Global field power helps separate respiratory-related evoked potentials from EMG contamination

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Daubenspeck, J. Andrew, Lisa M. Lim, and Metin Akay. Global field power helps separate respiratory-related evoked potentials from EMG contamination. J. Appl. Physiol. 88: 282–290, 2000.—Respiratory-related evoked potentials (RREPs) were stimulated by brief (200-ms) oral pressure pulses (−10 cmH2O) applied at the onset of inspiration in 12 subjects. Scalp potentials were measured at 30 sites on a rectangular grid that encompassed the right side of the scalp overlying the somatosensory cortex (SSC). Concurrent and significant masseter EMG (mEMG) activity was evoked by the pressure pulse, and we found correlational evidence for contamination of the RREP by the mEMG. The global field power (GFP) was used to provide a robust, reference-independent measure of SSC activation that provided partial insulation from mEMG contamination. The mean GFP from all subjects, reflective of afferent information from respiratory mechanoreceptors, showed a latency to onset of significant afferent SSC activity of ~25 ms. Scalp GFP activity during control experiments (absence of applied pressure) was significant and may reflect ongoing afferent activity from inspiration.

respiratory sensation; respiratory afferents; somatosensory cortex; masseter muscle electromyography

The existence of scalp potentials evoked by respiratory stimuli has attracted attention over the past 14 years, beginning with the report that inspiratory occlusion resulted in discernible components in the evoked responses with latencies as short as ~60 ms poststimulus (5). Use of small, brief negative pressure pulses has confirmed the existence of components in the respiratory-related evoked potential (RREP) with latencies as short as 25 ms poststimulus (23). These midlatency components in the scalp evoked potentials were hypothesized to correlate to the arrival of respiratory afferent information to the somatosensory cortex (SSC). Respiratory mechanoreceptor afferents, like other somatosensory afferents, project to the SSC with spatial and temporal specificity that depends on the particular site of mechanoreception (6, 7, 26). It is, therefore, highly desirable to develop reliable, noninvasive estimation techniques for quantifying this afferent traffic from the evoked potentials in the scalp electroencephalogram (EEG), since there is no alternative method to measure the mass afferent traffic from the combined set of respiratory mechanoreceptors that has the requisite spatial and temporal resolution characteristics. Assessment of the nature of this mass afferent mechanoreceptor signal in humans could provide useful insights into the phenomena of dyspnea and of altered perception of respiratory stimuli in some respiratory diseases.

The use of the patterns of RREPs on the scalp to localize the site of activation on the underlying cortex is problematic, however, because of the volume conduction properties of the cortex, cerebrospinal fluid, skull, and scalp. The skull is approximately two orders of magnitude less conductive than the other components, and this forces much of the neuronal activation currents to follow pathways that extend long distances, through the orifices provided by openings in the skull, and then tangentially along the scalp. These tangential currents add to those traversing radially through the skull (17), and potentials measured on the scalp are affected by the patterns of local currents, including these radial currents plus larger tangential currents from multiple, remote sites of activation. This “spatial blurring” limits the direct identification of activated sites on the SSC with use of scalp potential measurements. Theoretical studies show that this spatial blurring results in significant correlation between scalp EEG signals within 10–12 cm from uncorrelated sources; hence, determining the specific locations of those sources from the mapping of measured scalp potentials would be difficult (21).

A further problem in interpretation of the scalp RREP signals lies in the likely contamination of the RREP by electromyographic (EMG) artifacts due to the activation of upper airway, neck, and jaw muscles in response to an applied negative airway pressure stimulus. Sudden application of negative pressure at the mouth causes a rapid excitatory EMG response in the genioglossus (10), and airway occlusion produces an inhibitory scalene EMG response (2) that in both cases is seen within ~35 ms of the stimulus onset. We have observed concurrent activity in the masseter EMG and a bipolar scalp electrode pair (Cz-C4 in the international 10–20 layout) during voluntary jaw clenching and have investigated without success ways to separate these signals by use of advanced signal-processing techniques (1). We have also found that concurrent EMG activity in the masseter is commonly produced in response to oral pressure pulses or inspiratory occlusions (see below). Activation of a facial muscle creates
an EMG current that is primarily tangential across the scalp and can directly contaminate the scalp potentials, even when measured with closely spaced bipolar electrodes. Given that the stimulus to evoke the RREP may synchronously provoke an EMG response and that the response to an applied negative airway pressure in the genioglossus is very rapid (~35 ms poststimulus), any such EMG activation could contaminate the scalp evoked potential well within the time span of interest regarding midlatency RREP responses (<100 ms).

If it is assumed that sites of cortical activation produce radial current contributions to the evoked potentials measured over a scalp field, activation of those underlying sites will produce local distortion of the field from uniformity. The degree of “hilliness” of the field should vary directly with the strength of activation of local regions of the underlying cortex. Remotely activated cortical sites and EMG contamination will more broadly affect scalp potentials via tangential currents that will tend to raise or lower the potential across the entire scalp field. A measure of this field distortion was proposed for other evoked potential applications by Lehmann and Skrandies (13) and termed the global field power (GFP). This approach provides a reference-free measure of the local activation within a measured field to identify the timing of cortical activation relatively isolated from contamination by remote sources.

The goal of the research described here is to evaluate the utility of the GFP to describe midlatency events (~100 ms poststimulus onset) on the SSC evoked by oral pressure pulses and to determine the extent to which the GFP is insulated (compared with a representative scalp EEG) from contamination by facial EMG responses evoked by the pressure stimulus.

**METHODS**

Subjects. Results are from normal subjects who were paid to participate in the studies. Informed consent was obtained for protocols by using guidelines approved by our local Institutional Review Board. A total of 12 subjects were tested, 7 men and 5 women, ranging in age from 18 to 56 yr. Various numbers of replicate tests were performed in one-half of the subjects.

Experimental protocol. All subjects were fitted with a custom-molded mouthpiece formulated from high-viscosity dental impression material mounted on 0.75-in. polyvinylchloride tubing. This mouthpiece afforded subjects a comfortable connection to the apparatus that did not require biting down on a mouthpiece to maintain a leak-free seal and, thus, minimized tonic EMG activity in the jaw muscles. Subjects were seated on a comfortable dental chair set to provide head support with comfortable positioning to permit relaxation of postural muscles in the neck.

Experiments were performed in an isolated room, as shown in Fig. 1. Electrical shielding of the subject was provided by a Faraday cage; metal screening was used to enclose the dental chair and preamplifier equipment to minimize contamination of the EEG by interference from the power mains. Sound isolation prevented the subject from hearing the application of the pressure pulse stimulus. Subjects watched video movies during all experiments.

Electrodes were applied to the scalp by use of a custom-made, elastic cap (Electro-Cap International, Eaton, OH) with 30 electrodes mounted in a rectangular grid: 5 electrode columns in the anterior-posterior dimension and 6 rows in the medial-lateral direction, with the second row from the top positioned along the midline anterior-posterior chord, such that the vertex (Cz) was located at the intersection of this row with the middle column. The array was therefore centered over the central sulcus and postcentral gyrus, where midlatency somatosensory activity is expected to appear. Electrode spacing was 2.8 cm in the unstretched cap, although this distance varied as a function of position when the cap was actually in place. The region of the scalp monitored by this electrode field was ~14 cm lateral and 11 cm anterior-posterior, covering the right side of the scalp with some overlap (by ~3 cm) to the left side. The decision to focus on one side of the SSC was made because there is little reason to suspect that respiratory afferents have a preferential left-right projection and because we wished to keep the data acquisition and analysis burden manageable. A forehead electrode was used as the grounding point, and a reference electrode was applied to the right ear for all experiments. Electrodes were filled with conductive gel (Quik-Gel, Neuromedical Supplies, Herndon, VA); very mild abrasion was used, only if required, to achieve electrode impedances of ≤5 kΩ.

In addition to the application of EEG electrodes, a bipolar EMG electrode was applied to monitor activity in the masseter muscle in every experiment. The electrodes were spaced at ~4 cm to cover the body of the muscle, as estimated by voluntary jaw clenching.

The EEG signals were amplified and filtered by a set of low-noise, electrically isolated, carefully matched, high-impedance (10-GΩ) amplifiers (model EPA-6, Sensorium, Charlotte, VT) set with gains of 40,000 and band-pass filtering of 10–500 Hz. The masseter EMG was amplified by 1,000 with band-pass filtering of 10 Hz to 1 kHz (model DAM 5-A, WPI, Sarasota, FL).

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**Fig. 1.** Experimental apparatus used to stimulate and measure respiratory-related evoked potentials (RREPs) from a 30-channel scalp electrode montage referenced to right ear (A2). Experimental Faraday cage was located in a room separated from the rest of the apparatus. EMG, electromyogram; GND, ground.
Pressure pulses were generated using a vacuum cleaner and a pair of computer-controlled balloon valves (model 9230, Hans Rudolph, Kansas City, MO). A special-purpose, event-based instrument was designed using SuperScope II, a general-purpose data acquisition and control program (GW Instruments, Somerville, MA) running on a Macintosh computer (PowerMac 8500, Apple Computer, Sunnyvale, CA). Another computer system (WIN386, Everex Systems, Fremont, CA) also continuously monitored mouth pressure (model MP-45, Valdyne Instruments, Northbridge, CA), a single EEG channel (Cz-A2), and the masseter EMG with a separate data acquisition system (Codas, DATACQ, Cleveland, OH). The SuperScope instrument monitored mouth pressure and compared the level and direction of pressure changes with a threshold to determine when inspiration had commenced. On detection of the start of inspiration, the program triggered the balloon valve set in Fig. 1 to first apply and then remove the pressure pulse stimulus to the oral airway after 200 ms. Pressure pulses of −10 cmH2O were generally used. Data acquisition commenced at a per channel sampling rate of 2 kHz as soon as the start of inspiration was identified, although it usually required ∼35 ms to operate the balloon valves. Thus a period of prestimulus EEG was acquired that was used to estimate baseline responses (see below).

Each acquired set of EEG responses plus the EMG and oral pressure traces were displayed for review by the experimenter before application of the next stimulus. At this time, the experimenter checked the EEG signals for contamination by eye movements (an obvious slow variation in the trace baseline over the 200-ms period), obvious contamination of the EEG by EMG (large, correlated components in both signals), airway occlusion resulting from the applied pressure stimulus (large oscillations in the pressure signal), and faulty electrode connections (indicated by signal dropout or large spikes uncorrelated to activity in neighboring electrodes). If any of the above points raised concern, the experimenter rejected the trial and did not save it for inclusion in later, off-line analyses. If the trace appeared to be satisfactory by the above standards, it was saved in the data set to be processed further. A total of 100–120 acceptable trials were obtained in this test condition.

To evaluate the existence of EEG responses not evoked by the pressure pulse stimulus, every experiment included a control run of 100–120 trials in which the vacuum source was turned off but every other aspect of the experiment was operating, including the switching of the balloon valves at the start of inspiration.

Data analysis. Off-line analyses included trial-by-trial band-pass filtering (10–160 Hz) and ensemble averaging of the 30 channels of EEG and the masseter EMG signals. The filtering was performed using routines programmed in a general-purpose analysis package (MATLAB, Mathworks, Natick, MA) and was designed to filter each trial twice, once forward and then backward, to eliminate any phase shift due to the filtering. Ensemble averaging was also performed by routines programmed in MATLAB, and we calculated expected error bands for each signal to assist in determining when a signal should be considered significantly different from no response.

The GFP is defined (13) to be

\[ \text{GFP}(t) = \sqrt{\frac{\sum_{i=1}^{n} \sum_{j=1}^{n} (u_i(t) - u_j(t))}{2n}} \]  

where \( u_i(t) \) and \( u_j(t) \) are the RREP signals at each electrode at the time \( t \), taken in all possible pairs, measured relative to a common reference (here the right ear, A2), and \( n \) is the number of electrode positions used. The difference between \( u_i \) and \( u_j \) at time \( t \) is independent of the reference electrode used, and the GFP is therefore a reference-independent measure of the evoked activity. The GFP is a measure of the spatial variation of the potentials measured at each point in time over an electrode field and, as described in Eq. 1, represents a spatial standard deviation. It was computed for the set of electrodes measured in each experiment, nominally 30, although in some experiments trouble with electrodes required omitting 1–3 channels from the computations because of excessive noise, identified as large-amplitude signals with large confidence regions.

The stimulus onset time was identified from plots of the mouth pressure vs. time as the point where the inspiratory pressure trajectory deviated from the smooth decline of the ongoing inspiration. The EEG and EMG signals for the 20-ms period before the point of stimulus onset were used as a prestimulus control period for later analyses (see below).

RESULTS

A representative set of ensemble-averaged RREPs for the 30-electrode montage is shown in Fig. 2, together with the mouth pressure and masseter EMG signals for a typical subject. Although confidence regions were computed for each electrode, space precludes showing them in this plot. Control RREP responses generally were flat for all variables, as judged by the 95% confidence intervals relative to zero, and are not shown here. It is apparent that significant responses are evoked by the −10-cmH2O pressure pulse (Fig. 2, bottom left), which also serves to trigger an EMG response in the measured masseter signal (Fig. 2, bottom right). The timing of features in the EMG response is similar to features in the EEG channels shown above.

The GFP computed from the EEG signals shown in Fig. 2 between 20 ms prestimulus and 100 ms poststimulus, together with a composite plot of all 30 electrode signals and the ensemble-averaged masseter EMG signal, is displayed in Fig. 3. Peaks in the GFP correspond to points in time when the variation in potentials across the montage is large, not necessarily at extreme values of the evoked potentials. For example, the negative nadir in the EEG traces at ∼45 ms does not produce a peak in the GFP, since the EEG channels are relatively similar at this point. The 95% confidence region for the Cz-A2 signal does not include zero, so this would be judged a significant feature in the evoked potential at that time, but this is not so in the GFP. Rather, a significant feature in the GFP is noted at ∼54 ms, where the variation among the EEG channels is seen to expand greatly in Fig. 3B. At this time, the Cz-A2 confidence region encompasses 0 V, and a feature of significance would not be identified in that trace. This illustrates the fundamentally different information in the GFP, which identifies points in time where the regional inhomogeneity of the RREP signals is high. This contrasts with traditional evoked potential measurements, which mark points in time where the...
potentials are at extreme values, without regard to the uniformity of those potentials over the montage.

The ensemble-averaged masseter EMG signal in Fig. 3C shows features that correspond closely in time with those in the EEG signals, and the correlation coefficient over 0–100 ms poststimulus is −0.50, a highly significant value. (For 200-point correlation sequences as used here, the 95% confidence limit is about ±0.14.) This may indicate the extent to which the evoked EMG response from the combined effects of all facial and upper airway muscle contaminates the RREP signals measured here. The root-mean-square EMG voltage for the 0- to 100-ms span was computed for each subject in the control and test conditions and was significantly increased by application of the pressure pulse from 0.38 ± 0.09 to 1.05 ± 0.20 (SE) µV (P < 0.005, by ANOVA). Another measure of the effect of the pressure pulse can be assessed from the maximum amplitude of the EMG response over that time period, which increased significantly from 1.99 ± 0.58 to 4.82 ± 0.89 µV (P < 0.02, by ANOVA) between control and test conditions, averaged over the 12 subjects’ mean responses.

The individual GFP traces over the 100-ms poststimulus are shown in Fig. 4, together with the mean GFP(t) trace calculated over all 12 subjects. The same mean GFP(t), together with its 95% confidence interval, is shown in Fig. 5 for comparison to the value at the time of stimulus onset. The time when the confidence region just exceeds that level can be used as an indication of the time at which the GFP just shows a statistically significant increase and is an indicator of the arrival of information from respiratory mechanoreceptors to the SSC. This time of onset is 24.5 ms poststimulus. Peaks in the mean GFP occur at ~27, 47–52, 61, 68, and 82.5 ms, with the largest peak at 61 ms. As shown in Fig. 4, individual subjects show unique GFP morphologies, so it is difficult to ascertain with certainty which peaks ought to be considered similar across subjects to enable...
a more quantitative assessment of the timing of GFP peaks. Not surprisingly, Fig. 4 shows that many subjects individually have a GFP peak close to the 61-ms peak in the mean value, and some show individual peaks around the time of the 50-ms peak in the mean. The statistical approach used to define the onset time for significant GFP activity in Fig. 5 does not indicate how many subjects individually showed significant GFP activity at 24.5 ms poststimulus, and we cannot determine statistical significance from the individual GFP(t) signals, since we have a small number of estimates for each subject. To address this statistical evaluation, for each subject we used a 20-ms prestimulus span to compute a prestimulus GFP mean and variance. We then segmented the 100-ms poststimulus period into 20 5-ms segments of 10 points each and computed the individual means and variances for each of the 20 segments. We then used Dunnett’s test (19) to compare each of the 20 poststimulus segments with the prestimulus control period. (We verified in a large number of data sets that the serial autocorrelation decayed to insignificance within 5 ms.) We tallied across subjects those poststimulus segments that were significantly greater than the prestimulus level. We used two approaches to account for the different numbers of replicate tests performed in different subjects. The first was simply to use the ending time of the earliest significant bin of a set of replicate experiments as a measure of the most rapid arrival of information for each subject and then to average this quickest arrival time across subjects. For example, if the earliest significant bin for a subject were bin 5, we would count this as an arrival time of 25 ms (the end of the bin from 20 to 24.999 ms). Averaging this earliest significant onset time across subjects resulted in a mean of 20.8 ± 3.2 (SE) ms (median 25 ms) as the earliest arrival time estimated from the GFP across subjects.

The second approach uses Fig. 6, which shows the cumulative results from all subjects for time bins with significant GFP activity as judged by the procedures just described. Results are shown for control (no pressure pulse applied) and test runs. Fractional counts appear in Fig. 6 because of averaging across replicates within subjects to obtain a value from 0 to 1 for each subject describing the fraction of tests for each subject that resulted in statistically significant activity within a time bin. It is apparent that significant activation occurs during control runs (see below). The test results show a sudden increase in bin 5 (20–24.999 ms), as expected from the previous estimates, and peak counts at bins 12 and 13 (55–65 ms poststimulus).

To avoid distorting the test results with underlying control activation responses, we subtracted the ensemble-averaged control RREP signals for each electrode from the test RREPs and recomputed the GFP(t) for the control-compensated results. Figure 7 shows results similar to those in Fig. 6 with a clear earliest onset time during the 20- to 25-ms bin (bin 5). The peak of the distribution of activation times now occurs during the 60- to 65-ms bin (bin 13), consistent with the peak in the mean GFP signal of Fig. 5. This concurrence is not demanded, since Fig. 7 only describes the times when significant activation occurred in the GFP and is not dependent on the magnitude of the GFP activity, which is a determinant of the mean in Fig. 5.

If the GFP were less susceptible to contamination from concurrent EMG activity evoked synchronously with the stimulus, we would expect correlation between RREP and EMG signals to be greater than that between GFP and EMG signals. We used the masseter EMG as a representative contaminating EMG signal and computed correlation coefficients between it and both the GFP(t) and a typical RREP (Cz-A2). Sequences of 200 points corresponding to the 100-ms poststimulus span were used for test data (pressure pulse applied), and the computed correlation coefficients were compared with the \( \alpha = 0.05 \) level of 0.14. We compared and tested absolute values of the correlation coefficient, since the sign of any signal correlated to the EMG...
depends on the polarity of the connection to the EMG amplifier and the particular orientation of the electrode on the muscle. Because the sign (but not the magnitude) of the correlation could be altered simply by swapping the amplifier connections, it did not make sense to discriminate on the basis of sign, so the absolute value of the computed correlation coefficient was used to assess the strength of concordance between signals.

For this analysis, we used correlation coefficients computed for the subjects and tests previously described and further included data from test conditions from other experiments not otherwise suitable for inclusion in the present report because of missing control response data or the use of other aspects of the subjects’ responses in other reports. Forty-three sets of correlation data from 16 subjects were available, and one-way ANOVA was performed on the entire collection and on the data collection that included only those experiments in which the correlation between the EEG and EMG signals was significant (\( r > 0.14 \)). We monitored a single EMG response of the mass of possible contaminating EMG signals, and there is no guarantee that the masseter EMG as we measured it would characterize the entire EMG signal. So if we did not have a significant EMG-EEG correlation, we would not expect to see much effect of the GFP computation to reduce it further. Both approaches indicated a significantly lower correlation between GFP and EMG than between EEG and EMG by ANOVA (\( P < 0.04 \) for all data, \( P < 0.001 \) for the set including only EMG-EEG correlations >0.14). Figure 8 shows the paired comparison of the two correlations for the 14 subjects who had a significant EEG-EMG correlation, together with the mean values. The GFP-EMG correlation was reduced in 12 of the 14 subjects from 0.4 to 0.22 on average, indicating substantial insulation of the GFP measurement from the masseter EMG by comparison with the RREP measured by Cz-A2.

**DISCUSSION**

Utility of the GFP. RREPs appear in response to airway pressure stimuli with a latency that is consistent with representation of somatosensory afferent activity on the SSC (5). Shortest-latency components were seen as early as 46 ms poststimulus on average with midinspiratory occlusions (18) and 20 ms with
Fig. 8. Effect of masseter EMG contamination on Cz-A2 RREP [electroencephalogram (EEG)] compared with effect on GFP by use of absolute value of correlation coefficient computed for simultaneous 100-ms poststimulus series. Subjects from other experimental situations were included here. Responses are those for which EEG-EMG correlation was above critical value \((n = 200, \alpha = 0.05)\) of 0.14. Tendency of GFP-EMG correlation to be less than EEG-EMG correlation was significant by ANOVA.

applied oral pressure pulses (23). It is not possible to identify the source of this early afferent information, since sites of mechanoreception are distributed throughout the respiratory system and include receptors in the mouth and upper airway (including the larynx), the intrathoracic airway and lungs, and the respiratory muscles and joints. Respiratory pressure stimuli affect a large number of stimulus sites asynchronously, since propagation of the stimulus travels from mouth to muscle, and physical distortion of the tissue is required to instigate a response. This spatial propagation spreads the stimulus onset over time. Furthermore, the ongoing inspiration here provides for a background of continuous tissue distortion and ongoing afferent activity. Receptor location and tissue mechanical impedance determine when a receptor will sense an altered pattern of distortion due to the applied pressure pulse and transmit that message to the SSC. The transmission delay is obviously affected by the conduction velocity of the nerve and the distance to the SSC, adding further unpredictability to the observed latency from any given site. The observed features in the evoked scalp potentials reflect spatiotemporal summation of activity from many possible stimulated sites and may have fairly broad features by comparison with observations from more constrained evoked potential experiments (e.g., electrical stimulation of peripheral nerves). Because multiple active sites are likely to be involved in the evoked responses we measure, it is not fruitful to speculate on the sources of information contained in any specific feature of the RREPs or the GFP from the experiments and analyses we have performed here.

However, the GFP offers a relatively robust way to evaluate timing and intensity aspects of the activation of the SSC underlying the electrode field. Currents produced by volume conduction from remote activated sites (far-field sources) will affect the mapped field more uniformly through tangential scalp currents than will be the case for radial currents generated within the mapped region. Local activated sites will therefore be more likely to produce distortion in the mapped field (hilliness) than will be the case for remote sites. Because those remote sites include facial, neck, and upper airway muscle that may well be activated synchronously with the applied stimulus with latencies in the range of those measured from scalp potentials (2, 10), it is important to separate such EMG contamination from components of the scalp potentials that are reflective of SSC activation. At one time, we thought that the use of oral pressure pulses might be uniquely effective in activating a masseter response and wondered whether the use of a closely spaced, bipolar electrode configuration (Cz-C4) would provide better common mode rejection of muscle artifact than the A2 reference recording we previously used. We did preliminary tests to evaluate occlusion pressure as a less evocative stimulus with the bipolar configuration but found that this mode also evoked significant synchronous RREP and masseter EMG responses (Fig. 9).

The GFP, by providing a measure of the distortion of the measured field, rather than a measure of its height, does provide partial insulation from the effects of uniformly distributed tangential currents due to remote sources. The GFP will still be affected by "far-field" sources to the extent that these tangential currents are distributed nonuniformly over the measured field. The correlation results of Fig. 8 show that applying the GFP partially reduces the effect of EMG contamination, although these results need to be considered in this context: we have measured one EMG source and have compared it with one scalp electrode position. The masseter is a muscle known to share in responses to other respiratory stimuli similarly in some ways to the genioglossus (9). It is also known that the genioglossus is activated with short latency by negative airway pressure (10), so it is not surprising to see the sort of evoked EMG responses we found here. The use of the Cz-A2 position to evaluate EMG contamination is perhaps less favorable than an off-midline reference electrode might be because of the possibility of cancellation at the midline from symmetrically located EMG sources. In this light, the fact that correlations were reduced in 12 of 14 subjects with use of this information is remarkable and indicates the utility of the GFP.

Another advantage of the GFP is that it provides an estimate of SSC activation that is independent of the choice of a reference electrode. As Nunez (16) pointed out, features in components of the evoked potential, such as the magnitude of peaks and the spatial region over which polarity reversal occurs, depend on the selection of the reference electrode. Because there is no likelihood of obtaining a truly "quiet" reference electrode (or electrodes), as we and others have discovered (14, 17, p. 178–193), there will be continual controversy over the optimal reference selection with little hope of adopting a universal standard. It is, therefore, a great advantage to have a technique the results of which are independent of the particular choice of reference. A
simpler measure, the maximum voltage range, was also proposed by Lehmann and Skrandies (13) and shares many of the aspects of the GFP measure. We prefer the GFP because of its interpretation as a spatial standard deviation and the fact that it has been accepted in a wide range of evoked potential studies. The GFP has been used in identification of evoked responses from visual stimuli (20) and somatosensory evoked responses (11) and has been proposed as the method of choice for identification of latencies of responses evoked by audible tone bursts (8).

Onset time of SSC activation. Application of the GFP here provides a reference-independent technique to estimate the earliest arrival of respiratory afferent information to the SSC. It seems convincing that this information arrives at the SSC within 25 ms on average from the point of stimulus onset, defined as the time when the mouth pressure deviates from its normal smooth decline at the start of inspiration (Figs. 5–7). This time of earliest arrival (~25 ms) compares well with measurements made by us and others from RREPs evoked by occlusion and by applied pressure pulses (23, 25). With respect to specific respiratory afferent sources, Gandevia and Macefield (7) reported an onset latency for the cortical potential evoked by electrical stimulation of human intercostal muscles of ~21 ms. Stimulation of vagal afferents resulted in a latency to the peak of the first component (a negative peak) of the evoked potential that Tougas et al. (24) estimated to be ~70 ms. However, they show data for individual subjects that have a latency to peak for the earliest negative feature of ~50 ms (Fig. 1 in Ref. 24) or ~35 ms (Fig. 2 in Ref. 24). The latency to onset would be shorter than these peak latency measurements. Phrenic nerve stimulation in humans was shown by Straus et al. (22) to produce scalp evoked responses with an early peak latency of ~13 ms, corresponding to an onset latency for comparison here of ~9 ms. This latency must be considerably shorter than would be obtained from activation of phrenic afferents via oral pressure pulses, however. From the results reported here, we cannot attribute the early GFP signal to any specific site of mechanostimulation, although we provide information in a companion study (3) that indicates that the upper airway mechanoreceptors above the larynx are not likely to be responsible for this early information.

GFP activity in the control condition. The intensity of the GFP can be quantified by summing that signal to obtain an estimate of the effect of the stimulus on all exogenous evoked activity within the monitored field over the time span of interest. This results in average values over all 12 subjects for the summed control GFP of 185.9 ± 36.5 and 324.4 ± 34.7 (SE) μV for the summed test GFP, both taken over the span 0–100 ms poststimulus. It is apparent that there is substantial background activity in the summed GFP in the absence of any external stimulus, and this is also apparent in the histogram of time bins during which GFP activity was significantly elevated above the prestimulus 20-ms period (Fig. 6). The source of this control state activity is not well defined, although there are some likely explanations. One possibility that we do not favor is that this activity is triggered by the sound or vibration produced by activation of the apparatus. The balloon valves are located in a separate room and contained within a heavy, acoustically insulated plywood box and are connected to the subject’s mouthpiece by tubing with several rubber tubing connections that dampen vibrations. Although the valve operation can be heard at a subdued level in the experimental room, subjects watch video movies at normal volumes, which makes it difficult to hear the valves. A more likely explanation...
for the control evoked responses of the GPF is related to the triggering of the stimulus at inspiratory onset. Every trial is time locked to the pressure stimulus and somewhat less tightly to the onset of inspiratory activity. As soon as breathing commences and the respiratory system begins to change volume, mechanoreceptors throughout the system will begin to change theafferent information sent to the brain. Some of that altered signal will reach the SSC at times and sites related to the sources, and this activity will survive the ensemble averaging to produce a component to the measured GPF that adds to the evoked responses of interest. There is evidence in the results of Macefield and Gandevia (15) for such afferent activity from respiratory mechanoreceptors with breathing. They reported that a premotor, negative-going signal could be measured from scalp electrodes just before voluntary breathing maneuvers but that, once breathing movements commenced, a strong, broadly spread positivity was measured that they presumed was related to the arrival of sensory afferent information. We suspect that this is the case here and speculate that important information may be available in the scalp signals from spontaneous, unstimulated breaths. Operationally, it does make sense to subtract an estimate of this control activity from the test situation as we did to prepare Fig. 7 and as others have done (4, 12).

In summary, the GPF approach provides a robust tool that permits quantification and statistical evaluation of the time at which important evoked potential activity occurs within a measured field. It appears to provide partial insulation from contamination by far-field activity. As soon as breathing commences and the respiratory mechanoreceptors with breathing. They measured GFP that adds to the evoked responses of inspiratory occlusion in humans. J. Appl. Physiol. 60: 1843–1848, 1986.


