Mapping Repetition Suppression of the N100 Evoked Response to the Human Cerebral Cortex

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Background: Repetition suppression (RS) phenomena, such as those observed using paired-identical-stimulus (S1–S2) paradigms, likely reflect adaptive functions such as habituation and, more specifically, sensory gating.

Methods: To better characterize the neural networks underlying RS, we analyzed auditory S1–S2 data from electrodes placed on the cortices of 64 epilepsy patients who were being evaluated for surgical therapy. We identified regions with maximal amplitude responses to S1 (i.e., stimulus registration regions), regions with maximal suppression of responses to S2 relative to S1 (i.e., RS), and regions with no or minimal RS.

Results: Auditory perceptual regions, such as the superior temporal gyri, were shown to have significant initial registration activity (i.e., strong response to S1). Several prefrontal, cingulate, and parietal lobe regions were found to exhibit stronger RS than those recorded from the auditory perceptual areas.

Conclusions: The data strongly suggest that the neural network underlying repetition suppression may include regions not previously thought to be involved, such as the parietal and cingulate cortexes. In addition, the data also support the notion that the initial response to stimuli and the ability to suppress the stimuli if repeated are two separate, but likely related, functions.

Key Words: Cingulate gyrus, frontal lobes, habituation, parietal lobes, temporal lobes, thalamus

The ability to suppress responses to incoming redundant sensory input (i.e., habituation) is a recognized characteristic of the central nervous system (1,2) and has been extensively studied using evoked potential (EP) methodologies (3). In particular, the P50 and N100 midlatency auditory evoked responses (MLAER) have been used to examine habituation using repetition suppression (RS) paradigms. Considerable research has documented that EP habituation is not caused by the effector activity used in most studies to elicit the EP (4), and therefore, intermediate processes such as sensory encoding and stimulus evaluation are hypothesized (5).

Probing N100 RS in neuropsychiatric conditions is promising as evidenced by a growing literature (6–8). More generally, RS has been investigated in a large number of psychiatric and neurological conditions (9) and has proved useful in probing the genetics of neuropsychiatric disorders (10–12).

Average auditory EP responses recorded at the scalp exhibit a sequence of three major components: positive (P50), negative (N100), and positive (P200) deflections (13–15). In RS experiments using the paired-stimulus paradigm (PSP), each MLAER component is suppressed by stimulus repetition. The suppression ratios of the different MLAERs are not correlated (16) and therefore likely are associated with distinct, yet overlapping and interacting, phases of RS. Thus, knowledge about the RS properties of each MLAER component is prerequisite for understanding the entire RS system in the human brain. Although some work has been published regarding the circuitry underlying P50 gating (17,18), little work addresses the circuitry of N100 gating.

The PSP is widely used to study RS (19,20). When two identical stimuli (S1 and S2) are presented with a short interstimulus interval (ISI), the N100 response to S2 is suppressed. This "N100 suppression" is usually expressed as the S2:S1 ratio of the two N100 responses and is thought to index habituation at the early attentive phases of information processing.

In this study, we adopted an approach for direct functional mapping of N100 RS in the human brain by combining neuroimaging and intracranial electroencephalogram—an opportunity afforded by epilepsy patients who participated in a PSP study while undergoing evaluation as candidates for surgical treatment (21). Specifically, the study aimed to map amplitudes and RS ratios of the N100 using data obtained from grid and strip electrodes placed on various areas of the cortex. We then built on data from current as well as prior work to propose a preliminary model for N100 RS including structures not interrogated in this study, such as the thalamus and hippocampus (3,14).

Methods and Materials

Between 2001 and 2006, 79 patients with drug-resistant focal epilepsies were implanted with cortical electrodes for invasive seizure recordings as part of their presurgical evaluation. All data were collected from the Epilepsy Hospital, Bonn Univeristy, Bonn, Germany. Fifteen subjects were excluded because of extreme artifacts. Data presented here are from the remaining 64 subjects (32 men). Age ranged from 19 to 65 with a mean of 37 $\pm$ 12 years.

Patient Characteristics and Clinical Methods

The diagnostic presurgical workup included video-electroencephalogram recordings with surface and subdural/depth electrodes to determine the location of seizure onset, as well as high-resolution magnetic resonance imaging (MRI) (22). Psychiatric status and history were assessed by an experienced psychiatrist (23). All patients were on standard therapy with anticonvulsant drugs.

Electrode placement was verified visually using postimplantation MRI with axial and coronal T2-weighted and fluid-attenuated

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inversion recovery sequences (slice thicknesses 2 and 3 mm, respectively) as well as sagittal T1-weighted sequences. Of the 64 subjects, 30 had evidence of pathology on the right hemisphere, 25 on the left hemisphere, and 9 on both sides. Fourteen subjects had pathology localized to one of the medial temporal structures without evidence of neocortical lesions. All patients signed an informed consent approved by both the University of Bonn and Wayne State University.

EP Recording

In a PSP, 75 pairs of identical clicks (S1 and S2; sinusoidal waves, frequency 1500 Hz, Gaussian envelope, duration 4 msec, onset and decay phase of 1.2 msec each) were presented binaurally via headphones with an interstimulus interval of 500 msec and an interpair interval of 8 sec (24). Patients were asked simply to listen to the stimuli. MLAERs were recorded from subdural strip and grid electrodes (sampling rate 1000 Hz per channel, epoch length 1200 msec, prestimulus baseline 200 msec), with reference to both mastoids (bandpass filter setting .03–85 Hz, 12 dB/octave). Details of electrode coverage were published in prior publications (25,26). Figure S1 in Supplement 1 shows all cortical regions where electrodes were placed. Table S1 in Supplement 1 lists all the anatomic regions where electrodes were placed and the number of subjects with electrodes per each region.

All contacts exhibiting N100 responses to S1 were identified by visual inspection, noting the most prominent negative peak in the 70- to 150-msec time window following stimulus onset. A two-step process was employed to increase the confidence that the identified component represents the N100. First, we relied on the well-established scalp morphology of the Vertex Complex (i.e., N100/P200) (27). Components that clearly resembled the N100, as determined by two authors independently, were subjected to the following second step to confirm whether each given channel would be retained for further analysis. Single-trial segments with respect to S1 (–100 to 400 msec) were baseline corrected by subtracting the prestimulus interval (–100 to 0 msec) mean. Then, a paired *t* statistic waveform was obtained by normalizing the mean (across trials) by the standard error (across trials) for each time sample. (This is a paired *t* statistic because each single-trial time-sampled potential is compared against the trial's own baseline, which is identically zero due to prior baseline correction.) Finally, a given channel was confirmed for further analysis (labeled "good") if the largest negative *t* value in the N100 peaking interval was more negative than the largest negative *t* value in the baseline period; otherwise, the channel was rejected (labeled "bad") on statistical grounds. Figure S2 in Supplement 1 shows a waveform that was selected visually and confirmed statistically and one chosen visually but rejected statistically. Out of 1065 channels selected visually for all subjects, 271 were rejected, leaving 794 channels for analysis. In total, 107 classified brain regions contained valid data. No other sampled brain regions showed evidence (visual or statistical) of significant N100 activity.

For the S2 response, a similar two-step process was adopted but in a reverse order. Where an S1 was selected, the segmented single-trial S2 responses (–100 to 400 msec) were baseline corrected; *t* statistics were calculated as described for S1; and the largest negative *t* value during the N100 peaking interval was compared with the largest negative *t* value during the baseline period. For S2, the channels were labeled as response present versus response absent. For all channels with response present, N100 S2 components were visually identified. For channels with *t* statistic indicating a nonsignificant difference from baseline, the averages were inspected visually by two investigators to determine whether an S2 component could confidently be identified based on the morphology of the waveforms. Of the 794 channels over all subjects with confirmed N100 for S1, the S2 N100 was statistically absent for 244. Of these channels, 65 had no visually identifiable N100 and were labeled as having completely attenuated the S2 response (i.e., gating ratio = 0). S2 N100 components were visually identifiable from the remaining 179 channels (over all subjects). All visually identified N100 components were measured from peak to the preceding peak (8). RS was quantified as the S2/S1 × 100 ratio, with higher ratios indicating less effective RS. In patients exhibiting an N100 at several leads within a classified brain region (discussed subsequently), the electrode with the highest N100 amplitude was chosen for determining the degree of RS.

The anatomic regions indicated (Figure S1 in Supplement 1) were used as a guide for pooling the data within closely related anatomic areas. Each designated area had a maximum of three electrodes. From each set of electrodes, the largest (or most significant) value was chosen to represent this area. A number of regions that had more than three electrodes were arbitrarily divided into areas with only three electrodes.

Although negativities occurring around 100 msec poststimulation are detected from the hippocampal region and are likely to be involved in the RS process, we have not classified these as N100 components. Hippocampal results from the same data set have been reported elsewhere (23).

Grids with at least 64 channels (from 20 subjects) were submitted to source analysis. A weighted minimum norm technique (LORETA: low resolution electromagnetic tomography; Curry software implementation) (28) was used to estimate current density distributions for S1 N100 signals and for S1–S2 difference wave potentials. LORETA reconstructs smooth current distributions by assuming that neighboring sources have similar strengths. Individual single-compartment boundary element method (BEM) head models were created from the subjects' MRI data and used to solve the forward problem. Segmentation of the MRI data were performed by an automatic routine of realistic head modeling in Curry software via high resolution discretization of the surfaces with approximately 5000 nodes (about 2000 nodes representing the innermost brain compartment BEM surface). A rotating source type was used instead of fixed source orientations (i.e., cortical surface normals) to allow estimation of omnidirectional currents and to minimize the effects of nonoptimal surface segmentations.

Optimal head modeling for intracranial data are still a matter of research (29). Use of a single-compartment BEM model has been preferred (30), in conjunction with source space spatial smoothing to finesse the issue of whether source depth can be determined reliably from cortical grid recordings (31).

We sought to identify possible functions for those brain regions that were found to contribute to RS. Volumes of interest (VOIs) were defined for each electrode by classifying each gray matter voxel in Montreal Neurological Institute space, as identified using tissue probability map templates, to the nearest electrode position. For functional characterization, we used the BrainMap database (http://www.brainmap.org) to identify all experiments that reported at least one focus of activation within each VOI (32). The distribution of behavioral domains and paradigm classes associated with these experiments were then compared with the entirety of the database. The database also includes tasks that were more likely to activate a particular VOI than could be expected if their activations were equally distributed. This in turn allows inference about the functional characteristics of the VOIs (33,34).