Infrequent Events Transiently Activate Human Prefrontal and Parietal Cortex as Measured by Functional MRI

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McCarthy, Gregory, Marie Luby, John Gore, and Patricia Goldman-Rakic. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. J. Neurophysiol. 77: 1630–1634, 1997. P300 is an event-related potential elicited by infrequent target events whose amplitude is dependent on the context provided by the immediately preceding sequence of stimuli, suggesting its dependence on working memory. We employed magnetic resonance imaging sequences sensitive to blood oxygenation level to identify regional changes evoked by infrequent visual target stimuli presented in a task typically used to elicit P300. Targets evoked transient event-related activation bilaterally in the middle frontal gyrus, in the inferior parietal lobe, and near the inferior aspect of the posterior cingulate gyrus beginning within 1.5 s of target onset and peaking between 4.5 and 6 s. These regions have been identified in previous neuroimaging studies in humans, and in single-unit recordings in monkeys, as components of a neural system mediating working memory, which suggests that this system may be activated by the same events that evoke P300.

METHODS
Subjects
Ten neurologically normal right-handed volunteers (5 males) participated. Subjects ranged in age between 19 and 42 yr with a mean age of 29 yr. All subjects were experienced in neuroimaging studies and provided informed consent.

Task
Visual stimuli were delivered by computer to an active matrix liquid crystal display panel and back-projected onto a translucent Plexiglas screen mounted on the patient gurney of the scanner. The subject viewed the stimuli through a mirror mounted in the head coil. The stimuli consisted of two letter strings (OOOOO and Xxxxxx) presented as white characters centered against a dark field. A run consisted of a series of 128 successive stimuli presented at a rate of one string per 1.5 s with a duration of 0.5 s. Most of the stimuli were OOOOO strings (standards); however, six to eight stimuli per run were Xxxxxx strings (targets). The latter were randomly intermixed into the series with the constraint that ≥12 standards occurred between successive targets. Subjects were required to count mentally the number of targets and report that number at the end of the run. Subjects were cautioned against blinks, changes in breathing patterns, or movements coincident with counting. There were eight experimental runs in each session, resulting in a total of 55–63 targets for each subject.

Imaging
Echoplanar magnetic resonance (MR) images were continuously acquired during task performance at a rate of one image every 1.5 s with the use of sequences sensitive to blood oxygenation level (Kwong et al. 1992; Ogawa et al. 1992; for review see Moseley and Glover 1995). A 1.5-T MR imaging (MRI) scanner (General Electric Signa, Milwaukee, WI) with a quadrature head coil and echoplanar capability (Instascan, ANMR Systems, Wilmington, MA) was used. The subject’s head was immobilized with the use of a vacuum cushion and forehead strap. High-resolution sagittal scans were obtained (TR = 500 ms, TE = 11 ms, NEX = 1, FOV = 24 cm, slice thickness = 5 mm, skip = 2.5 mm, imaging...
matrix $256 \times 192$) to identify the anterior commissure (AC) and posterior commissure (PC). Four T1-weighted coronal scans ($TR = 500\ ms, TE = 11\ ms, NEX = 2, FOV = 40\ cm, skip = 0\ mm, slice\ thickness = 7\ mm$, imaging\ matrix $256 \times 192$) were then acquired at distances measured along the AC-PC line. Two images were centered 40 mm anterior to the AC to investigate prefrontal cortex. An additional two images were centered 5 mm posterior to the PC; the more anterior to study the midbody of the hippocampus and the more posterior to study parietal cortex. Additional images were acquired of these same slices for anatomic reference with the use of an echoplanar sequence ($TR = 3,000\ ms, TE = 80\ ms, NEX = 4, FOV = 40 \times 20\ cm, slice\ thickness = 7\ mm, skip = 0, imaging\ matrix 128 \times 64$). Functional images were acquired with the use of a gradient-echo echoplanar image acquisition sequence ($TR = 1,500\ ms, TE = 45\ ms, \alpha = 60^\circ, NEX = 1, FOV = 40 \times 20\ cm, slice\ thickness = 7\ mm, skip = 0, imaging\ matrix 128 \times 64$). Each 196-s run consisted of the acquisition of 128 images for each of the four coronal slices.

**FIG. 1.** Average activations ($P < 0.01$) across all 10 subjects depicted on spatially normalized averaged magnetic resonance images for frontal (A and B) and posterior (C and D) anatomic slices. The activations shown occurred 6 s after target onset.
Figure 2. Group-average target-synchronized segment for prefrontal cortex showing activations that exceeded the mean signal intensity of the 6 pretarget images at $P < 0.01$. Top left image: target onset; each succeeding image depicts an increment of 1.5 s. The largest activations occurred at 4.5–7.5 s and declined thereafter. The 5 pretarget images showed no activation and are not shown.

RESULTS

Group-averaged images

The spatially normalized, group-averaged data corresponding to the mean activation pattern at 4.5 s after target onset are presented in Fig. 1. The middle frontal gyrus was activated bilaterally (Fig. 1, A and B), with a somewhat more extensive activation in the right hemisphere. Bilateral activation of the inferior parietal lobe was also clearly evident (Fig. 1D), primarily in the supramarginal gyrus and adjacent postcentral sulcus, a region corresponding to Brodmann’s area 40. This parietal activation diminished in the more anterior slice (Fig. 1C), which encroached on somatosensory cortex. In both posterior slices, a discrete patch of activation was noted in the supracallosal region near the inferior aspect of the cingulate.

No differences were observed in the pattern of activation between males and females. No clusters were identified in which targets evoked a significant signal decrease. In contrast to the robust activation observed in the group-averaged data synchronized to targets, no activated clusters were observed in the group-averaged control images that were randomly synchronized to standards.

Activation time course

The time course of the evoked MR signal change can be seen in Fig. 2, in which group-averaged data for the prefrontal slice (corresponding to Fig. 1B) are shown. The top left image represents target onset (corresponding to the 6th image of the 15-image segment) and each succeeding image occurred at a 1.5-s increment. Activation exceeded threshold at 3 s in the left middle frontal gyrus and reached peak values at 4.5–6 s.

The clusters of activation observed in Fig. 1, A and B, for the middle frontal gyri were used to interrogate each image of the group-averaged data for both target-synchronized and randomly synchronized segments. Figure 3A shows a peak signal change of 0.32% at 6 s posttarget onset for the target-synchronized segment. By 1.5 s after target onset, the in-
crease in signal well exceeded the noise level represented by the randomly synchronized segments. These averaged transient activations will be referred to as event-related activations (ERAs) by analogy with ERPs, which also use averaging to improve the signal-to-noise ratio of signals embedded in biological and nonbiological noise.

Similar analyses were performed for the activated clusters in the inferior parietal lobe (Fig. 3B), which also showed an ERA within 1.5 s after target onset. The ERA peaked 1.5 s earlier in the parietal than the prefrontal region and reached a smaller overall level (0.21%) of signal change. The parietal ERA was also shorter in duration and declined to noise levels by 10 s after target onset.

The activation of the supracallosal region also showed a brisk onset, with peak activation at 4.5 s. The time course of activation for the supracallosal region was similar to that of parietal cortex but larger in magnitude, reaching a peak of 0.45%. The time courses and magnitudes of activation for all regions were similar when the activations were independently interrogated and compared for each hemisphere.

**DISCUSSION**

These results reveal that detection of infrequent target stimuli elicited a small, transient MR signal increase that began within 1.5 s of target onset and peaked within 4.5–6 s. These activations were observed primarily in the middle frontal gyri and inferior parietal lobule, regions previously shown to be active in working memory tasks (Cohen et al. 1994; Goldman-Rakic 1987; McCarthy et al. 1994, 1996; Smith et al. 1995). P300 is readily elicited in scalp and intracranial recordings in humans and monkeys by the same infrequent targets as used here (e.g., Halgren et al. 1980; McCarthy et al. 1989; Paller et al. 1992; Puce et al. 1989).
Thus the infrequent targets that elicit P300 also activate some of the same neural circuitry active in working memory tasks in both humans and monkeys.

A precise anatomical description of the activated region of supracallosal cortex is difficult to provide because it occurred at the junction of the cingulate and supracallosal gyri. This region gives rise to the cingulum bundle, a major afferent input to limbic regions including the hippocampus, and may thus play an important role in a circuit underlying working memory. However, this region also contains large blood vessels whose contribution to this activation cannot be excluded.

ERPs analogous to P300 have been recorded from widespread sites within the brain including the frontal and parietal lobes, posterior cingulate, and hippocampus (Baudena et al. 1995; Halgren et al. 1995a,b; McCarthy and Wood 1987; McCarthy et al. 1989; Paller et al. 1992; Puce et al. 1989). It is noteworthy that we did not observe consistent ERAs of the hippocampus in individual subject or group functional MRI (fMRI) data. Our failure to demonstrate hippocampal fMRI activation in a task in which electrophysiological activation is readily demonstrated may simply reflect the relative sensitivities of the two techniques. Alternatively, it may reflect a more complex mapping between activation measured by fMRI and electrophysiological events. The fMRI activations obtained in the present study may not reflect blood oxygenation changes caused by the brief synaptic activity associated with P300 per se, but rather the sustained activity of a neuronal system triggered by the target event. The target may evoke a more sustained activation in prefrontal and parietal cortex than that evoked in the hippocampus. Regardless of the resolution of this issue, the present study demonstrates that fMRI can provide a sensitive measure of cognitive processes engendered by brief and unpredictable stimuli.

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