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Research Report

NEURAL MECHANISMS OF ERP CHANGE: COMBINING INSIGHTS FROM ELECTROPHYSIOLOGY AND MATHEMATICAL MODELING

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Using a standardized database of EEG data, recorded during the habituation and oddball paradigms, changes in the auditory event-related potential (ERP) are demonstrated on the time scale of seconds and minutes. Based on previous research and a mathematical model of neural activity, neural mechanisms that could account for these changes are proposed. When the stimulus tones are not relevant to a task, N100 magnitude decreases substantially for the first repetition of a stimulus pattern and increases in response to a variant tone. It is argued these short-term changes are consistent with the hypothesis that there is a refractory period in the neural elements underlying the ERP. In the oddball paradigm, when the stimulus tones are task-relevant, the magnitudes of both N100 and P200 for backgrounds decrease over the entire six-minute recording session. It is argued that these changes are mediated by a decreasing arousal level, and consistent with this, a subject's electrodermal activity (EDA) is shown to reduce over the recording session. By fitting ERPs generated by a biophysical model of neural activity, it is shown that the changes in the background ERPs over the recording session can be reproduced by changing the strength of connections between populations of cortical neurons. For ERPs elicited by infrequent stimuli, there is no corresponding trend in the magnitudes of N100 or P300 components. The effects of stimuli serial order on ERPs are also assessed, showing that the N100 for background ERPs and the N100 and P300 for target ERPs increases as the probability, and expectancy, of receiving a task relevant stimulus increases. Cortical neuromodulation by acetylcholine (ACh) is proposed as a candidate mechanism to mediate the ERP changes associated with attention and arousal.

Keywords: EEG; N100; acetylcholine; modeling; electrophysiology.

1. Introduction

An auditory evoked potential (ERP) is a transient response in the brain's electroencephalograph (EEG), time-locked to the occurrence of a particular auditory stimulus. These changes in electrical potential, measured at the scalp, reflect underlying neural activity. The prominent negative deflection in the ERP signal with a latency of approximately 100 ms is known as the N100 (see Fig. 1). The magnitude and latency of the N100 is modulated by the physical characteristics of the sensory stimuli, and by the internal state of the subject, and as such it is a useful, non-invasive window into neural activity and cognition. Although much is known about how the ERP signal changes in response to different stimulus patterns or to changes in the internal state of the subject, the actual generation of ERPs and their physiological underpinnings remain poorly understood. In this study, we demonstrate both long and short-term changes in the ERP signal from a standardized database of EEG recordings, and then, based on previous research and a mathematical model of neural activity, we propose neural mechanisms that could account for these changes.

A larger N100 amplitude reflects greater neural activity, or increased synchrony [25, 41], in response to a sensory stimulus. There are several systematic changes in N100 amplitude that are well documented: N100 amplitude is relatively large to the first stimulus in a series, but it decreases for subsequent stimulus repetitions [4,7,47]; N100 amplitude increases with interstimulus interval (ISI) [13]; N100 amplitude is enhanced when the eliciting stimuli are attended to [19]; N100 amplitude is increased when the subject expects to receive a relevant stimulus [6, 18]; and N100 amplitude decreases over long sequences of repeating stimuli [30].

The decrease in N100 amplitude for the first few stimulus repetitions has been proposed to be due to either a refractory period in ability of the brain to generate an ERP, or a process of habituation [7]. The ERP refractory hypothesis assumes some collective refractory mechanism, which has the effect that a neuronal group takes some time to fully regain its ability to fire again after participating in an ERP. The habituation account states that the neuronal representation of a particular stimulus is updated with stimulus repetition, and the decreased N100 amplitude is due to a loss of novelty. The refractory hypothesis predicts a rapid drop-off for the first repetition of a stimulus, whereas a habituation response implies a progressive reduction in N100 amplitude with stimulus repetition. Evidence favors the ERP refractory hypothesis, and the finding that N100 amplitude is dependent on ISI is more consistent with the refractory hypothesis: a larger ISI allows a neuronal population to progress further through its refractory period, and hence produce a larger N100 [7]. Note that a similar reduction in the amplitude of early ERP components (P50 and N100) has been shown in the paired click paradigm, in which two stimuli are presented close (< 1 s) together [1, 4]. This is often referred to as sensory gating, and the reduction is interpreted in terms of the brain's capacity to inhibit the additional sensory information. Neither sensory gating nor the refractory hypothesis are precise

descriptions of the neural mechanisms that underlie the reduction in N100 amplitude; accordingly, the relationship between them and their relative contributions to the N100 amplitude reduction are unclear.

It is also unclear what neural processes underlie the other changes in N100 amplitude. The decrease in N100 amplitude over the long-term has been proposed to be caused by decreased arousal [as discussed in 30]. However, this is not a neuronal level description of N100 change, and any attempt to use the concept of arousal change as a link to neuronal mechanisms is limited because there are multiple systems in the brain that act to ensure an appropriate level of brain arousal [33]. These include the cholinergic, noradrenergic, dopaminergic, and serotonergic pathways of the brainstem ascending arousal system [33]. Thus, even if it is the case that decreased arousal is associated with the reduction in N100 amplitude, then one still needs to distinguish between the multiple neural processes that regulate brain arousal in order to describe the change in ERP signal at a neuronal level. To complicate matters further, the systems in the brain that regulate arousal are often involved in other processes and have complex effects on the brain. For example, ACh not only acts to regulate brain arousal [12], but also plays a crucial role in attentional processes by gating the flow of sensory information into the cortex [22], and enables learning and memory by enhancing synaptic plasticity [17]. Almost all sensory information reaches the cortex via the thalamus, and increased levels of cortical ACh amplify thalamic afferents and suppress intracortical connections [8,15,22,28], while simultaneously making a cortical neuron more likely to respond [23,26,27,42] to excitatory input.

Similar problems exist for the other mechanisms proposed for the change in N100. Because we do not yet know enough about the brain to describe expectation, attention, habituation, or arousal at a cellular level, it is unclear what is the precise relationship between these processes. For example, assuming that a greater expectation of receiving a particular stimulus causes an increased level of attention and arousal, then it may be that the effects due to expectation could be mediated by the neural processes related to arousal and attention.

Addressing the difficulty of linking the ERP signal to neural mechanisms, Rennie *et al.* [34] generalized a model of the brain's electrical activity [37] so that it generated realistic ERPs. By modeling average neural behavior over sub-millimeter scales [14,24,31,37,46], Rennie *et al.* [34] was able to simulate whole brain activity with a model that was biologically realistic and directly related to the underlying physiology of the brain. Rennie *et al.* [34] explored the sensitivity of ERPs generated by their model to parameter changes, and inferred that an important physiological quantity in determining N100 amplitude was the strength of neuronal coupling between cortical neurons. Parameters in their model that did not significantly affect the N100 amplitude were related to: the length of axons and the velocity of action potentials along axons; the time constants involved in the rise and fall of the post-synaptic potential at the cell body; and the strength of neuronal coupling in the thalamus. The initial findings from Rennie *et al.* [34] were consistent with

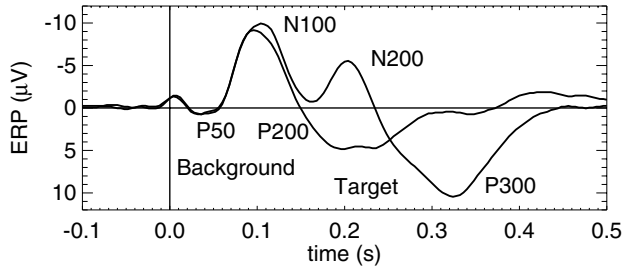

Fig. 1. Typical background and target auditory ERPs, with prominent features labeled.

later modeling work that included the influence of acetylcholine (ACh) on neural activity. Clearwater *et al.* [9] introduced the neuromodulator ACh into the model of Robinson and Rennie [34, 37], thus constraining parameters to change only in ways consistent with the physiology of cholinergic neural receptors. This led to the prediction that increased levels of ACh in the cortex would cause an increase in N100 amplitude [9, 10].

In the auditory oddball ERP paradigm, subjects listen to frequent (background) tones and infrequent (target) tones, and have to respond to the target stimuli. Background and target stimuli elicit the different ERPs shown in the Fig. 1. These ERPs are commonly averaged across trials and subjects to characterize different stimulus responses and clinical groups. However, based on the electrophysiological and mathematical work summarized above, the ERP should change systematically throughout a trial due to the refractory period of the neural response and the process of habituation, and it should change as the subject's level of arousal, attention and expectancy of receiving particular stimuli changes. This leads to the following predictions:

(1) Consistent with the refractory hypothesis, N100 amplitude will decrease for the first repetition of a stimulus pattern, but this amplitude reduction will stabilize for subsequent stimulus presentations;
(2) The N100 for both target and background ERPs will increase as the expectation of receiving a target stimulus increases;
(3) The N100 amplitude will decrease for both background and target ERPs over the duration of a recording session, and this decrease will be at the same rate as the subject's decrease in arousal level as indicated by the EDA.

Based on the literature presented above, these predictions are the main changes we expect to see in the ERP over the recording session. The change associated with the first prediction is well established in ERP literature, while the evidence for the second and third predictions is less clear cut [30]. Our goal is to produce all these changes from a standardized database of EEG recordings, and use the different dynamics of these changes to inform a discussion on the possible neural processes that could underlie each change.

To test our predictions regarding N100 change in relation to ERP refractoriness, habituation, expectancy and arousal, we analyze the data from two standard auditory ERP paradigms. The first test is referred to as the habituation paradigm. In this, 16 tones are presented that are not relevant to any task. Because this test is short we assume arousal to be steady, and because the tones are not task-relevant we assume expectation to be stable. Furthermore, the habituation task is performed first in the battery of tests performed in this study, so the stimulus tones are still entirely novel. This task therefore emphasizes ERP changes associated with refractoriness and/or habituation, and it shows the magnitude and the time course for the short-term decrease in the N100 amplitude with tone repetition. The second paradigm is the typical oddball task, and this data is examined in the Decile Study and the Sequence Study. In the Decile Study, we investigate how the ERP changes over the longer time scale by averaging each ERP depending on which decile of the recording session it falls in. We also record electrodermal activity (EDA) over the session to test for changes in arousal. In the Sequence Study, we investigate how the serial order of the stimuli influences the ERP. We group target and background ERPs according to the number of preceding consecutive background stimuli. As the number of consecutive background stimuli grows, the local target probability, sometimes called subjective probability, increases. We assume that the expectation of receiving a target stimulus is proportional to this local target probability, so sequences with an increased number of consecutive backgrounds are associated with higher expectancy of a receiving a target stimulus. By looking at changes over the six minutes of recording in the Decile Study, and over sequences of up to ten ERPs in the Sequence Study, we aim to quantify some of the changes in the ERP signal and thereby inform a discussion on possible neural mechanisms that could account for the changes.

In order to gain further information regarding the physiological changes that could take place to cause the changes in the ERP, we also fit a biophysical model to the ERP waveforms [21]. This model fitting technique has advantages over the traditional peak scoring approach of measuring the magnitude and latencies of particular peaks in ERP: (1) In peak scoring, much of the information content of the ERP is lost because only a few points are looked at in a noisy signal, whereas by model-fitting the whole signal is included; (2) because all parameters in this model represent physiological quantities, the change in the model parameters required to reproduce the ERPs indicate possible neural processes that could underlie the ERP changes.

Motivation for this research comes from the fact that the lack of understanding of the physiological processes behind ERP generation limits the use of ERPs in clinical diagnoses and brain research. Furthermore, the ERP shows characteristic changes with several neural disorders, in particular the N100 amplitudes of schizophrenic patients exhibit different behavior from that of healthy individuals [6]. In schizophrenics, there is not as much reduction in N100 amplitude with stimulus repetition [4], and the usual amplitude difference between backgrounds occurring

immediately before and after target stimuli is not seen [6]. A better understanding of the N100 may help to shed light on the physiological basis of schizophrenia.

In Sec. 2 we describe the methods used to obtain and analyze the data. In Sec. 3 we present our major results, and in Secs. 4 and 5 we discuss and summarize these findings.

2. Methods

2.1. *Data acquisition*

The EEG data used in this study were obtained from 50 healthy, non-smoking males, aged between 20 and 30 years, via the Brain Resource International Database (BRID) [16]. Scalp recordings were made with a 100 Hz anti-aliasing filter, and a 500 Hz sampling rate, from 26 sites of the International 10/10 system using an electrode cap, following previously-described methods for acquisition and artifact removal [16, 38]. Referencing was to the average of the two ear electrodes. Artifacts arising from eye-blinks were corrected by performing a bilinear regression of each EEG channel against both vertical and horizontal electrooculogram (EOG) signals, and then subtracting the predicted channel-specific EOG artifact. Baselines were removed by a 0.5 Hz high-pass filter. Mains frequency interference was not filtered because it did not effect any of our results. All EEG data presented in this research were recorded from the site Cz; however, other sites were examined to check for consistency. In one subject, the Cz site was faulty so the subject's oddball data was removed, leaving 49 complete sets of data.

To obtain the EDA data used in this study, skin conductance was measured between the index and middle fingers on the non-dominant hand. In 24 subjects, the EDA recording was faulty and the data was not used, leaving 26 complete sets of EDA data. Faulty data was easily identified by eye, and all spurious data was excluded by setting the criteria for inclusion to be $4\,\mu\text{S} < \bar{x} < 20\,\mu\text{S}$, where $\bar{x}$ is the mean EDA over the recording session.

The auditory habituation and auditory oddball task recordings used here were obtained as part of a wider battery of electrophysiological tests [16]. For both the habituation and the oddball tasks, participants were seated in a quiet, dimly-lit laboratory, facing a video screen and wearing a pair of headphones. In the habituation task, participants listened to a series of 16 tones, with a constant interstimulus interval (ISI) of 1 s between each tone. The first ten and last five tones were at 500 Hz, while the 11th (dishabituation) tone was at 1000 Hz. Each tone lasted 50 ms including a 10 ms rise and fall time. Participants were told that they would hear some sounds, but were instructed to ignore them. In the auditory oddball task, participants were presented with a series of target tones (1000 Hz) and background tones (500 Hz) at 75 dB, with a constant ISI of 1 s. Each tone lasted 50 ms including a 10 ms rise and fall time. A total of 280 background and 60 target tones were presented in a quasi-random order, apart from two target stimuli never occurring

consecutively. Subjects were required to ignore background tones, but to respond to target tones with a button press. The task lasted six minutes.

2.2. *ERP extraction*

ERP data were extracted from EEG recordings using a window from −200 ms to 800 ms relative to the stimulus onset.

For each of the 16 tones in the habituation paradigm, an average ERP was calculated by averaging overall subjects. Accordingly, 16 average ERPs were generated that corresponded to the stimulus presentation order. Likewise for the oddball paradigm, an ERP was calculated for each of the 340 tones by averaging overall subjects. These 280 background ERPs and 60 target ERPs were then analyzed in two separate studies that focused on distinct time scales. Because participants were required to respond to target stimuli in the oddball paradigm and their responses were checked for correctness, we can assume their level of attention remained relatively constant. However, the subject's arousal level is likely to decrease as they become familiar with their environment and the novelty of the task decreases. The change in ERP over the duration of the recording session was assessed in the Decile Study. Also, the probability of receiving a target stimuli increases with the number of consecutive background stimuli, and hence the participant's expectancy of receiving a target stimulus will increase. To see the effect of expectation on the ERP, target and background ERPs were grouped according to sequential order and studied in the Sequence Study.

Decile Study. To see how the ERP changed over the duration of the recording session, the target and background ERPs were separately grouped according to which temporal decile of the recording session they occurred in. This produced ten target and ten background average ERPs. In each decile of the six-minute recording session there were 28 background stimuli and six target stimuli.

Our hypothesis was that the N100 would decrease over the recording session as the participant's arousal decreased, where arousal is defined by the general state of physiological and psychological activation. This level of arousal is mirrored by the activity of the sympathetic nervous system, which can be quantified by measuring electrodermal activity (EDA) [11]. Accordingly we also examined the subjects' EDA for each decile in the recording session.

Sequence Study. To see the effect of expectation on the ERP, target and background ERPs were grouped in sequential order. The 60 target ERPs were sorted into five groups according to the number of consecutive preceding background stimuli; each group had approximately the same number of target ERPs. The groups were: one preceding background before the target (TBT); two consecutive backgrounds before the target (TBBT); either three or four consecutive backgrounds before the target (T3–4BT); between five and nine consecutive backgrounds before the target (T5–9BT); or ten consecutive backgrounds before the target (T10BT). The groups

TBT, TBBT and T10BT had 12 target ERPs, the group T5–9BT had ten target ERPs and the group T3–4BT had 13 target ERPs. The first target heard by the subject was not included in this grouping as it is a special case, so the total number of target ERPs classified by this method was 59. Background ERPs were similarly grouped into one of five bins according to the number of consecutive preceding background ERPs: background straight after a target (TB); one preceding background (TBB); two or three consecutive background before the background (T2–3BB); between four and eight consecutive preceding background (T4–8BB); or nine consecutive preceding background (T9BB). These groups had a relatively wide range of numbers of background ERPs in each group: TB (59); TBB (47); T2–3BB (68); T4–8BB (90); T9BB (12). The first four tones in the oddball paradigm are background tones so they do not have a relationship to preceding target. Therefore they were excluded from this study and total number of backgrounds classified in this manner was 276.

2.3. *Analysis of ERPs*

2.3.1. *Peak scoring and curve fitting*

The magnitude (base to peak) and latencies of peaks in the ERP signal were measured, using previously-determined latency windows to define the components [2,45]. In this study we investigated N100 (80–140 ms, target and background), P200 (140–270 ms, background only), and P300 (270–550 ms, target only). All trend lines reported in this study were obtained using the method of weighted linear least squares. Paired t-tests were used to test the significance of the difference between peak magnitudes.

2.3.2. *Model-based analysis*

A physiologically-based model of neural activity was used to generate theoretical ERPs, and these were fitted to the set of background ERPs from the Decile Study. This model-based fitting methodology makes use of all the data in the ERP signal, and provides additional information on the underlying physiology of the brain that is not available using standard peak scoring methods [21].

Fitting was performed using the Robinson *et al.* corticothalamic model [35], following previously published methods [21, 38]. All parameters in this model are constrained by physiology and by our previous modeling work; for full details of the development of this model and the relationship of parameters to physiological quantities see [21, 34–38]. In brief, the model consists of five neural populations: excitatory cortical (e), inhibitory cortical (i), reticular thalamic (r), relay thalamic (s), and external input (n). Gain values G_{ab} represent the strength of coupling from neuronal population b to neuronal population a and they depend on the number and strength of synaptic connections, and on the average excitability of the receiving neuronal population. For clarity, we denote the product of gains G_{ab} and G_{bc} as

G_{abc}. As in previous publications, the linear transfer function for the corticothalamic model — relating cortical excitatory activity to thalamic driving signal at angular frequency ω and wave number k — is

$$\frac{\phi_e}{\phi_n} = \frac{G_{es}L}{1-G_{ei}L}\frac{G_{sn}Le^{i\omega t_0/2}}{1-G_{srs}L^2}\frac{1}{k^2r_e^2+q^2r_e^2}, \tag{2.1}$$

$$q^2r_e^2 = \left(1-\frac{i\omega}{\gamma_e}\right)^2 - \frac{L}{1-G_{ei}L}\left[G_{ee}+\frac{(G_{ese}+G_{esre}L)L}{1-G_{srs}L^2}e^{i\omega t_0}\right], \tag{2.2}$$

$$L = \left(1-\frac{i\omega}{\alpha}\right)^{-1}\left(1-\frac{i\omega}{\beta}\right)^{-1}, \tag{2.3}$$

where $1/\alpha$ and $1/\beta$ respectively are the time constants of the fall and rise of the voltage signal at the cell body, and γ_a is the spatial damping rate, which is tied to the range of cortical axons (r_e), and the velocity of signals that travel along them. Driving Eq. (2.1) with an appropriate form of the input signal ϕ_n, such as a spatial and temporal Gaussian, produces realistic auditory ERPs. Parameters of the driving signal and those of the transfer function both change the shape of the ERP. However, because the driving tones were identical for all background stimuli, an identical input signal was assumed for all fits and only parameters in the transfer function were varied to fit the ERPs.

Fitting of the model to the first decile ERP was by a Monte Carlo procedure. Parameters found by Kerr *et al.* [21] to correspond to group average standard ERPs were used as a common starting point for fits to the first decile. Then, for each Monte Carlo run, these initial values were randomly perturbed, and fitting was performed by varying the parameters of the theoretical ERP to maximize goodness-of-fit using the Levenberg-Marquardt method of linear least-squares fitting [39]. Calculated fits were checked to ensure model stability, physiological plausibility, and sufficient goodness-of-fit. All acceptable fits were combined to give an overall estimate for each parameter value. This resulted in parameter values that lay within acceptable ranges established in previous studies [21,38]. Once fits to the first decile were completed, fits to subsequent deciles were performed as above, except that initial parameters were provided by fits to the first decile, and only certain subsets of the parameters were allowed to vary. As discussed below, this was done to allow specific hypotheses about the physiological basis of the trends to be tested.

3. Results

In this section, changes in the ERP components within the habituation and oddball paradigms are described. The results from the habituation study are shown first, and short-term changes are further characterized by the Sequence Study. Changes in the ERP over longer time scales are then demonstrated by the Decile Study. Finally the model fits and corresponding parameter changes are shown.

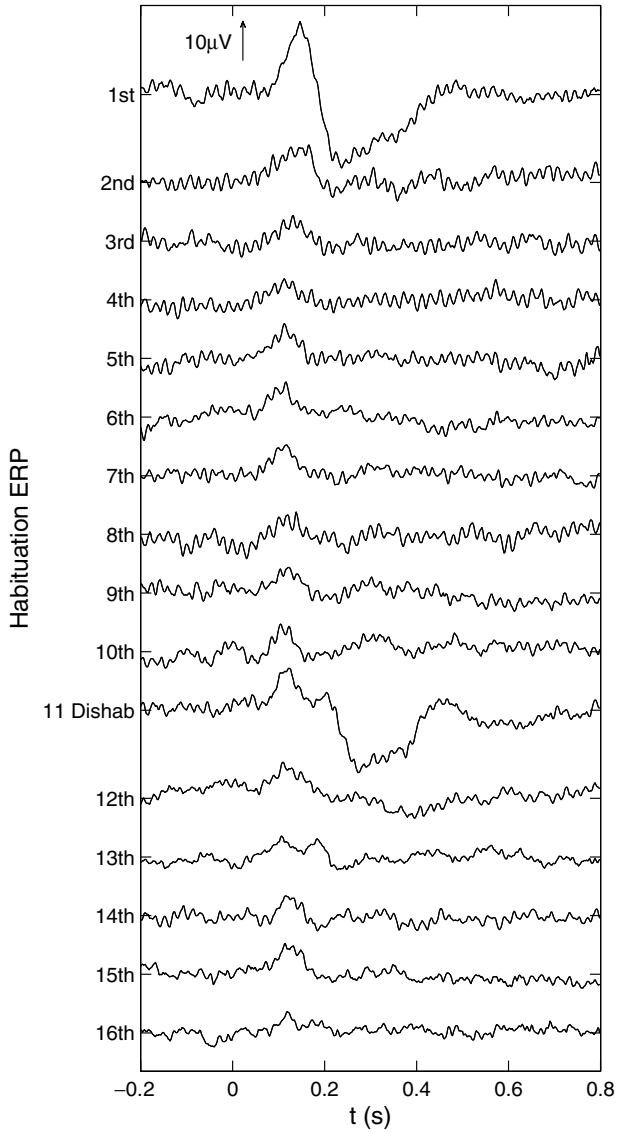

Fig. 2. ERPs recorded during the habituation sessions, averaged over all subjects. The vertical axis indicates the sequence in which subjects heard the tones. The 11th stimulus in sequence was the dishabituation tone.

3.1. *Habituation study*

The ERPs recorded during the habituation paradigm are shown in Fig. 2, and the corresponding N100 amplitudes are summarized in Fig. 3. There is a significant reduction in N100 amplitude from the first to the second tone, paired $t(49) = 3.1$, $p = 0.003$. This amplitude reduction plateaus for subsequent stimulus presentations, and the fitted linear trend line to the data points from the second to the tenth tone (not shown) has a gradient of -0.27 with 95% confidence interval $(-0.54, 0.01)$.

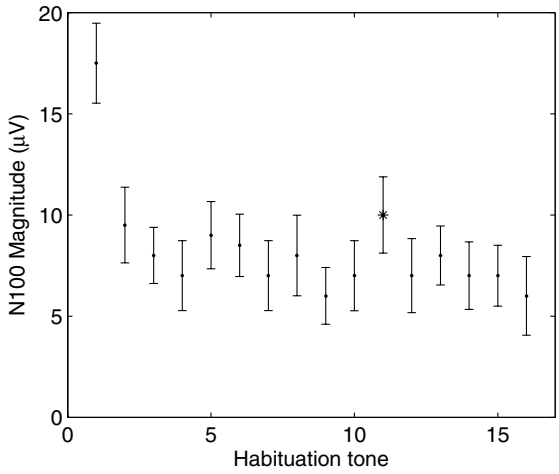

Fig. 3. The N100 amplitude of average ERPs during the habituation paradigm. The dishabituation response is marked with an asterisk. Error bars indicate the standard error of the mean.

Because the interval for the gradient includes a slope of zero we conclude that there is no significant linear trend in N100 amplitude over these tone presentations at the 95% confidence level. Discounting the initial stimulus, the N100 response is largest to the eleventh (dishabituation) tone, but the increase in N100 magnitude from the tenth to the eleventh tone is not significant, paired $t(49) = 0.77$, $p = 0.44$. As shown in Fig. 2, this tone caused a target-like ERP response. The N100 response to the stimulus after the dishabituation tone did not increase in amplitude in comparison to the preceding tones.

3.2. *Sequence study*

The background and target ERPs from the Sequence Study are shown in Fig. 4.

In Fig. 5, it is shown that as the number of consecutive background stimuli increases, the N100 of the following background generally increases in magnitude — the slope of the fitted linear trend line is strictly positive within the 95% confidence interval. There is no clear trend for the magnitude of the background P200.

For target ERPs shown in Fig. 6, as the number of consecutive preceding backgrounds increases, the N100 magnitude generally increases — the 95% confidence interval of the slope of the fitted linear trend is positive. The magnitude of the target P300 does not have significant increasing or decreasing linear trend, but the P300 magnitude in the sequence TBBT is bigger than the P300 TBT response, paired $t(48) = 2.7$, $p = 0.009$.

3.3. *Decile study*

Both target and background ERPs for each decile in the recording session are shown in Fig. 7. As can be seen in Fig. 8, the magnitudes of both the background N100

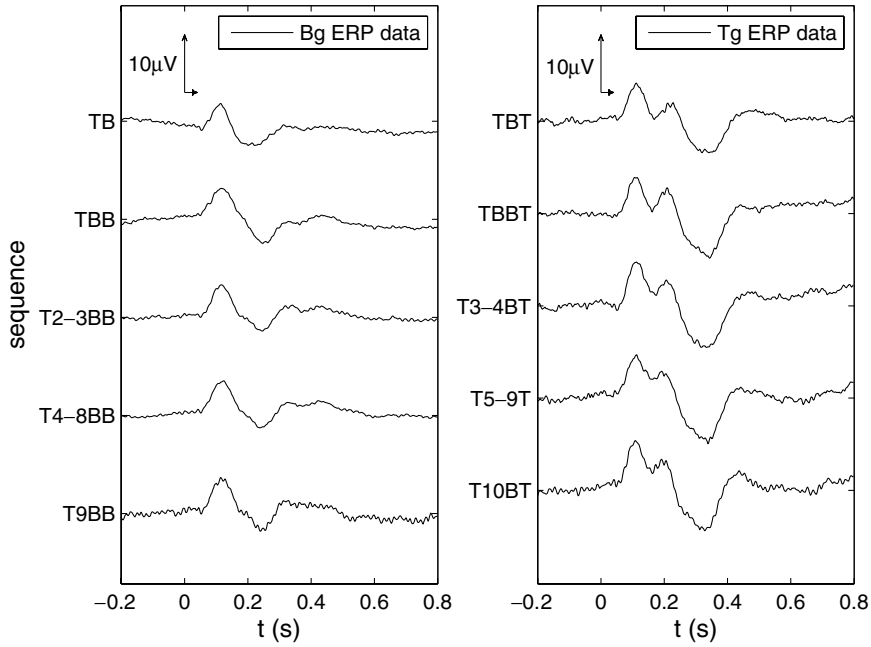

Fig. 4. Background (left panel) and target (right panel) ERPs averaged according to where they come in the sequence. The labels on the vertical axis indicate where the background and target came in the sequences described in Sec. 2.2.

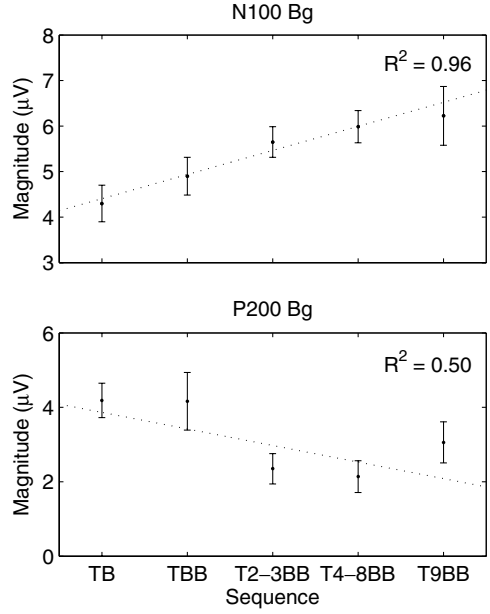

Fig. 5. The amplitude of background N100 and background P200, grouped according to the number of consecutive preceding background stimuli. The dotted lines show the fitted linear trend. The trend-line for N100 amplitude has slope 0.53 with 95% confidence interval (0.32, 0.74), while the P200 amplitude has slope −0.45 with 95% confidence interval (−1.3, 0.37). Error bars indicate the standard error of the mean.

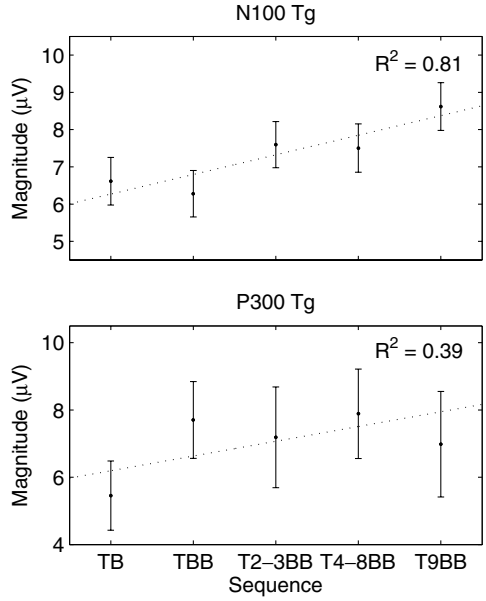

Fig. 6. The amplitude of target N100 and target P300, grouped according to the number of consecutive preceding background stimuli. The dotted lines indicate the fitted linear trend. The fitted linear trend for N100 amplitude has a slope of 0.53 and 95% confidence interval (0.06, 1.0), and the fitted linear trend for P300 amplitude has a slope of 0.44 and 95% confidence interval (−0.57, 1.4). Error bars indicate the standard error of the mean.

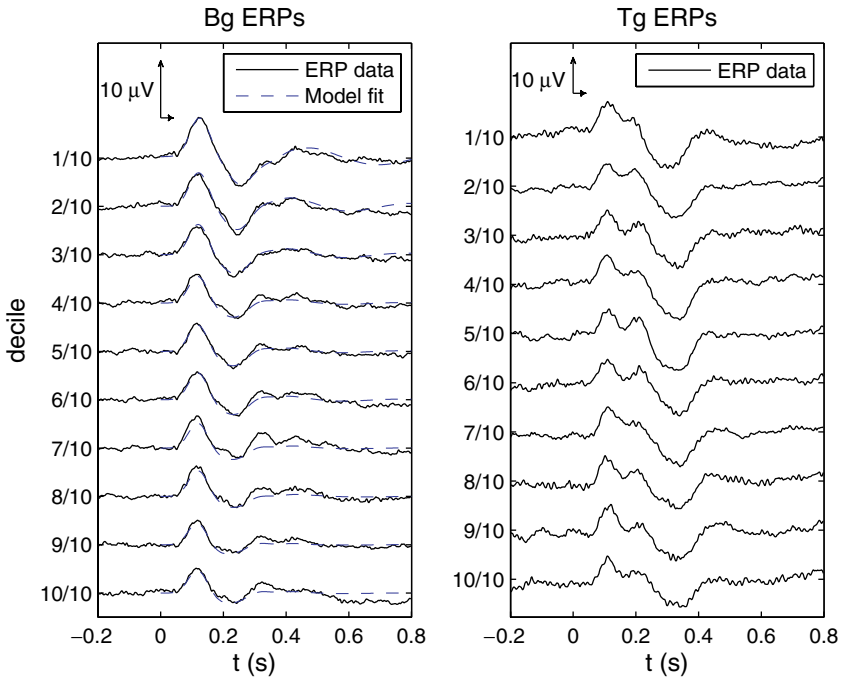

Fig. 7. Background (left panel) and target (right panel) ERPs averaged over each decile of a recording session. The dashed lines in the left panel show the mean-field model fits.

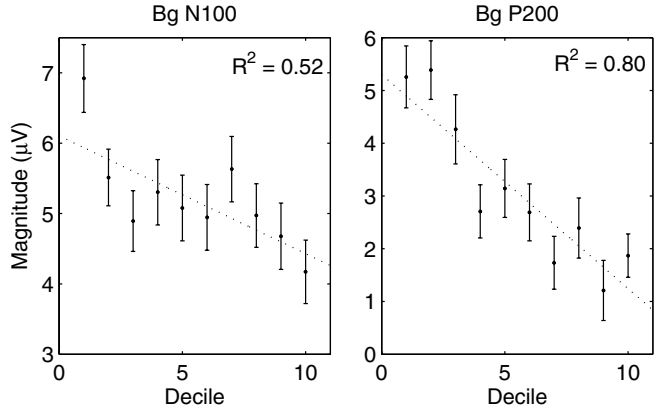

Fig. 8. The amplitude of the N100 and P200 for background ERPs, averaged within the ten deciles of the recording session, with error bars indicating the standard error of the mean. The dotted line in the left-hand panel shows the fitted linear trend that has slope −0.17 with 95% confidence interval (−0.30, −0.04). The fitted linear trend in the right-hand panel has slope −0.41 with 95% confidence interval (−0.57, −0.24).

and P200 peaks show a clear decreasing trend over the entire recording session; the slopes of the fitted linear trend lines for both are strictly negative at the 95% confidence level. This is in contrast to the N100 amplitude in the habituation study shown in Fig. 3, which decreases to an asymptote within two stimuli presentations.

As shown in Fig. 9, there is no clear trend in the N100 magnitude of target ERPs. The target P300 decreases slightly over the recording session, but the fitted linear trend includes a slope of zero in the 95% confidence interval and the R^2 value

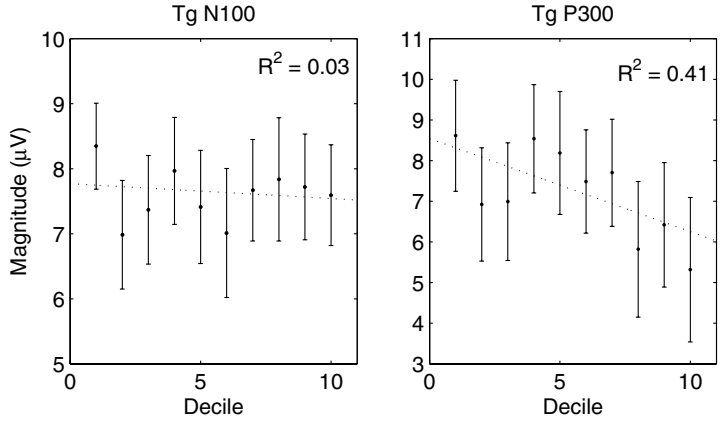

Fig. 9. The amplitude of the N100 and P300 for target ERPs, averaged within the ten deciles of the recording session, with dotted lines indicating the fitted linear trend. The fitted linear trend for N100 magnitude has the slope −0.02 with 95% confidence interval (−0.13, 0.09), and for P300 magnitude the slope is −0.23 with 95% confidence interval (−0.46, 0.00). Error bars indicate the standard error of the mean.

is relatively low (0.41), indicating that this decreasing linear trend is weak, and that it does not account for much of the variance in amplitude.

In addition to measuring the change in amplitude of the individual ERP components, the background ERPs from the Decile Study were reproduced using the mean-field model of neural activity described in Sec. 2.3.2. Most parameters in Eq. (2.1) describe physiological properties that do not change over the time scale of minutes, such as the time constants for the rise and fall of the voltage at the cell body, the range of axons and the conduction velocity of nerves. Accordingly, these were kept fixed, and only gain values were allowed to vary during fitting of the Decile Study ERPs. Gain values represent the coupling strength between neuronal populations, which is determined by strength and number of synaptic connections and the excitability of the receiving populations. Because a similar quality of fit was obtained by allowing different subsets of gains to vary, fits were ranked according to the number of parameters that were allowed to vary in order to obtain good quality fits. A set of fits that used fewer varying parameters was regarded as better on the grounds of parsimony. The best fits with the simplest set of parameter changes were obtained by allowing only intracortical gains G_{ee} and G_{ei} to vary. The results of these fits are plotted in Fig. 7, and as can be seen, the simulated ERPs are in excellent agreement with the real ERPs. The actual values used for G_{ee} and G_{ei} in the fitting routine are plotted in Fig. 10. Both of these gains increased in magnitude over the duration of the recording session. Note that a similar quality of fit was also obtained by allowing different subsets of three gains to vary; however, none of these showed consistent parameter changes, suggesting that these fits were over-parameterized.

In order to obtain an objective measure of arousal level during the Decile Study, each individual's EDA was recorded during the oddball paradigm. As can be seen in Fig. 11, EDA declines over the six-minute recording session.

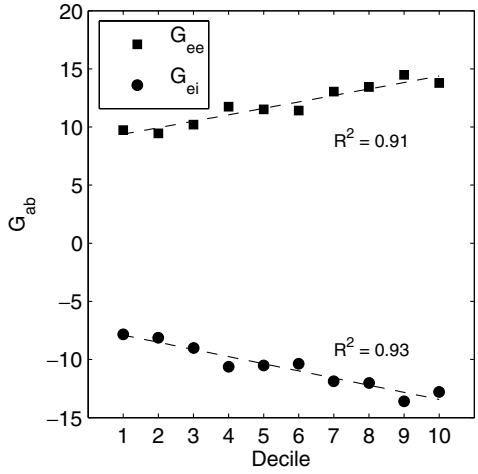

Fig. 10. The values of G_{ee} and G_{ei} used to model background ERPs in the Decile Study.

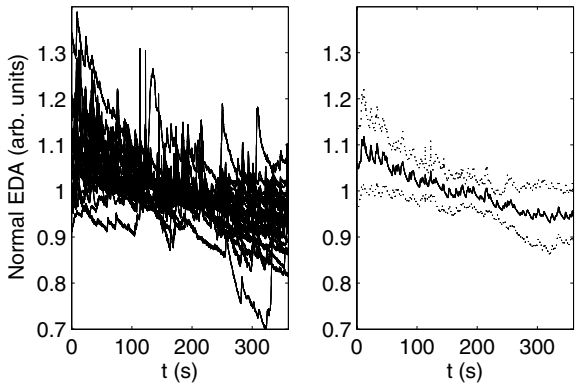

Fig. 11. Plots of EDA recorded over the six-minute auditory oddball paradigm. The left panel shows the traces of each of the 26 datasets, and the right panel shows the average EDA (solid line) plus and minus the standard deviation (dotted line). Each EDA trace was normalized to its mean value over the six-minute recording session, so units are normalized to the mean.

4. Discussion

In this section, the results are interpreted in context of the electrophysiological and pharmacological literature. In Sec. 1 we predicted that: (1) N100 amplitude would decrease with short sequences of repeating stimuli due to the refractory period of the neural generators of the ERP; (2) N100 for both target and background ERPs would increase as the expectation of receiving a target stimuli increases; and (3) N100 amplitude would decrease for both background and target ERPs over the duration of a recording session at the same rate as the subject's arousal level decreased.

Consistent with the first prediction, in the habituation study N100 amplitude dropped significantly in response to the second tone (Figs. 2 and 3), and then stabilized for additional stimulus presentations. Furthermore it increased slightly for the dishabituation tone. These changes are consistent with the refractory hypothesis [7]. Repetition of stimulus presentation leads to the repeated activation of a particular group of frequency-specific neurons. After participating in an ERP event these neurons have a refractory period, in which they have a reduced response to identical input stimulus. The state of refractoriness is set by how far through the refractory period the group of neurons is. The first stimulus in the sequence elicited the largest N100 response because, as there were no prior ERP events, no neuronal groups were in a refractory period. In fact, because the habituation paradigm is the first of the BRID battery of tests, the first response is especially novel — it is the very first test tone a subject hears [16]. A stimulus with a different frequency, such as the dishabituation tone, will elicit a larger N100 because a different neuronal group participates in the ERP.

The second prediction states that as the expectation of receiving a target stimulus increases, the N100 for both target and background ERPs should increase in magnitude. As can be seen in Figs. 4–6, the N100 amplitudes for background and target

ERPs increase as the number of consecutive background stimuli increases, with both background and target N100 magnitudes increasing by approximately 2 μV. This is consistent with the second prediction because the number of consecutive background stimuli is directly related to the subjective probability and expectation of receiving a target stimulus. Because there is a one second gap between stimuli and we see an increasing trend in N100 amplitude based on sequences of between one and nine consecutive background ERPs, the neural processes responsible for causing this change in the ERP have to be capable of acting on the time scale of seconds. Possible physiological processes that operate on this time scale are changes in synaptic plasticity, short-term memory, and modulation via the ascending arousal activating system from the brainstem.

The third prediction from Sec. 1 is that N100 amplitude for both target and background ERPs will decrease over the recording session, with the same time course as the EDA. Consistent with this the background N100, background P200, and EDA decrease over the entire recording session (Figs. 7, 8, and 11), indicating that the hypothesis that the N100 decrease is due to a decreased arousal is plausible. However, contrary to this prediction there is no corresponding trend in the target N100 amplitudes (Fig. 9), and this is discussed at the end of this section. In this Decile Study, the ERP is shown to change systematically over the six-minute recording session, constraining our search for the neural mechanisms responsible for this change to those capable of acting over such a time scale. Possible candidates include changes in synaptic plasticity associated with long-term memory and modulation via the ascending arousal activating system.

In order to shed more light on the neural processes underlying the ERP changes, a physiologically-based brain model was used to reproduce the background ERPs recorded over the duration of the recording session in the Decile Study. Excellent fits to the averaged ERPs were obtained by fixing all parameter values apart from the gains between intracortical neurons (see Figs. 7 and 10). Both the reciprocal gain between excitatory neurons and the gain between excitatory and inhibitory neurons increased in magnitude. Since gain values in the model are a function of the number and strength of connection between neuronal populations, and since the number of connections remain fixed over the duration of the recording session, changes in synaptic strengths are the most likely cause of the changes in gain. Thus, model-based fitting suggests that the neural mechanism responsible for the changes in the ERP over the recording session is in the cortex, and it involves something capable of changing the synaptic strength of connection between neurons on the time scale of seconds. In Sec. 1, neuromodulation by ACh was proposed as a possible mechanism regulating the N100 magnitude. ACh acts to reduce the synaptic strength of connections between cortical neurons and is expected to have its biggest effect at the beginning of the recording session. Our research is consistent with this proposal: a reduction in ACh concentration over the recording session could explain the increase in intracortical gains, and the corresponding decrease in N100 magnitude. Thus, because of ACh's role in attention and arousal and its

ability to gate sensory input into the cortex, and because of the modeling work discussed above, it is a prime cellular level candidate to contribute to some of the N100 change. Very few studies have investigated the influence of ACh on the ERP, but Pekkonen *et al.* [32] showed that application of a muscarinic antagonist delays the N100 peak, and Baldewag *et al.* [3] demonstrated that nicotine augments the mismatch negativity in schizophrenic patients.

In Fig. 10 it is shown that the gain parameters for intracortical excitation and intracortical inhibition both increase in magnitude by approximately the same amount. While large changes in G_{ee} and G_{ei} affect both the shape and amplitude of the ERP, small changes affect only the amplitude, leading to slight degeneracy between these parameters. The mirror-image noise fluctuations seen in Fig. 10 are due to this redundancy. It is intriguing to note that these gain changes are consistent with the idea of a balanced network [40]. By increasing or decreasing both gains, the balance of excitation to inhibition in our model stays approximately the same, $G_{ee}/|G_{ei}| \approx 1$. This ensures that the system remains stable, and allows it to become more or less responsive [40]. Future work will investigate the relationship between ERPs, neuromodulation and balanced networks in more detail.

As stated above, in the Decile Study, N100 magnitude for background ERPs behaved as predicted but the N100 magnitude for targets did not. This is difficult to account for. However, there are several well-documented differences between the N100 components of target and background ERPs that could confound these results. These differences include: the mismatch negativity, which is the relative negativity of the target ERPs relative to background ERPs that begins approximately 100 ms post-stimulus [29]; an augmented N100 amplitude in targets due to the differences in refractoriness of the neural populations activated by the two stimuli [44]; changes in the N100 due to the differences in the physical characteristics of the stimulus (target stimuli are, by definition, different enough from background stimuli to elicit a different neural response) [30]. These additional factors modulate the magnitude and latency of the target N100 response relative to backgrounds, and as such these effects may dominate the small increase in N100 amplitude associated with decreased arousal. Consistent with this, the mean N100 magnitude for target ERPs is $7.5 \pm 0.8\,\mu$V, which is larger than the mean N100 background magnitude of $5.2 \pm 0.5\,\mu$V. The mean latency to target N100 peak was 112 ± 5 ms, which is slightly shorter than the mean latency to background N100 peak (120 ± 4 ms).

As shown in Fig. 6, target P300 amplitude increased when the number of preceding background stimuli increased from one (TBT) to two (TBBT), but this increasing trend did not continue for sequences with additional backgrounds. Previous research has shown a relationship between P300 amplitude and both the global probability of receiving a target stimulus (the percentage of all tones that are targets) and the local target probability (the sequence of immediately preceding stimuli) [20,43]. In this study we have only examined the effects of local target probability, and our results are inconclusive. An additional reason for caution in interpreting these P300 results is that recent evidence has shown that the probability of receiving a target

stimulus affects the likelihood that a P300 will be generated, and it may be this that accounts for the apparent amplitude modulation [5].

5. Summary

In this study we have analyzed the changes in the auditory ERP signal over the course of a typical habituation and oddball paradigm. It is argued that: the N100 reduces over the short-term due to a refractory period in the ability of the brain to generate an ERP; the N100 reduces over the long-term due to decreased arousal levels; and an increased expectancy of receiving task-relevant stimuli increases the size of the N100. Furthermore, the ERPs produced in each decile of the recording session were reproduced by a physiologically-based model of neural activity. Changing the strength of neuronal coupling in the cortex, in a manner similar to what would be expected with a reduction in cortical ACh concentration, was sufficient to account for the change in ERP over the recording session.

In addition to arguing for the plausibility of ACh in modulating the size of the N100 amplitude, our results also raise two additional points. The first is that, given the amount of variance over the recording session, the usual practice of grand averaging ERPs may mask information contained in the ERP signal. Potentially, in regard to clinical work, it may be that the change in the ERP has more diagnostic value than averaging over these changes and looking at a single signal. The second point is that background ERPs contain far more information than usually given credit for. They reflect arousal state, attentional processing, and level of expectation, and may be a fruitful target for future research.

The results above demonstrate the benefits of an integrative neuroscience approach. By combining electrophysiological data with mathematical modeling, and constraining our conclusions based on neurophysiology and the dynamics of neuromodulator effects, we shed new light on the neural mechanisms of ERP change.

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