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Mapping repetition suppression of the P50 evoked response to the human cerebral cortex

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HIGHLIGHTS

- We mapped the cortical regions contributing to repetition suppression (RS).
- Cingulate, parietal, as well as new frontal lobe regions were shown for the first time to be involved.
- Data highlights the complex system mediating RS in the human brain.

ABSTRACT

Objective: The cerebral network subserving repetition suppression (RS) of the P50 auditory evoked response as observed using paired-identical-stimulus (S1–S2) paradigms is not well-described.
Methods: We analyzed S1–S2 data from electrodes placed on the cortices of 64 epilepsy patients. We identified regions with maximal amplitude responses to S1 (i.e., stimulus registration), regions with maximal suppression of responses to S2 relative to S1 (i.e., RS), and regions with no or minimal RS 30–80 ms post stimulation.
Results: Several temporal, parietal and cingulate area regions were shown to have significant initial registration activity (i.e., strong P50 response to S1). Moreover, prefrontal, cingulate, and parietal lobe regions not previously proposed to be part of the P50 habituation neural circuitry were found to exhibit significant RS.
Conclusions: The data suggest that the neural network underlying the initial phases of the RS process may include regions not previously thought to be involved like the parietal and cingulate cortexes. In addition, a significant role for the frontal lobe in mediating this function is supported.
Significance: A number of regions of interest are identified through invasive recording that will allow further probing of the RS function using less invasive technology.

1. Introduction

The ability to suppress responses to incoming redundant sensory input (i.e., habituation) is a recognized characteristic of the central nervous system (CNS) (Venables, 1964; Eisenstein and Eisenstein, 2006). Habituation has been postulated as a protective function for the CNS, failure of which is proposed as a significant contributor to cognitive dysfunction or psychosis. The cerebral networks and processes, by which this function is mediated, however, are far from being well-described. Habituation in the CNS has been extensively studied utilizing Evoked Potential (EP) methodologies (Cromwell et al., 2008). In particular, the P50 and N100 auditory evoked responses (AERs) have been used to examine habituation using repetition suppression (RS) paradigms. A sizeable volume of research documented that EP habituation is not caused by the effector activity used in most studies to elicit the EP (Roemer et al., 1984). Therefore, scalp-recorded EPs should reflect intermediate processes such as sensory encoding and stimulus evaluation (Davis and Heninger, 1972). Probing P50 RS in a number of neuropsychiatric conditions has been shown to be a promising tool to help further our understanding of the neurobiological aberrations (Franks et al., 1983; Brockhaus-Dumke et al., 2008; Patterson et al., 2008) and genetic vulnerability (Adler et al., 1982; Siegel et al., 1984; Anokhin et al., 2007) associated with these conditions.

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Averaged EPs, recorded at the scalp following auditory stimulation, contain a temporal sequence of three major components subsequent to the brainstem auditory evoked responses: positive (P50), negative (N100), and positive (P200) deflections (Buchsbaum, 1977; Boutros and Belger, 1999). In RS experiments using the paired-stimulus paradigm (PSP), all three AERs are suppressed by stimulus repetition. The degrees to which the different AER amplitudes are suppressed with repetition are not correlated (Boutros et al., 2004a), and are therefore likely to be associated with distinct but possibly overlapping and interacting phases of RS. The study of RS in the human brain would benefit from the study of each component eventually leading to the elucidation of the entire system.

The PSP is widely used for examining RS (Smith et al., 1994; Rentzsch et al., 2008). When two identical stimuli (S1 and S2) are presented with a short interstimulus interval (ISI), the second P50 response is suppressed. This "P50 suppression" is thought to indicate habituation at a pre-attentive phase of information processing. Technically, suppression of the second stimulus is usually expressed as the S2/S1 ratio of the two P50 responses. As evidence of RS preceding the P50 stage of information processing is almost non-existent, it is likely that P50 RS represents the first or earliest stage of habituation of evoked responses in the CNS. Understanding this early phase of RS is essential for the eventual understanding of the entire process.

The most direct way to obtain a functional mapping of P50 RS would apply a combination of neuroimaging and intracranial P50 recording procedures directly from cortical regions in the same individuals as occurs in the presurgical evaluation of epilepsy (Spencer et al., 1997). The current study capitalized on the unique opportunity provided by treatment-resistant epileptic patients, who are being worked-up for therapeutic respective surgery, to map the amplitudes and RS of the P50 AER using data obtained from grid and strip electrodes placed on various areas of the cortex.

2. Materials and methods

Between 2001 and 2006, a total of 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 Epilepsy Surgery Center. Fifteen subjects were excluded due to extreme artifacts. Data presented here are from the remaining 64 subjects. There were 32 men, and ages ranged from 19 to 65 with a mean of 37 ± 12 years.

2.1. Patient characteristics and clinical methods

The standard diagnostic presurgical work-up included interictal and ictal video-electroencephalogram recordings with surface and subdural/depth electrodes to determine the exact location of seizure onset, and high-resolution MRI (Kral et al., 2002). Psychiatric status and history were assessed by an experienced psychiatrist (Boutros et al., 2006). It should be noted that psychiatric problems were minimal in this patient sample (Boutros et al., 2005). Of the 64 included subjects only 14 had any psychiatric history. None were diagnosed with either schizophrenia or bipolar disorders. The most frequent problems were history of depression or anxiety and none of the patients were on psychotropic medications at the time of recording. On the other hand, at the time of recording, all patients were on standard therapy with anticonvulsant drugs (AEDs). While in some patients AEDs were lowered to allow seizures to occur, none of the patients were completely off AEDs. Given that the number of electrodes exhibiting P50 responses at any one location varies between 4 and 18 and in view of the different AEDs used in different subjects, examination of the effects of individual AEDs on P50 and its gating was not attempted. Similarly, the possible effects of seizure variables (i.e., seizure frequency) were not attempted.

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. RS experiments were performed after the individual invasive diagnostic program was finished, while patients were waiting for their therapeutic surgical procedure and/or electrode extraction. All patients signed an informed consent approved by both the University of Bonn and Wayne State University.

2.2. EP recording

All recordings were performed in a sound-shielded room which utilized a digital EPAS system (Schwarzer, Munich, Germany) and Harmonie EEG software (Stellate, Quebec, Canada). One hundred pairs of identical clicks were presented in a single session lasting about 14 min (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 (Zouridakis and Boutros, 1992). No formal hearing examinations were performed. Patients reporting history of hearing difficulty were not included in the study. Prior to starting the recording procedure, hearing was tested clinically (equal hearing of a wrist watch and finger rubbing bilaterally). None of the subjects included had difficulties with these tests. Stimuli were presented binaurally via calibrated headphones with an intensity of 85 dB. This intensity has been found by this group to reliably generate P50 responses and not cause a startle reaction. Patients were asked to listen to the stimuli without additional tasks. Patients were asked to focus their gaze on a spot on the wall in front of them to minimize eye movements. They were encouraged to blink after they hear the second of the pair of stimuli (they had an interval of 8 s). An EEG technologist monitored the ongoing EEG to make sure subjects did not drift into drowsiness or sleep. Prior studies showed that only focused attention on the pairs of stimuli (e.g., counting odd pairs embedded among standard pairs) can influence the P50 response or its gating (Guterman et al., 1992; Jerger et al., 1992; Gjini et al., 2011). AERs were recorded from subdural strip and grid electrodes (sampling rate 1000 Hz per channel), with reference to both mastoids (the most common reference used for gating studies). Raw data were collected utilizing a band pass filter setting 0.03–85 Hz, 12 dB/octave. Prior to P50 analyses, data were further digitally filtered with a narrower bandpass filter of 1–45 Hz, with a notch filter for 50 Hz main line frequency noise (data collected in Germany). Data were segmented to epoch lengths of 500 ms, prestimulus baseline 100 ms. Details of electrode coverage were published in prior publications (Boutros et al., 2011). In brief, subdural electrodes consisted of strips or grids with stainless steel contacts with an interelectrode spacing of 1 cm (Behrens et al., 1994). An ECG electrode was glued to the patient shoulder for grounding purposes. In the extensive experience at the Bonn Epilepsy Center, this is the most convenient location and it had no effects on EEG recordings or source analysis. A figure showing all cortical regions where electrodes were placed has been previously published and is available online (Fig. S1 in the Supplementary Material of Boutros et al., 2011). 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.