.

P50 sensory gating ratios (left) and amplitude of the evoked P50 waves (right) during non-REM and REM sleep (active sleep in the infant). During REM sleep, the amplitude of the P50 response to the second sound is decreased relative to the amplitude of response to the first sound. This is reflected in a sensory gating ratio significantly less than 1. During non-REM sleep, there is no significant difference in the amplitude of response to the second as compared to the first sound, reflected in a ratio not significantly different from 1.

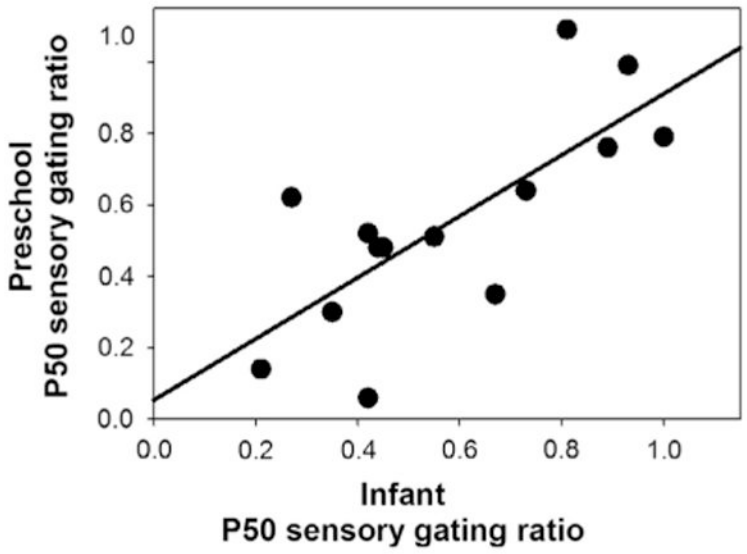

Fig. 3.
Relationship of S2/S1 ratio in Infancy with S2/S1 ratio at 4 years of age (r = .73, p = .003).

Table 1

Means (SD) and correlations for amplitudes and latencies of evoked P50 responses during REM (active sleep in infancy) and non-REM (NREM) sleep in infants and 4 year olds.

	Sleep stage	Infany	4 Year-olds	r [a]	p	ICC[b]	p	Statistical analyses [c]
Amplitude S1 (μV)	REM	2.32 (1.17)	2.45 (0.79)	.09	.77	.15	.30	Significant or trending effects: Sleep stage by stimulus type: $F(1,12) = 17.1$, $p = .001$ Stimulus number: $F(1,12) = 4.1$, $p = .004$ Age by sleep stage: $F(1,12) = 4.1$, $p = .064$ Sleep stage: $F(1,12) = 3.9$, $p = .072$
	NREM	2.10 (0.66)	2.48 (0.75)	.23	.46	.06	.41	
Amplitude S2 (μV)	REM	1.41 (0.82)	1.20 (0.85)	.33	.25	.42	.06	
	NREM	1.83 (0.97)	2.46 (1.19)	−.29	.35	.17	.27	
P50 sensory gating ratio	REM	.58 (0.25)	.49 (0.28)	.73	.003	.74	.001	Significant or trending effects: Sleep stage: $F(1,12) = 15.8$, $p = .002$
	NREM	.91 (0.54)	.95 (0.48)	−.05	.88	.17	.27	
Latency S1 (ms)	REM	64.5 (15.5)	63.3 (8.5)	−.04	.90	.06	.42	Significant or trending effects: Sleep stage: $F(1,12) = 17.1$, $p = .023$ Age by sleep stage: $F = 4.6$, $p = .053$
	NREM	75.2 (18.0)	63.7 (4.7)	.12	.69	.10	.36	
Latency S2 (ms)	REM	65.5 (15.2)	65.1 (8.6)	.12	.68	.08	.38	
	NREM	75.5 (19.8)	63.5 (5.9)	.30	.32	.22	.21	

Amplitudes are significantly reduced in response to the second sound as compared to the first, in both infants and 4 years, during REM but not NREM sleep. Latency of the P50 evoked response is mildly elevated during NREM sleep as compared to REM sleep in infants, but not in 4-year-olds. There is robust P50 sensory gating during REM but not NREM sleep in both infants and 4-year-old children.

S1 refers to the evoked response to the first sound; S2 refers to the evoked response to the second sound.

[a] Pearson correlation.

[b] Intra-class correlation.

[c] Repeated measures ANOVA: age × sleep stage × stimulus type (amplitude and latency analyses); age × sleep stage (P50 sensory gating analysis).