

Reliability of P50 auditory sensory gating measures in infants during active sleep

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This study assessed reliability of auditory sensory gating in young infants from 1–4 months of age using a paired-click paradigm in which auditory ‘clicks’ were presented at an interstimulus interval of 500 ms. Evoked potential component P1 was measured during periods of active sleep on two different occasions. Amplitudes, latencies, and ratio of the evoked potentials to each of the auditory clicks were compared. Significant reliability was found in the response ratio, response latency to the first stimulus, and

response amplitude to the second stimulus, with a trend toward significance for response latency to the second stimulus and response amplitude to the first stimulus. The results suggest that auditory sensory gating can be reliably measured during active sleep in young infants and might be a useful tool in the study of neurodevelopmental disorders. *NeuroReport* 19:79–82 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The use of event-related potentials is rapidly becoming an important and useful tool in the study of infant development. This technique allows researchers to explore brain development and provides converging lines of evidence to complement traditional behavioral measures of development [1–4]. This methodology allows for the detection of subtle differences in brain development and functioning; therefore, it can provide valuable information before the behavioral measures – or the onset of clinical signs – necessary for diagnosis are available or practical [3,5–7]. This, in turn, paves the way for earlier intervention. One such event-related potential is the P50 (P1), which is used to measure auditory sensory gating.

The P50 (P1) is a midlatency brain event-related response elicited by the presentation of an auditory stimulus occurring approximately 50 ms after the stimulus presentation. Auditory sensory gating is measured by comparing the amplitudes of the brain’s responses, using a paired-click paradigm. In this paradigm, two auditory stimuli (‘clicks’) are presented 500 ms apart, and the brain’s response to each stimulus is measured and compared. Sensory gating is said to be ‘intact’ when the ratio of the brain’s response to the second click is significantly less than its response to the first click (test/conditioning ratio or T/C ratio). Comparing these two responses allows one to gauge the brain’s ability to inhibit or filter irrelevant information (gate). In one recent study, this electrophysiological measure of sensory gating was shown to be proportional to an individual’s ability to filter out irrelevant stimuli [8].

Auditory sensory gating is relatively robust in most healthy adults, with about 80% of the population showing

measurable response suppression to the test stimulus (i.e. T/C ratio <0.40). Inadequate or weak suppression of the evoked response to the test stimulus has, however, been identified in certain psychiatric and neurological disorders such as schizophrenia (for a review see Refs [9,10]), posttraumatic stress disorder [10], and Parkinson’s disease [11]. For debilitating disorders such as schizophrenia that are argued to be the result of abnormal brain development, electrophysiological measures such as those used in the measurement of auditory sensory gating might prove useful in identifying individuals with increased risk, thus allowing for early intervention.

The use of auditory sensory gating as a tool to evaluate early brain development is a relatively new endeavor and one not without its issues and concerns. The first major issue one must address in this area is that of state dependency. It has been demonstrated that gating failure, that is, weak suppression of the electrophysiological response to the second auditory stimulus, can be affected by acute stress [12,13]. As many infants often become stressed or upset when subjected to new surroundings such as a laboratory and/or to having electrodes placed on their scalps and faces, this issue is paramount. Controlling stress by recording during sleep has been demonstrated to be a viable alternative [8,14,15].

A second major issue has to do with intraindividual and interindividual variability. Studies have shown that auditory sensory gating tends to be highly variable from child to child and from test to test within children [16]. In fact, attempts to demonstrate the reliability of this measure in adults has also proved difficult (see Ref. [17]). It has been suggested that at least some of the variability might be

attributed to state dependency (e.g. stress, boredom) [18], but this has yet to be demonstrated.

A third issue is movement, as it affects electrophysiological recordings by increasing the artifacts. Adult participants can be instructed to remain still and not blink their eyes; however, this is obviously not the case with infants. Furthermore, attempts to restrain infants run the risk of increasing stress, the effect of which was previously addressed.

In an effort to circumvent the issues of movement and state dependency, two studies [14,19] demonstrated the reliability of sensory gating in adult individuals during waking and rapid eye movement (REM) sleep. Kisley *et al.* [15] went on to demonstrate the feasibility of P1 assessment in infants during active sleep. By recording during active sleep, issues of state, arousal, movement, and attentional and motivational confounds that proved problematic for others attempting to record children [20], and perhaps adults, are reduced. For example, it has been demonstrated that when adults enter REM sleep, noradrenergic neurons (which are a major component of the acute stress response) are inactive [19]. These studies, however, did not address the issue of intraindividual variability by recording individuals on multiple occasions.

The current study was designed to extend the findings of Kisley *et al.* [15], in their characterization of the development of the P50 auditory sensory gating response in infants during active sleep, by evaluating the reliability of this measure in early infancy. By understanding the parameters and developmental course of this response in infants without increased risk for abnormal development, we hope to lay the groundwork for future uses with other populations in which risks are a concern, such as infants who have a parent with schizophrenia.

Methodology

Participants

Infants were recruited from the Denver metropolitan area through a random birth registry. A total of 27 infants were recruited to make repeated visits to the Developmental Research Group perinatal laboratory at the University of Colorado at Denver and the Health Sciences Center. Ninety-three percent ($N=25$) of the recruited infants returned for at least two visits; 8% (two) participated during one visit. Fifteen infants (69%) provided usable data during both visits. Inability to fall asleep, active sleep of less than the minimum of 15 min, and noisy recordings were reasons for attrition. Table 1 contains descriptive data on these participants.

Procedures

Informed parental consent was obtained as monitored by a local institutional review board. Demographic information was collected, which included the gestational age of the infant at the time of birth (based on estimated due date), delivery information, and whether the infant was breast-fed or formula-fed.

Table 1 Mean conceptual age by visit and sex

	Infant boys ($N=8$)	Infant girls ($N=7$)	<i>P</i> value
Conceptual age at first visit (months)	50.0 (3.07)	53.0 (4.28)	0.139
Conceptual age at second visit	51.5 (2.67)	54.4 (4.50)	0.143

Gold-plated electrodes (Grass; West Warwick, Rhode Island, USA), attached with Ten20 conductive paste (DO Weaver; Aurora, Colorado, USA) and adhesive medical tape, were used to record a continuous electroencephalogram (EEG) from site Cz, a bipolar electrooculogram, and a submental electromyogram. A Grass breathing-effort strap was used to record respiration. All signals were recorded using NuAmps (Neuroscan Labs, Sterling, Virginia, USA). EEG signals were amplified 5000 times and filtered between 0.05 and 100 Hz; electrooculogram signals were amplified 1000 times and filtered between 1 and 200 Hz; and electromyogram signals were amplified 10000 times and filtered between 1 and 200 Hz. Respiration strap (Grass) output was amplified 100 times and filtered between 0.05 Hz and 30 Hz. Sampling rate occurred at 1000 Hz. The continuously recorded data were converted from the Scan 4.1 software (Neuroscan Labs; Sterling, Virginia, USA) format to the ASCII format. MatLab (Mathworks; Natick, Massachusetts, USA) software was used for further analysis.

Once the electrode impedances were determined to be below 10 k Ω and the infants were asleep, paired clicks were presented through two speakers positioned at either side of the infants' heads at a distance of 0.50 m from the ear. The volume of the speakers was adjusted so that the peak loudness of the auditory clicks was an 85-dB sound pressure level at the ear. Recording continued for as long as the infant remained asleep.

Sleep state was identified offline by visual inspection of the continuous recording in 20-s epochs. Active sleep was identified by the presence of REMs, low amplitude, and high frequency activity in the EEG record, and by irregular breathing as recorded by the breathing strap [21]. From the identified active sleep periods, the first 15-min period (approximately 85 stimulus pairs) was retained and used for further analyses (see Ref. [15]). Single-trial-evoked potentials were extracted from 100 ms before each click to 200 ms following each click. Trials, in which the signal on the recording of any of these identified periods exceeded ± 75 mV, were excluded from further analysis. The average waveforms computed from these single trials were band-pass filtered between 10 and 50 Hz, to accentuate middle latency components.

For each participant, the amplitude and latency of the largest positive peak (P1) between 50 and 100 ms after a click, preceded by a negative trough, was determined. Sensory gating was measured by comparing the average amplitudes of P1 evoked by the second click (test) to the average amplitudes of P1 evoked by the first (conditioning) click. A resulting ratio (T/C ratio) was calculated. A ratio closer to 0 is indicative of response suppression (gating), whereas a ratio closer to 1 is indicative of failed sensory gating. In previous studies, T/C ratios of more than 0.40 were determined to be indicative of significant impairment in adult populations [22]. Kisley *et al.* [15], however, reported a mean T/C ratio of 0.57 for the infants tested in their study. Reliability was assessed for each of the auditory sensory gating components by calculating intraclass correlations between the two sessions.

Results

The traditional measures of auditory sensory gating were examined first. Figure 1 presents examples of evoked-potential waveforms from two participants in this study.

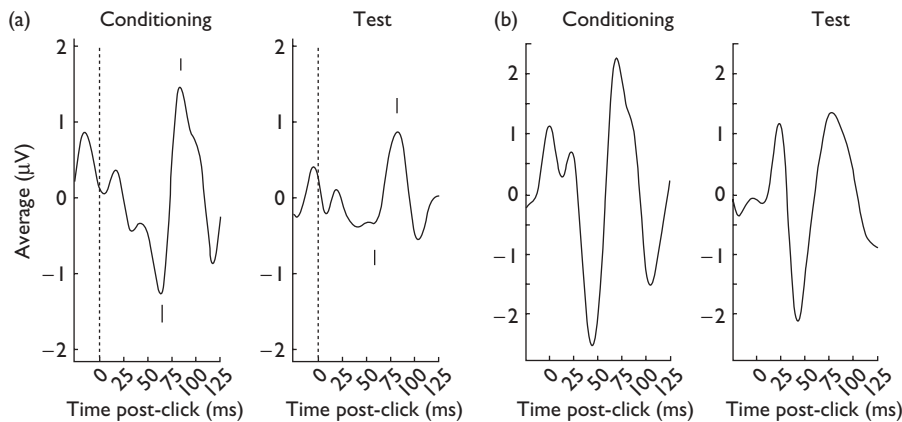


Fig. 1 Individual examples (a and b) of P50 responses evoked during rapid eye movement (REM) sleep. Clicks occur at 0 ms and tick marks indicate preceding negativity and peak. (a) Is an example of an infant (49 weeks' gestational age) whose PI response to the test stimulus was significantly reduced compared with that for the conditioning stimulus test/conditioning ratio (T/C=0.40). (b) Is an example of an infant (59 weeks' gestational age) whose PI response to the test stimulus was similar to that for the conditioning stimulus, demonstrating lack of response suppression (T/C=0.97).

Table 2 Latency (Lat), amplitude (Amp), test/conditioning (T/C) ratios, and intraclass correlations for the first and second visits

Lat C1	73.10 (14.85)	Lat C2	72.8 (14.80)	ICC=0.71	<i>P</i> <0.01
Lat T1	74.00 (13.80)	Lat T2	70.6 (16.90)	ICC=0.55	<i>P</i> <0.07
Amp C1	2.58 (1.14)	Amp C2	2.0 (1.02)	ICC=0.50	<i>P</i> =0.10
Amp T1	1.30 (0.93)	Amp T2	0.94 (0.67)	ICC=0.71	<i>P</i> <0.01
T/C ratio 1	0.47	T/C ratio 2	0.48	ICC=0.84	<i>P</i> <0.01

Mean latency (SD), amplitude (SD) and test/conditioning ratios for evoked response to first click (conditioning stimulus) for visit 1 (C1) and visit 2 (C2), second clicks (test stimulus) for visit 1 (T1) and visit 2 (T2). Intraclass correlations (ICC) for each of these variables are also presented with resultant *P* values.

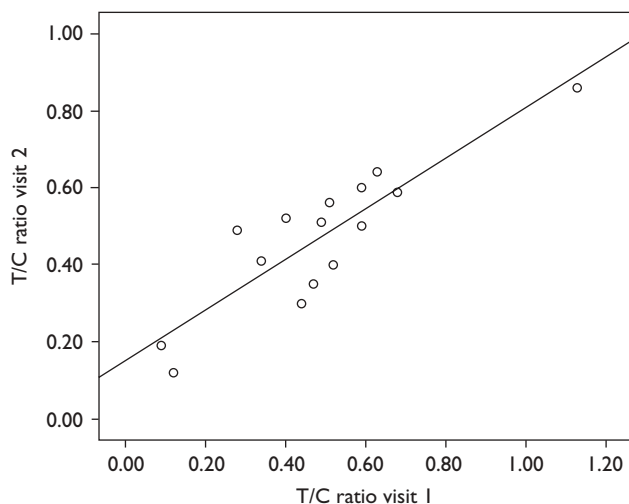


Fig. 2 Relationship between test/conditioning (T/C) ratio during visit 1 and T/C ratio during visit 2.

The overall mean conditioning latencies were 73.07 (SD=14.85) and 72.80 ms (SD=14.80 ms); the amplitude in response to conditioning stimulus, 2.58 (SD=1.14) and 2.00 µV (SD=1.02 µV), respectively; latency to the test stimulus, 74.00 (SD=13.80) and 70.60 ms (SD=16.90 ms), respectively; and the amplitude in response to the test stimulus 1.30 (SD=0.93) and 0.95 µV (SD=0.67 µV), respectively. The overall T/C ratios were 0.47 (SD=0.18) and 0.48 (SD=0.25) for the first and second sessions, respectively. The average numbers of test and conditioning stimuli were,

respectively, 73 and 71 for the first visit; they were 81 and 80 for the second visit. Mean T/C ratios were different from 1 (*P*<0.01) for both sessions, indicating significant suppression of test responses compared with conditioning responses. Table 2 presents a summary of these data.

As intraindividual and interindividual variability were the primary foci of this study, the reliability of the auditory sensory gating measures was addressed next. Significant reliability in most of the P50 indices measures was demonstrated, with the exception of the amplitude for the conditioning stimulus and the latency of the responses to the test stimulus. The intraclass correlations and associated *P* values are summarized in Table 2. Figure 2 presents a plot of the T/C ratios during the first and second visits.

Discussion

The purpose of this study was to expand our understanding of the development of sensory gating in infants by evaluating the reliability of intraindividual and interindividual responses over time. This is particularly important for a couple of reasons. First, existing literature on the reliability of response measures has been mixed (see Ref. [17] for a review): the usefulness of this measure, particularly in areas of research that report differences in suppression in clinical populations such as schizophrenia patients, has been questioned. We suggest that a potential explanation for the lack of reliability is the state dependency of auditory sensory gating. Although many studies indicate that steps have been taken to ensure state stability, such as online elimination of trials with slow wave sleep [9,17,22], it is

difficult to know how effective these attempts were. Studies often report stability of test and conditioning responses separately; however, they rarely report stability in the recording of the T/C ratio, which is the most frequently reported measure of suppression, one demonstrating consistent differences in clinical populations [23]. As we discussed in the introduction to this paper, recording infants during periods of active sleep (or REM in older children and adults) offers a way to control a number of factors that often prove problematic with this measure: anxiety, stress, drowsiness, movement, and others. During REM (and active sleep in infants) noradrenergic neurons, which are central to stress response and arousal, are inactive [24]. This is particularly important for the recording of sensory gating-evoked potentials, as stress and anxiety are considered as the most problematic factors. Additionally, if infant participants' sensory gating can be reliably measured during active sleep, as indicated by the results of this study, we have the added benefit of reducing attrition due to mood states or to lack of sleep during a particular visit. Attrition routinely results in the loss of valuable participant data that plagues much of developmental research, particularly that dealing with infants.

Conclusion

The purpose of this study was to evaluate the reliability of P1 components across different testing periods. Increasing our understanding of the genetic and environmental contributors to this evoked response might be particularly useful to our knowledge of neurodevelopmental disorders such as schizophrenia.

Acknowledgements

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