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Mapping repetition suppression of the N100 evoked response to the human cerebral cortex

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Abstract

Introduction—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 cortices. 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.

Keywords

Cingulate gyrus; frontal lobes; habituation; parietal lobes; thalamus; temporal lobes

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Introduction

The ability to suppress responses to incoming redundant sensory input (i.e., habituation) is a recognized characteristic of the central nervous system (CNS)(1-2). Habituation in the CNS has been extensively studied utilizing evoked potential (EP) methodologies (3). In particular, the P50 and N100 mid-latency 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 proven 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. While some work has been published regarding the circuitry underlying P50 gating (17-18), very little work addresses the circuitry of N100 gating.

The PSP is widely used to study RS (19-20). When two identical stimuli (S1 & 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.

The current study adopts an approach for direct functional mapping of N100 RS in the human brain by combining neuroimaging and intracranial EEG—an opportunity afforded by epilepsy patients who participated in a PSP study while undergoing evaluation as candidates for surgical treatment (21). Specifically, the current 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 build on data from current as well as prior work to propose a preliminary model for N100 RS including structures not interrogated in the current study like the thalamus and hippocampus (3,14).

Materials and Methods

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 at the University of Bonn. Fifteen subjects were excluded due to extreme artifacts. Data presented here are from the remaining 64 subjects (32 men). Ages ranged from 19 to 65 with a mean of 37 ± 12 years.

Patient characteristics and clinical methods

The diagnostic presurgical work-up included video-electroencephalogram recordings with surface and subdural/depth electrodes to determine the location of seizure onset, and high-resolution 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 post-implantation MRI with axial and coronal T2-weighted and FLAIR-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 nine 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 ms, onset and decay phase of 1.2 ms each) were presented binaurally via headphones with an interstimulus interval of 500 ms and an interpair interval of 8 s (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 ms, prestimulus baseline 200 ms), 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 (see Supplement) shows all cortical regions where electrodes were placed. Table S1 (Supplement) lists all the anatomical 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 – 150 ms time window following stimulus onset. A two-step process was employed in order 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 400ms) were baseline corrected by subtracting the prestimulus interval (–100 to 0ms) 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 (see Supplement) 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 2-step process was adopted but in a reverse order. Where an S1 was selected, the segmented single-trial S2 responses (–100 to 400ms) 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 non-significant difference from baseline, the averages were inspected visually by two investigators to determine if an S2 component could confidently be identified based on the morphology of the waveforms. Out 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=zero). 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 $S2/S1 \times 100$ ratio, with higher ratios indicating less effective RS. In patients exhibiting an N100 at several leads within a classified brain region (see below), the electrode with the highest N100 amplitude was chosen for determining the degree of RS.

The anatomical regions indicated (Figure S1 in the Supplement) were used as a guide for pooling the data within closely related anatomical 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 which had more than three electrodes were arbitrarily divided into areas with only three electrodes.

While negativities occurring around 100ms post-stimulation 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 dataset 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 BEM (boundary element method) head models were created from the subjects' MRI data and used to solve the forward problem. Segmentation of the MRI data was performed by an automatic routine of realistic head modeling in Curry software via high resolution discretisation 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) in order to allow estimation of omnidirectional currents and to minimize the effects of nonoptimal surface segmentations.

Optimal head modeling for intracranial data is 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 which were found to contribute to RS. Volumes of interest (VOIs) were defined for each electrode by classifying each gray matter voxel in MNI (Montreal Neurological Institute) space--as identified using tissue probability map templates--to the nearest electrode position. For functional characterization, we used the BrainMap database (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 to the entirety of the database. The database also includes tasks which 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).

Results

Means and standard deviations of N100 amplitudes in the 20 brain regions exhibiting the largest N100 amplitudes are presented in Table S2 (Supplement). The recorded N100 components are unlikely to reflect passive volume conduction as contiguous regions showed highly different amplitudes as seen in Figure S3 (see Supplement).

The largest amplitudes were noted on the dorsal-most part of the right superior temporal gyrus (r-STG) followed by a right parietal region, the dorsal-most part of the middle parietal gyrus (r-MPG). The next five highest amplitudes were recorded from different temporal lobe regions. Thus five of the six highest amplitude N100 regions were in the STG and MTG (mostly dorsal regions).

Additional regions exhibiting well-formed relatively high-amplitude N100s included one other temporal lobe region, five more parietal lobe areas, four cingulate regions, one occipital lobe area, and two frontal regions. Thus seven of the 20 highest amplitude regions were parietal and mainly from the inferior parietal gyri (IPG). The right and the left mid-cingulate regions also exhibited well-formed high-amplitude N100s. Included also was the unexpected observation of well-formed N100s on the ventral region of the right inferior occipital gyrus. Finally, two frontal lobe regions also exhibited well-formed relatively high-amplitude N100s (right and left inferior frontal gyri: IFG). As can be seen from Figure S3 (see Supplement), not all regions listed in Table S1 (Supplement) show the expected robust grand averages. This reflects increased latency variability in these regions. The calculated means used for Table S1 (Supplement) ignore latency variability. It should be noted from Table S1 (Supplement) that seven of the ten listed highest amplitude regions were from the right hemisphere while only three regions were from the left hemisphere.

Utilizing paired t-tests to assess the 107 sampled brain regions exhibiting significant RS, the majority (59) exhibited RS, while 38 exhibited no significant RS (10 regions had trends level RS) (Table S3 in the Supplement). The ten lowest N100 RS ratios (strongest RS) derived from the different brain regions are given in Table S4 (Supplement). This table also lists the ten regions with least RS of the N100 (highest ratios). It should be noted that the RS ratios did not significantly differ among the listed strong RS or among the weak RS regions. The table thus represents a listing of the regions exhibiting most and regions exhibiting least RS. Strongest N100 RS were recorded from electrodes overlaying the ventral right mid-cingulate area, the ventral region of the left superior parietal gyrus, the dorsal region of the left superior frontal gyrus, the middle regions of the left orbito-frontal and right inferior temporal gyrus (r-ITG) regions. Strong RS was also recorded from the middle area of the left inferior, and the ventral area of the left superior, frontal gyri; the ventral aspect of the left inferior temporal region; the left mid-cingulate; and the superior ventral region of the right inferior parietal gyrus (r-IPG). So while six of the highest N100 amplitude regions were temporal, only one temporal region (which did not particularly have high amplitude S1) exhibited strong RS. On the other hand, four frontal regions exhibited strong RS, while there were no frontal regions among the ten highest amplitude N100 regions. Both the cingulate and parietal regions seem to be involved in both the response to S1 and RS.

Regions with the least RS (Table S4 in the Supplement & Figure 1) included the lateral-most area of the left orbitofrontal region and the mid-dorsal region of the right frontal pole. It is of interest that among the least gating areas are two regions in close proximity to the area of most gating (i.e., ventral area of the left frontal pole)--namely the superior and inferior dorsal regions of the left frontal pole.

Source reconstruction from grid data over the lateral surface of the left hemisphere localized N100 generators for the S1 signal in the STG areas (in 5 out of 6 grid placements encompassing the left lateral sulcus), in the posterior part of SFG (2 out of 5 cases with coverage for that area), and left ventral prefrontal cortex (3 out of 6 cases). RS generators from the difference wave (S1–S2) N100 potentials localized to left ventral prefrontal cortex (5 out of 6 cases with that area coverage), the posterior part of SFG (2 out of 5 cases), and the posterior part of STG (in 3 out of 6 grid placements encompassing the left lateral sulcus) (Figure 2: subject 3, and Figure S4 in Supplement).

For subjects with grids placed over the lateral surface of the right hemisphere, N100 generators for the S1 signal were localized in STG areas (in 7 out of 7 grid placements encompassing the right lateral sulcus) and in the SPG area (in 3 out of 6 grid placements covering that area), inferior parietal (in 5 out of 7 cases), and the posterior part of SFG (2 out of 3 cases) cortices. RS generators for N100 S1–S2 difference wave potentials were localized in STG areas (in 6 out of 7 cases with respective grid coverage), the SPG area (2 out of 6 cases), inferior parietal cortex (in 5 out of 7 grid placements), the posterior part of SFG (3 out of 3 cases), and the right occipital lobe (1 case) (Figure 2: subjects 16 and 18, and Figure S4 in Supplement).

Discussion

This study represents a survey of brain regions, monitored for the purpose localizing epileptic lesions, for their initial response to auditory stimuli and the degree of RS. As expected, the temporal cortices exhibited the largest amplitudes N100s (35·36). From the 10 regions exhibiting the largest N100s, six were temporal, two parietal, and two cingulate. Five more parietal regions, two cingulate, two frontal, and one occipital region also exhibited large N100s. These observations suggest that, in addition to the dorsal regions of the STG and MTG, parietal, cingulate and frontal regions seem also to be involved in the information processing reflected by the N100.

In this data set, four frontal regions exhibited strong RS: dorsal and ventral regions of the left SFG, left orbito-frontal cortex, and the middle region of the left IFG. No frontal regions were among the 10 areas exhibiting largest-amplitude N100s. The data thus support a significant role of the frontal lobes in mediating RS (31·37·38). Within the frontal pole area were regions that are within millimeters from each other and yet exhibiting strong or minimal RS. As we now postulate that regions with no RS may also be playing a role in mediating the function, we propose that this functional arrangement is likely of some significance. The frontal pole regions were the only areas where this functional arrangement was detected.

The data also suggest that the parietal and cingulate regions are involved in both stimulus registration (S1) and RS. A number of parietal and cingulate regions exhibited both large N100s and strong RS. This is the first report suggesting the involvement of these regions either in the registration of the stimulus or its RS.

The data strongly suggest that S1 amplitude and RS reflect two distinct functions that are served by different neural circuitries. This assertion is born out from the difference of the topography of the S1 and the S1–S2 difference wave seen in figure 2 and Figure S4 (Supplement). As can be seen from these figures, there is less overlap between the two topographies over the left ventral cortex, the posterior STG, and right occipital cortex. Source reconstruction also showed similar differences between the locations of the generators of S1–S2 difference wave and pure S1 N100 potential generators. It should be underlined that data derived from grid electrodes are limited to the locations of the electrodes and do not fully reflect activity from other brain regions. Based on our recent work (39) we believe that the ratio measure (which could not be used for source reconstruction) is more closely linked to S2, while the difference measure is more closely related to S1 amplitudes. Hence, we believe that the ratio measure more closely reflects the phenomenon under investigation (i.e., RS). The main purpose of providing the source localization data was to underscore the fact that the two phenomena (i.e., amplitude of S1 and the degree of attenuation of S2) are different functions, possibly mediated by different circuitries. By employing the difference, which (as mentioned) is more closely linked to S1 (40), we may have underestimated the degree of difference between the two functions.

Given that the two topographies did not completely overlap in our sample, these data support our hypothesis that the functional anatomy of stimulus registration differs from that of RS.

We also advance the hypothesis that areas exhibiting least RS may be important for the RS functional network, reasoning that some regions must remain responsive for the RS network to evaluate all incoming stimuli. Among the ten regions exhibiting least RS, five were frontal. Only one temporal region exhibited low RS. Regions with almost no RS were mainly on the left side (seven of ten regions). These observations suggest that, while the temporal lobe is paramount for the initial registration of sensory input, it is the frontal lobe (and perhaps the left frontal cortex) that modulates responses to repeating stimuli.

Sable et al. (41) provided evidence that N100 RS is not a simple matter of refractoriness, but more likely reflects an active inhibitory process. This view was earlier challenged (42) by relating the degree of attenuation to the degree of refractoriness based on the closeness of stimulus repetition. It is important to highlight the fact that, while the strongest RS areas were outside the STG, the STG exhibited significant RS from 40 to 60%, which is similar to what is reported in the literature (43).

Based on correlations between functional studies and the MNI idealized MRI, different patterns of functional significance emerge for the strong vs. weak RS regions (Table S4 in Supplement). Strong RS regions seem to relate mostly to sensory monitoring, while the weak RS areas are mostly related to cognition. It is thus possible to speculate that both weak and strong RS regions may be playing different roles in mediating the RS function and relating it to subsequent, more elaborate cognitive functioning.

The currently proposed model for P50 RS is centered on the CA3 region of the hippocampus, and suggests that the first stimulus (S1) activates both the pyramidal cells and the inhibitory interneurons. Upon arrival of the second stimulus (S2), the still-active inhibitory interneuron prevents or attenuates the response from the pyramidal cells (17-18). This model is too simple, as RS has been shown to be a multistage process (13-44). In addition, a number of regions are involved in RS. Central among these are temporal neocortex and hippocampus, while accumulating evidence strongly points to the prefrontal cortex as crucial to this function. It is thus possible to consider these three regions as the nuclear auditory RS apparatus. Most prominent among other brain regions that have been implicated in RS, is the thalamus—particularly the reticular nucleus (nRT) (45). The involvement of the thalamus was also supported by the observation of worsening somatosensory RS in patients with thalamic strokes (46). Other regions implicated include the amygdala (47-48), proposed to be important in mediating rapid auditory sensory processing involved in emotional conditioning. The current study further identifies parietal and cingulate regions as likely contributors, perhaps modulating the nuclear three-site circuit. It is currently not known if activity in one sensory stream (auditory, visual or somatosensory) influences RS in other systems. However, the hypothesis that different sensory streams are not completely independent can help to explain the significant involvement of parietal and occipital cortices in the auditory RS paradigm. The above data also implicated the cingulate region. We now postulate that the hippocampal and cingulate regions are engaged in gating the post-P50 stage of preattentive RS. This is supported by the absence of significant hippocampal activity during the P50 time frame (23-49). As there is some evidence of frontal activation around the P50 time frame, we postulate that it is involved in the pre-attentive phase. We also hypothesize a role for the thalamus at the junction between the preattentive (bottom up) RS process and the early attentive stages (or beginning of a top-down phase) of sensory RS. This role is crucial, as the progression between these two phases is likely to depend on the proper recruitment of the other

structures that have been implicated in RS such as the hippocampus, cingulate cortex, and the amygdala.

It should be acknowledged that utilizing data from individuals with significant brain pathology places serious limitations on the overall interpretation of the results. While we elected to merge all participants as one group, it is likely that some of the data were influenced by the laterality of the pathology. However, our prior investigation of this possibility did not yield any major findings (50). Also, psychopathology was minimally represented in this group (51). Another limitation of the employed methodology is that the sampling of brain areas is not based on hypotheses by dictated by the clinical situation of the individual subjects. As much as this can be mitigated by the large sample size, there are salient regions that are never sampled using this patient sample, most prominently the thalamus. Data provided here may help guide future imaging, MEG, or dense electrode scalp studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The ten cortical regions exhibiting maximal gating of the N100 (dark shaded regions), the ten regions exhibiting the least gating (light shaded areas), and the evoked responses (S1-thick line and S2-thin line) from each region.

Figure 2.

Topographies of the cortical potentials and estimated current densities for three selected subjects (out of 20) showing differences in cortical potential distributions and generators of S1 signal N100 potential (stimulus registration) and S1–S2 difference waves (sensory gating). Differences are mostly shown in terms of individual regions that are involved in both (subject 16) or predominantly in one (subjects 3 and 18) of two processes; stimulus registration and repetition suppression. Data from 20 subjects are shown in the Supplemental Materials section.