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Potentials evoked in human and monkey medial temporal lobe during auditory and visual oddball paradigms

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Summary Event-related potentials (ERPs) were recorded from epileptic patients with electrodes chronically implanted in the medial temporal lobe (MTL) and other intracranial locations, and from monkeys with epidural, transcortical, and MTL electrodes. For both humans and monkeys, the eliciting events consisted of trains of auditory or visual stimuli in which a random 10–20% deviated in pitch or pattern from the remaining stimuli. The distribution of ERPs elicited by the rare (oddball) stimuli in both species was similar, consisting of a P3 recorded from the scalp or cortical surface and a slightly later, but temporally overlapping, focal negativity in the hippocampus and nearby MTL structures. The similarity between the patterns of ERPs in humans and monkeys establishes the feasibility of studying the electrogenesis of P3-like activity with detailed intracranial recordings in an animal model. The data also establish that the MTL ERPs in human patients represent a normal neurophysiological process unrelated to epilepsy.

Key words: Cognitive ERPs; Medial temporal lobe; Human-monkey comparison; P3; Intracranial recordings

Event-related potentials (ERPs) recorded from scalp electrodes have been used widely to study human cognitive processes and their neural substrates. Progress has been limited by the difficulty in specifying the neural generators responsible for ERPs recorded at the scalp. One approach to this problem is to record directly from neuronal structures. For example, intracranial recordings in humans combined with more extensive investigations in animals have been useful in establishing the neural generators of sensory ERPs (e.g., Allison et al. 1991; McCarthy et al. 1991b).

The most thoroughly studied ERP related to cognitive processing is the P3 or P300, which reliably occurs after unexpected or informative events (see reviews by Donchin et al. 1986; Donchin and Coles 1988; Verleger 1988). In humans, intracranial recordings indicate that ERPs are generated in the hippocampus and adjacent structures in the medial temporal lobe (MTL) in response to the same events that elicit P3 in scalp recordings (Halgren et al. 1980, 1986; Wood et al. 1980; McCarthy and Wood 1987; McCarthy et al. 1989; Puce et al. 1989). These studies were conducted in epileptic patients in whom electrodes were placed intracranially for seizure monitoring (e.g., Spencer et al. 1982). Such opportunities for making systematic intracranial recordings in humans are limited and have yet to determine conclusively how and where the scalp-recorded P3 and the P3-like MTL potentials are generated.

Animal models for P3 have been sought in monkeys, cats, and other species to enable a more thorough investigation of its neural generators (reviewed by Paller 1991). In particular, P3-like ERPs recorded in monkeys display many similarities to P3 in humans (Arthur and Starr 1984; Neville and Foote 1984; Pineda et al. 1987, 1988; Paller et al. 1988; Glover et al. 1991). Two experimental paradigms were used in these studies: *active paradigms*, in which monkeys were trained to make discriminative responses to stimuli, and *passive paradigms*, in which unusual or infrequent stimuli were presented but no behavioral responses were required. These paradigms were used by Paller et al. (1988) to test the hypothesis that the monkey P3 is generated in the MTL. Bilateral damage to a portion of the MTL including hippocampus, amygdala, and adjacent neocortex did not modify P3 recorded from frontal and parietal epidural locations. A similar absence of lesion effects on P3 has been reported following unilateral temporal lobectomy in humans (Stapleton et al. 1987;

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Johnson 1988; but see McCarthy et al. 1987 for evidence of alterations over temporal scalp ipsilateral to an epileptic focus in the MTL).

Two key findings that motivated the present experiments were that, in humans, MTL potentials are evoked by the same stimulus and task conditions that evoke the scalp-recorded P3 (McCarthy et al. 1989), and in monkeys, MTL lesions do not disrupt P3-like ERPs recorded from the cortical surface (Paller et al. 1988). These results can be explained by the hypothesis that neural generators not dependent upon the MTL are responsible for most of the P3 obtained in scalp recordings, but that the same events that activate these generators also instigate MTL activity. Two alternative explanations are: (1) MTL ERPs associated with P3 in epileptic humans are abnormal, disease-related responses, and (2) P3-like ERPs in monkeys differ fundamentally from humans in that they are not associated with coincident activation of the MTL. To test these hypotheses we recorded task-related ERPs from the MTL and scalp of humans and from the MTL and cortical surface of monkeys. Our results suggest that P3-like potentials recorded from the MTL reflect a normal neurophysiological process which is similar in the two species.

Methods

Human recordings

Scalp and intracranial recordings were made during a target detection task from two patients with medically intractable partial complex seizures who were being monitored with intracranial electrodes for possible surgical treatment (Spencer et al. 1982). In patient S18, platinum-iridium depth electrodes were placed and localized using techniques described by McCarthy et al. (1989). In patient W3, nichrome depth electrodes were placed using MRI-guided stereotaxic procedures and were later imaged in place using MRI to determine their precise locations (McCarthy et al. 1991a).

In the auditory task the patient was asked to count high tones (*targets*) that occurred infrequently ($P = 0.2$) in a sequence of low tones (*non-targets*). In the visual task the patient was asked to count "OOOOO" strings (*targets*) that occurred infrequently ($P = 0.2$) in a sequence of "XXXXX" strings (*non-targets*). ERPs from 64 recording sites were amplified simultaneously (0.1–100 Hz bandpass, −3 dB), digitized (4 msec/sample), and written to tape. Recordings were referential to an earlobe or mastoid. The protocols used in this study were approved by the Human Investigation Committees of the West Haven VA Medical Center and Yale University School of Medicine, and informed consent was obtained.

Monkey recordings

Two female rhesus monkeys (*Macaca mulatta*) were studied. They were captured in Burma and were about 4 years of age at the time of testing. They weighed 3–4 kg and were housed in adjacent cages. Their diet consisted of primate chow and fresh fruit. Water was available ad lib except prior to experimental sessions in which apple juice was used as reinforcement. Monkeys were treated in accordance with the NIH Guide for the Care and Use of Laboratory Animals, and protocols were approved by the VA and Yale animal use committees.

Surgery. Electrodes were implanted under sodium pentothal anesthesia (35 mg/kg i.v., with supplemental doses as required) following ketamine hydrochloride sedation (0.5 mg/kg i.m.). With the head placed in a stereotaxic frame, scalp and temporal muscles were reflected and the surface of the skull was cleaned. Three types of electrodes were implanted: (1) Depth probes consisted of an array of 8 fine wires, the tips of which were exposed for 0.25 mm and spaced 1.0 mm apart. These probes were placed bilaterally with a vertical trajectory in anterior and posterior areas of the MTL using the stereotaxic atlas of Snider and Lee (1961). (2) Epidural electrodes consisted of stainless steel screws (1 mm diameter, 3 mm length) with wire leads. They were implanted at 9–11 locations in frontal, parietal, and occipital skull. The tips of the screws rested on, or in some cases dimpled, the dura. (3) Transcortical electrodes consisted of two contacts. The ring contact (cortical surface) was a 2 mm diameter loop of exposed wire. The deep contact (white matter) passed through the ring and was exposed for 0.5 mm at the tip, which was situated 4 mm below the ring. Transcortical electrodes were implanted bilaterally in frontal and parietal cortex. Electrode leads were attached to two 31-pin connectors and fixed to the skull with acrylic cement. To allow head immobilization during recordings, a metal tube was fixed to the occipital skull.

Procedure. Prior to each recording session, a pole-and-collar system was used to lead the monkey into a primate chair. The chair was wheeled into a recording chamber in an adjacent room. The head was immobilized by fixing a rod between the implanted metal tube and the chair. Electrodes were then attached for use as the reference and for monitoring the electrooculogram (EOG). These electrodes were either platinum alloy needles applied subdermally or gold-plated disks filled with conductive paste and affixed to the skin. ERPs were recorded simultaneously from 32 locations as described above. The root mean square voltage of the EOG was used to eliminate epochs contaminated by ocular artifacts or artifacts caused by licking. ERPs were computed off-line on the basis of stimulus class and behavioral response for epochs extending from 100

msec prior to stimulus onset to 924 msec after stimulus onset. Two experimental paradigms were used: a *passive condition with auditory stimuli* and an *active categorization task with visual stimuli*. Each paradigm was used in approximately 10 sessions with each monkey, with different electrode montages in different sessions.

Passive condition with auditory stimuli. Stimulus sequences were composed of 2 types of stimulus: frequent clicks ($P = 0.9$) produced by a 1 msec pulse; and rare tones ($P = 0.1$) consisting of a 100 msec tone sweep beginning at 2 kHz. Stimuli were presented in a random order at a rate of 1 stimulus every 1100 msec.

Categorization task with visual stimuli. A video monitor fitted with a touch screen presented stimuli and monitored responses. Responses were detected via disruption of a surface acoustic wave generated in the screen, thus minimizing problems with electrical artifacts in the recordings. Stimuli were viewed from a distance of 24 cm and were presented centrally on a white background in an area measuring 4 × 4 cm (3 × 3°

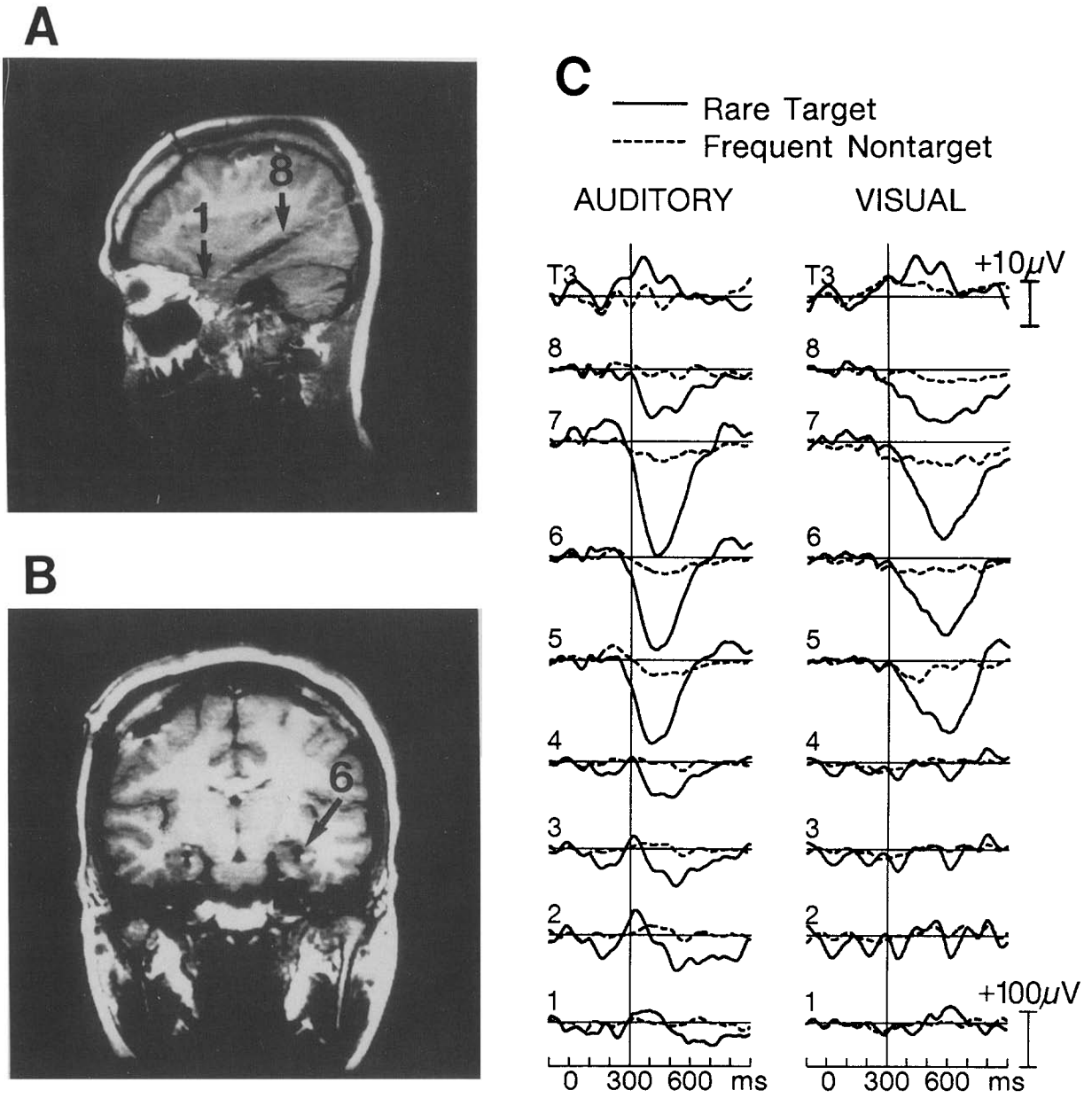

Fig. 1. ERPs recorded from patient W1. A: parasagittal magnetic resonance image of the left hemisphere depth probe. B: coronal image of electrode 6 (arrow) in the left hippocampus. C: ERPs recorded simultaneously from the scalp (T_3) and from locations 1 to 8 of the depth probe while the patient performed auditory and visual categorization tasks. Isolatency lines are at 300 msec. Note the different amplitude calibration for scalp (10 μV) and depth (100 μV) ERPs. In this and the following figures stimuli were delivered at 0 msec, and positivity at the active recording site is displayed upward.

visual angle). Three types of stimulus were used: a grey square ($P = 0.8$), a red-and-white checkerboard ($P = 0.1$), and a black-and-white checkerboard ($P = 0.1$). These stimuli were designated the *frequent non-target*, the *rare non-target*, and the *target*, respectively. Stimulus parameters were selected so that the target differed from one non-target primarily in form and from the other non-target primarily in color, which may promote the allocation of attention to making the discrimination (Triesman and Gelade 1980). Both the stimulus duration and the interstimulus interval were 1 sec. Sequences were randomly ordered and were initiated when the monkey touched the *start stimulus*, a black-and-white checkerboard displayed for 5 sec. The monkey was trained through successive approximations to the final task to make a discriminative response to the target. When the monkey touched the target, a squirt of apple juice was delivered 300 msec later via a tube to the monkey's mouth. When the monkey touched the screen at any other time (such as when a non-target was displayed), the sequence was discontinued and a delay of 20–40 sec ensued. The screen was blank during the delay and a start stimulus appeared when the delay was over. The delay was extended by a variable amount whenever 4 consecutive targets had not been touched. Auditory stimuli occurred concurrently with each juice reward (2 kHz pure tone) and with any touch of the screen (click).

Localization of electrodes. At the conclusion of the experiments, brains were removed following intracardiac perfusion with saline and formalin under deep barbiturate anesthesia. Epidural and transcortical electrode locations were determined by examination of the skull and cortex. Frozen coronal sections were cut at 40 μm and stained with cresyl violet to determine depth probe locations. Although the depth probe placements were designed to penetrate the hippocampus proper, trajectories of the posterior electrode tracks were 2–3 mm medial to the hippocampus (e.g., Fig. 3B). The anterior depth probes, however, did penetrate the more medially situated pes hippocampus (e.g., Fig. 3A). Measurement revealed that the stereotaxic target coordinates were achieved, but that the location of the hippocampus in these monkeys did not correspond to the stereotaxic atlas. This discrepancy may reflect differences in brain morphology of Burmese and Indian subspecies of rhesus monkeys.

Results

Human recordings

Here we show results from two cases to illustrate the basic findings obtained in a series of over 120 patients with chronically implanted electrodes in the MTL and other structures (Wood et al. 1980, 1988; McCarthy and Wood 1987; McCarthy et al. 1987, 1989). The accuracy of techniques for determining the locations of intracranial electrodes has recently been improved by the use of MRI (McCarthy et al. 1991a) as shown in Fig. 1. ERPs recorded from the left MTL during auditory and visual "oddball" categorization tasks are shown in Fig. 1C. A positive ERP corresponding to P3 was recorded from the left temporal scalp (T_3) to the rare targets in both modalities. As is typical in scalp recordings, P3 was shorter in latency for auditory than for visual tasks. The ERPs recorded simultaneously from contacts 4 to 8 of the depth probe exhibited a large negative ERP which overlapped temporally

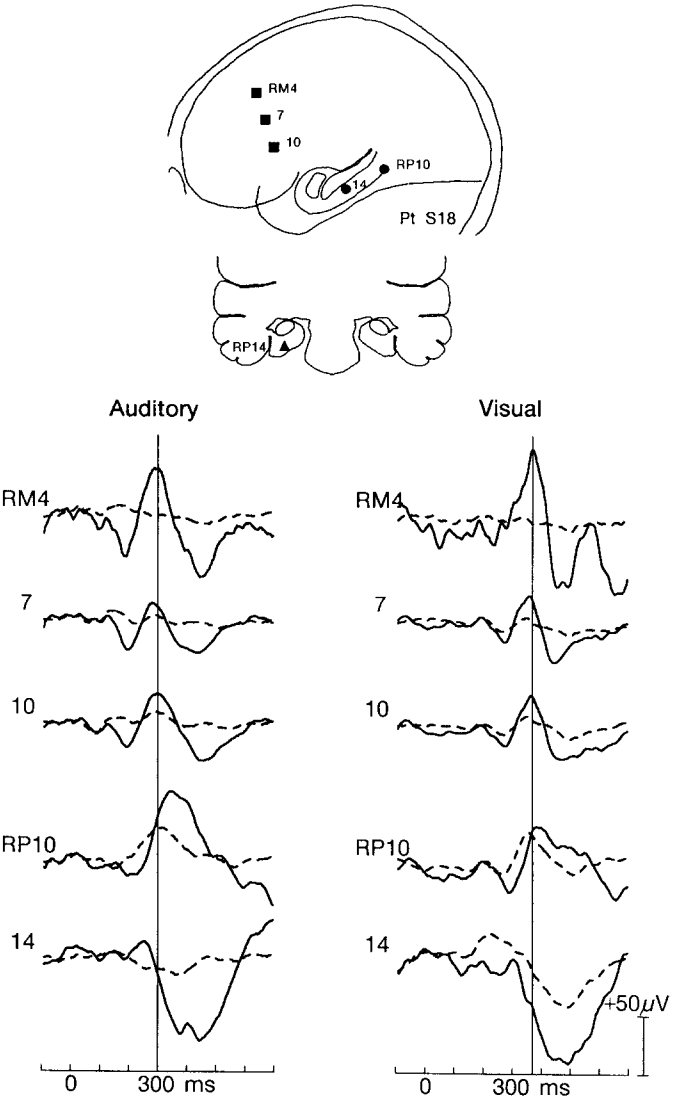

Fig. 2. ERPs recorded from patient S18. A: estimated depth probe electrode locations based on methods described in McCarthy et al. (1989). Depth probe RM entered the frontal lobe approximately 3 cm from the midline and was targeted for the anterior temporal region; electrode RM4 was near the cortical surface. B: ERPs evoked by rare (solid traces) and frequent (dashed traces) stimuli in auditory and visual categorization tasks. Isolatency lines are at the peak of P3 recorded at RM4 in the auditory (300 msec) and visual (370 msec) tasks.

with the scalp P3 but which reached its peak amplitude approximately 50 msec later. Like the scalp-recorded P3, the latency of this negative ERP was 70–100 msec later for visual than for auditory targets.

Fig. 1B shows that electrode 6, from which the rare target elicited a large (> 100 μV) negative ERP, was within the hippocampus. A positive ERP was elicited by the auditory targets at locations anterior to the hippocampus (electrodes 1–3). Similar positive ERPs at anterior MTL locations were reported by McCarthy et al. (1989).

Fig. 2 shows recordings from 2 electrodes in the MTL and 3 electrodes in the frontal lobe. Electrode RP 14, located inferior to the hippocampus, recorded a negative ERP to the rare targets similar to that seen in Fig. 1C. In contrast, positive ERPs were generally recorded posterior to the hippocampus (e.g., location RP 10). Electrodes in the frontal lobe recorded a triphasic ERP elicited by the rare targets with a large positive ERP peaking about 100 msec earlier than the negativity recorded in the MTL.

Monkey recordings

Passive condition with auditory stimuli. Locations of depth probe electrodes for monkey L are shown in Fig. 3. The left anterior (LA) probe passed through the anterior tip of the hippocampus in the region of the pes. Electrodes 1–3 were in or near the subiculum and presubiculum; electrode 4 was near the dentate gyrus; 5 and 6 were in the CA3 field of the hippocampus; and 7 and 8 were superior to the MTL. On the left posterior (LP) probe, electrodes 1–6 extended from entorhinal cortex near the rhinal sulcus through subiculum and presubiculum; 7 and 8 were in the pulvinar.

Representative results from epidural and depth probe electrodes are shown in Fig. 4. Larger potentials were elicited by rare tone sweeps than by frequent clicks. In epidural recordings, the tone elicited positive peaks at 30 and 160 msec and a negative peak at 70–90 msec. The positive ERP between 100 and 300 msec resembles P3-like ERPs recorded in previous monkey experiments, with a latency earlier than typically recorded from the human scalp. In depth recordings, rare tones elicited a negative potential at 50 msec (N50) that was quite large at a few contacts (LA2, LA4, and LP5–7). The large voltage gradients between N50 potentials at these locations and ERPs at adjacent locations suggest that the potentials were locally generated. Other deflections were also apparent in the first 200 msec. These will not be discussed further since the focus of this report is on the later, P3-like ERPs. In particular, a large negative peak near 210 msec (N210)

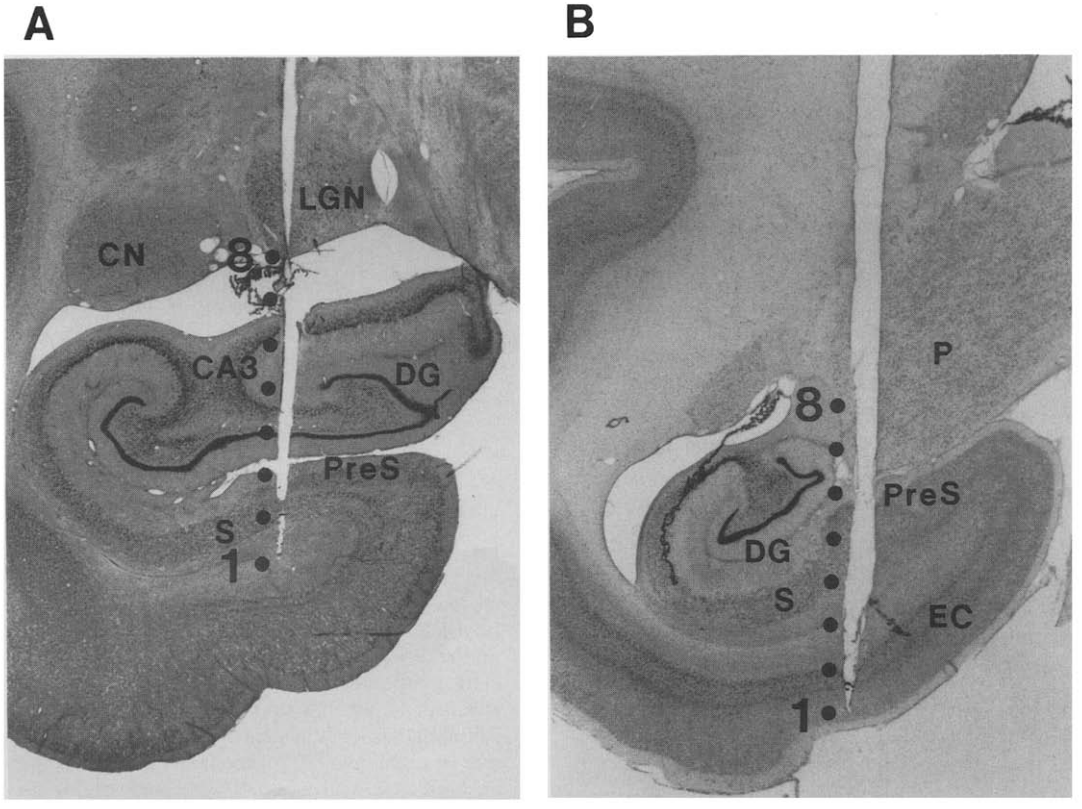

Fig. 3. Coronal sections showing the locations of electrodes on the left anterior (A) and left posterior (B) depth probes in monkey L. Abbreviations: CN, caudate nucleus; DG, dentate gyrus; EC, entorhinal cortex; LGN, lateral geniculate nucleus; P, pulvinar; PreS, presubiculum; S, subiculum.

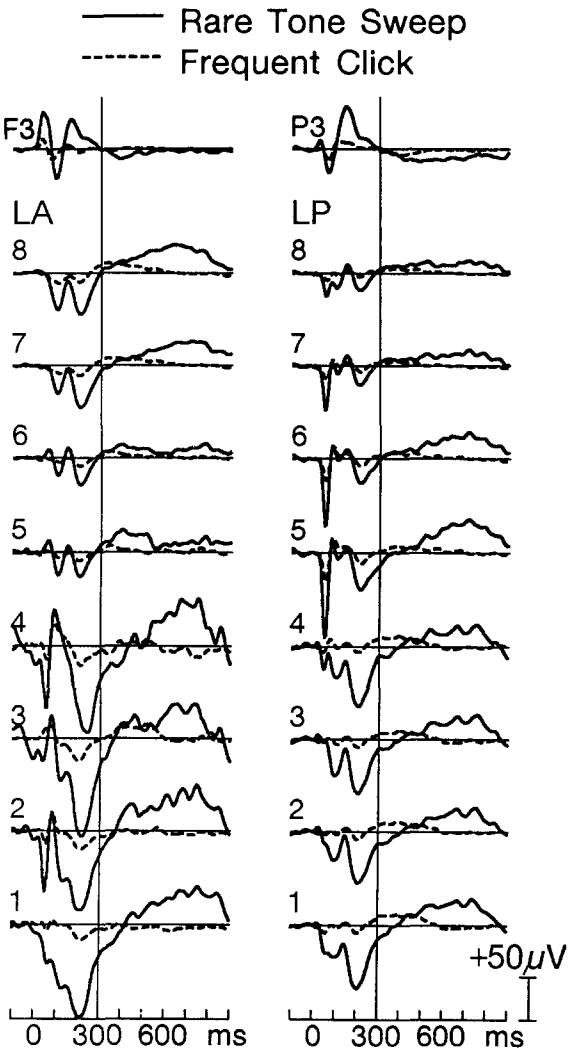

Fig. 4. ERPs recorded from monkey L during the passive auditory condition. Recordings are shown for representative epidural locations (F_3 and P_3) and for left anterior (LA) and left posterior (LP) depth probes. The reference was a disk electrode on the left earlobe. The number of responses averaged was 95 for the rare tone sweep and 805 for the frequent click.

was apparent at many locations, often preceded by a small positive peak near 150 msec. N210 was largest at locations 1–4 on the LA probe, with a peak amplitude ranging from −88 to −112 μV. There was thus a steep voltage gradient for the N210 between contacts LA4 and LA5. On the LP probe, the N210 reached a maximal amplitude of −68 μV at LP1 and at LP4 and was also evident at nearby contacts. N210 was much smaller when elicited by frequent clicks. In general, N210 peaked about 50 msec later than the second positive peak recorded from epidural locations.

Categorization task with visual stimuli. Monkeys were trained to perform this task by selectively touching the central area of the screen when the target (black-and-white checkerboard pattern) was displayed there. ERPs presented below were averaged for targets that were touched (i.e., hits) and for non-targets that were not touched. In one session, monkey L responded to 70% of the targets that were presented. None of the frequent non-targets were touched and only 7% of the rare non-targets were touched. The mean reaction time

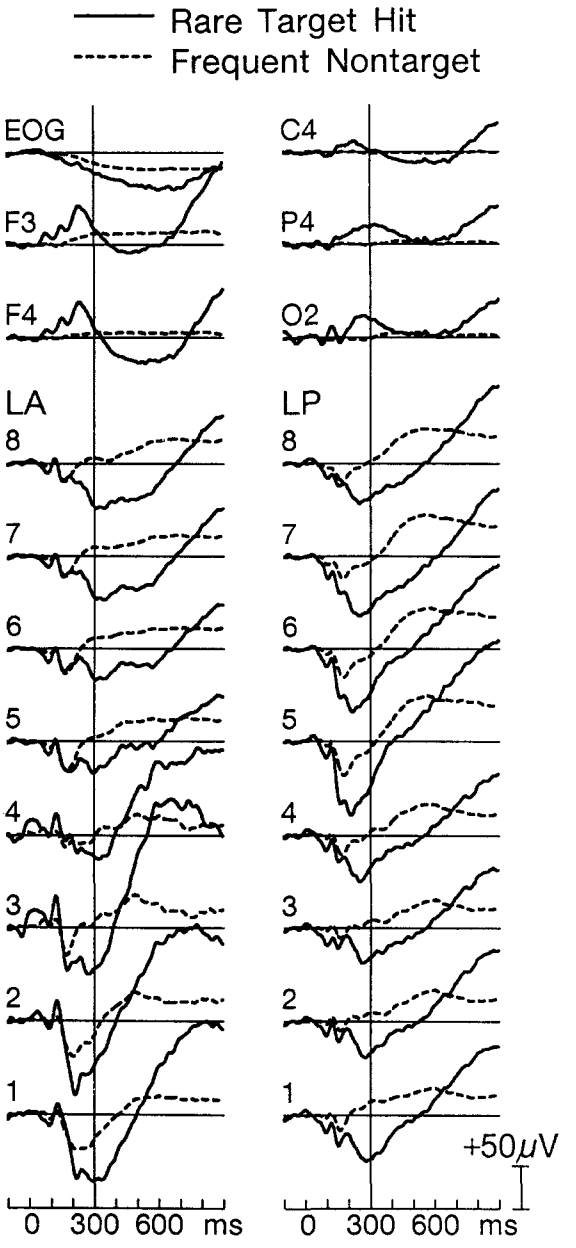

Fig. 5. ERPs recorded from monkey L during the visual categorization task. Recordings were made from the outer canthus of the left eye (EOG), from 5 epidural electrodes (F_3, F_4, C_4, P_4, and O_2), and from left anterior (LA) and left posterior (LP) depth probes. The reference was a subdermal electrode near the right mastoid process. Only trials associated with the correct behavioral response were included. Recordings from the probes were made during the first half of the session; the number of responses averaged was 104 for the rare target hit and 852 for the frequent non-target. Recordings from epidural and EOG locations were made during the second half of the session; the number of responses averaged was 73 for the rare target hit and 1726 for the frequent non-target. The difference in the ratio of targets to non-targets was due to poorer performance in the second half of the session.

for target detection was 655 ± 126 msec (mean ± standard deviation). Since the reward was delivered 300 msec after each correct response, the reward (and associated drinking movements) occurred, on average, beyond the end of the ERP recording epoch. Recordings made during this session are shown in Fig. 5. The target elicited a positive ERP with a peak at about 230 msec at anterior epidural locations (e.g., F_3 and F_4) and a later peak at posterior epidural locations (e.g., P_4 and O_2). At most locations on the LA probe, a negative deflection was evident in the 200–500 msec latency range, followed by a broad positive deflection. The negativity could be characterized as consisting of two parts. The earlier part reached a maximum at 210 msec at location LA2 (−84 μV). The later part was largest at location LA1 (−79 μV), and its peak latency (about 300 msec) was about 50 msec later than that of the positivity recorded from epidural locations. Negative peaks in the 200–300 msec latency range were also apparent at all locations on the LP probe. The maximum negativity was found at 200 msec at LP5 (−90 μV), with amplitude decreasing and latency increasing at adjacent locations.

Similar results were obtained from the other monkey in the visual categorization task. In one session, monkey E responded correctly to 81% of the targets and did not respond to any of the non-targets. Reaction times to targets in the first and second halves of the session were 573 ± 93 msec and 654 ± 121 msec, respectively. The locations of the anterior depth probes are shown in Fig. 6 and recordings from these and other locations are shown in Fig. 7. In general, ERPs elicited by targets in the 200–600 msec latency range were positive at epidural locations and negative at MTL locations (Fig. 7A). The large, positive ERPs at epidural locations had peak latencies of about 260 msec. The similarity of ERPs recorded in the first and second halves of the session (left and right columns in Fig. 7A) demonstrates the reliability of the results. Recordings from the LA probe showed a series of deflections, including N90, P120, N160, P200, and culminating in a broad negativity peaking between 250 and 320 msec. This negativity peaked 50–100 msec later than the positivity recorded from epidural locations. Recordings from the right anterior (RA) probe showed a similar pattern of ERPs. Maximal amplitudes of N250–320 (100–117 μV) were found at the two inferior locations on each probe. RA5 was the only location at which greater negativity was elicited by the frequent non-target than by the target. The largest voltage gradients thus occurred at locations LA2–3, RA2–3, and RA4–6. The EOG recordings showed

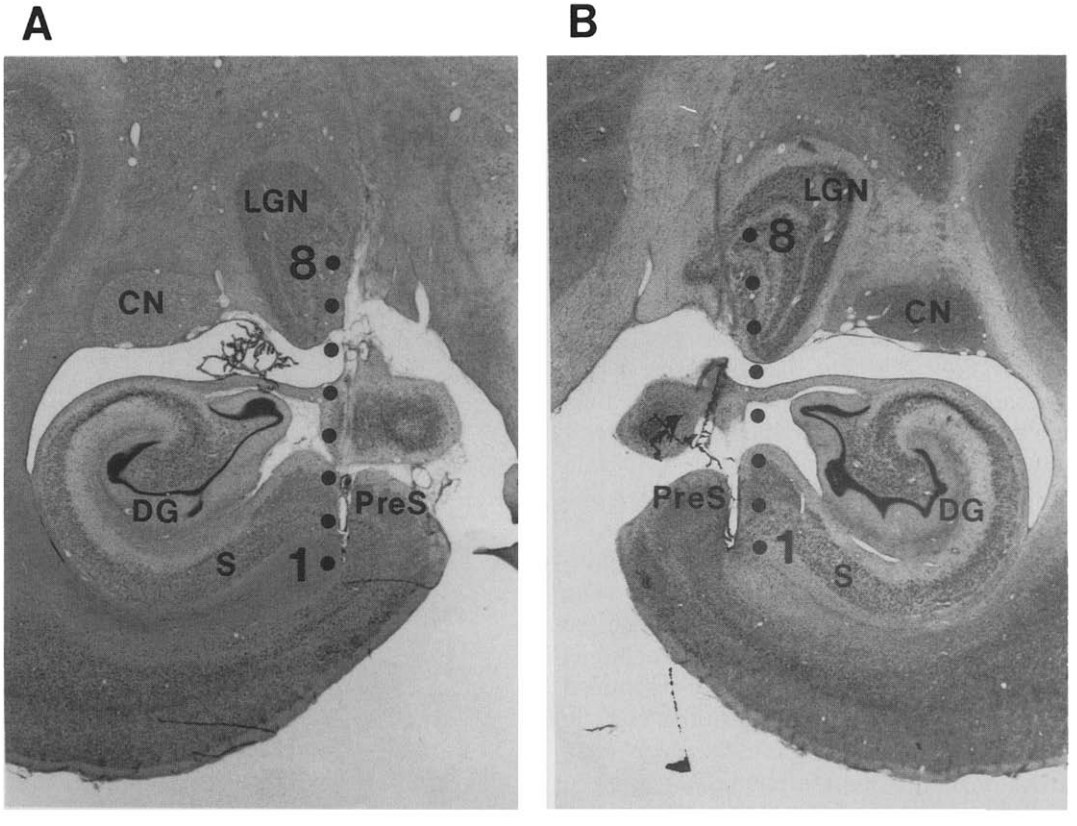

Fig. 6. Coronal sections showing the locations of electrodes on the left anterior (A) and right anterior (B) depth probes in monkey E. Abbreviations as in Fig. 3.

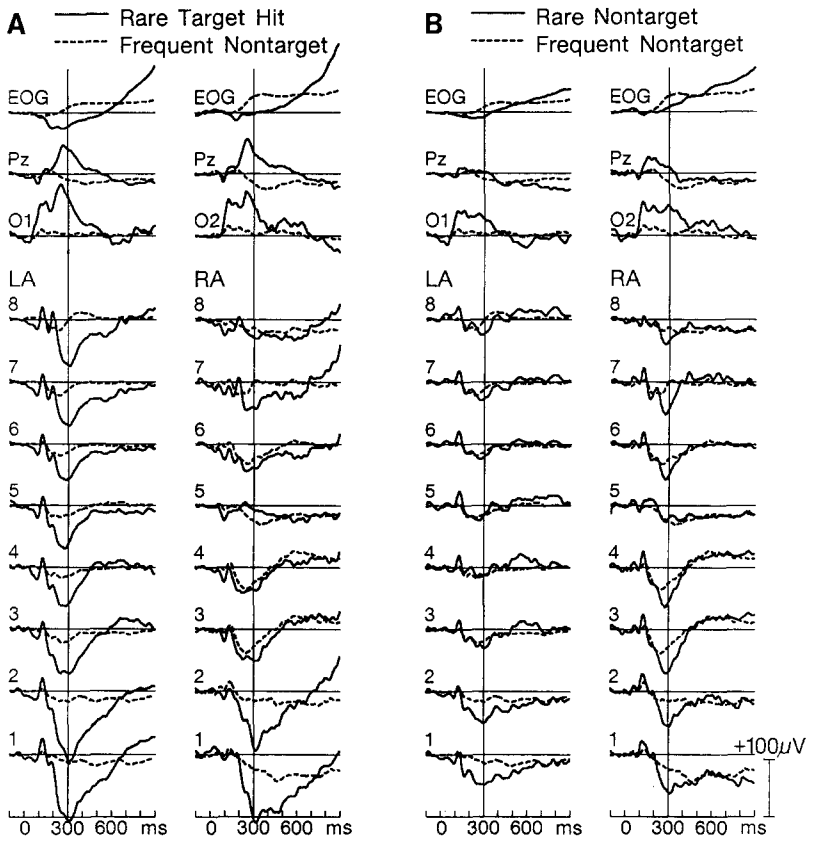

Fig. 7. ERPs recorded from monkey E during the visual categorization task. A: ERPs to correctly detected rare targets. B: ERPs to rare non-targets. Recordings in the left column were made during the first half of the session; those in the right column during the second half of the session. Recordings from EOG and P_z were made during both halves of the session. The EOG trace is shown at half gain. The reference was a subdermal electrode near the left mastoid process. Only trials associated with the correct behavioral response were included. The number of responses averaged was 76 for the rare target hit, 85 for the rare non-target, and 551 for the frequent non-target on the left side; the number of responses averaged was 35 for the rare target hit, 37 for the rare non-target, and 203 for the frequent non-target on the right side.

some residual artifact that differed between target and non-target conditions, especially after 600 msec. It is unlikely that this artifact contributed significantly to either the epidural or depth ERPs, because they were relatively uninfluenced by omitting trials based on EOG artifacts, and because similar ERPs were elicited by rare non-targets (Fig. 7B). The late negative ERPs elicited by rare non-targets were generally smaller than those elicited by targets, and also showed the largest voltage gradients at LA2–3 and RA4–6. Note that EOG potentials differed very little between rare and frequent non-targets.

Transcortical recordings from the left posterior parietal cortex of monkey E were obtained during the same recording session (Fig. 8). The ERP recorded from the cortical surface showed a series of deflections including N100, P150, N190, and P270. This ERP resembled those recorded from nearby epidural locations (e.g., P_z in Fig. 7A). The ERP recorded from the deep electrode at the white matter margin showed a series of deflections including N100, P130, N160, P200, and N300. The cortical surface P270 and the white matter N300 thus constituted a transcortical polarity inversion,

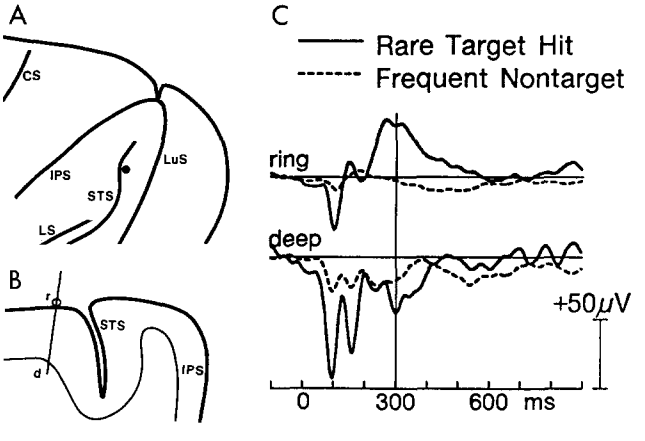

Fig. 8. Transcortical recording from monkey E during the visual categorization task (same session as in Fig. 7). A: location of transcortical electrode (solid circle) in posterior parietal cortex. Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; LS, lateral sulcus; LuS, lunate sulcus; STS, superior temporal sulcus. B: location of the ring (r) electrode on the cortical surface and the deep (d) electrode in white matter in a coronal section. C: ERPs recorded from the transcortical electrodes, each referenced to a subdermal electrode near the left mastoid process. The number of responses averaged was 76 for the rare target hit and 551 for the frequent non-target.

suggesting that some of the late activity was locally generated.

Discussion

The major conclusion of this study is that P3-like ERPs recorded from humans and monkeys during oddball paradigms were similar in 6 important respects: (1) rare target stimuli elicited a positive ERP several hundred milliseconds following stimulus onset from electrodes on the cortical surface or scalp; (2) rare target stimuli elicited a broad negative ERP, consisting of several subpeaks, from electrodes in the MTL; (3) the peak of the major negativity recorded from the MTL occurred 50–100 msec later than the positive peak recorded from epidural or scalp locations; (4) similar ERPs were elicited by auditory and visual stimuli; (5) these ERPs were affected by stimulus probability in that they were elicited preferentially by infrequently occurring stimuli; and (6) the amplitude of these ERPs was enhanced for rare stimuli that were task-relevant.

Previous studies in macaques also concluded that epidural potentials recorded during oddball tasks are similar to the human P3 (Arthur and Starr 1984; Glover et al. 1986, 1991; Paller et al. 1988; for studies in squirrel monkeys see Neville and Foote 1984; Pineda et al. 1987, 1988). These P3-like potentials were positive deflections in the 200–400 msec latency range, they were largest at central and parietal locations, they were elicited by auditory or visual stimuli that occurred infrequently, and they were enhanced when these stimuli were targets in categorization tasks. Although stimulus parameters were not manipulated systematically in the present recordings, prior experiments have demonstrated that infrequent events can elicit P3-like ERPs regardless of the physical properties of the stimuli. Our prior human studies have shown that similar MTL ERPs are elicited by visual, auditory, and somatic stimuli, as well as by stimulus omissions (McCarthy et al. 1989). Scalp P3s are also elicited by stimuli of different modalities (Simson et al. 1977; Desmedt and Debecker 1979; Snyder et al. 1980), although the commonly held notion that P3 scalp distribution is modality non-specific has recently been challenged (Johnson 1989).

The present study establishes a fuller correspondence between the human P3 and its monkey analog than has heretofore been provided. Although direct comparisons between the active and passive oddball conditions are limited, the finding that similar MTL ERPs were elicited is encouraging support for the monkey P3 analog. Polich (1989) concluded that the human P3 elicited in passive auditory conditions was similar to that elicited in an active oddball task. Here, it is noteworthy that the monkey MTL ERPs elicited by rare stimuli in the passive condition were similar to those elicited in the active categorization task (cf., Figs. 4 and 5). The two paradigms differed in that operant training was used to shape performance in the active task, whereas recordings from the passive condition were obtained without training. However, the monkey P3-like ERPs in the passive condition were subject to habituation and may not be appropriate for detailed studies requiring numerous stimulus repetitions. The two monkeys studied here did not exhibit large-amplitude P3s from epidural electrodes in the passive condition, although MTL potentials were still apparent. This finding suggests that the generators of the ERPs recorded epidurally and from the MTL may be dissociable by task manipulations.

Experiments in monkeys can provide a more fine-grained analysis of the intracranial distribution of ERPs than is possible in the limited clinical context in which intracranial recordings are conducted in humans. However, the present sampling of the potential fields within the monkey MTL was insufficient to locate the neural generators of the P3-like ERPs, especially as the electrodes passed medial to the hippocampus in most cases. Human studies suggest that some generators of MTL ERPs may be located in pyramidal cell layers of the hippocampus (Halgren et al. 1980, 1986; McCarthy et al. 1989). This idea is supported by the finding that the magnitude of the human MTL P3-like ERP is positively correlated with neuronal cell density in the CA pyramidal fields (Wood et al. 1988). In addition, it is likely that the primary hippocampal input (entorhinal cortex) and output (subiculum) regions are also involved in the generation of this ERP. The present recordings in humans (e.g., Fig. 2, location RP 14) and monkeys (e.g., Fig. 7A, locations 1–3) suggest that the presubiculum, subiculum, and entorhinal cortex may contribute to the MTL negativity.

Further study of these MTL potentials and of the neocortical P3-like ERPs is needed in order to understand their electrogenesis. The transcortical recordings of Fig. 8 were indicative of P3-like activity in parietal cortex. Because only two transcortical electrodes were well placed in each monkey, no conclusions can be drawn concerning the location and extent of cortical regions which generate P3-like ERPs. Interestingly, studies of P3 in humans with cortical lesions suggest that the scalp-recorded P3 depends in part on the integrity of cortex of the parieto-temporal junction (Knight et al. 1989), which may correspond to the region from which locally generated P3-like activity was seen in monkey E (Fig. 8).

Finally, the fact that MTL ERPs were observed in monkeys with no history of seizures or treatment with anticonvulsant drugs supports the generalizability of the human intracranial results. Previous studies have shown that ERPs tend to be abnormal or absent in an

MTL in which there is an epileptic focus (Squires et al. 1983; McCarthy et al. 1987; Meador et al. 1987; Wood et al. 1988). It is nevertheless conceivable that ERPs recorded from the MTL contralateral to an epileptic focus may not be representative of MTL ERPs in a non-epileptic population. The present results are inconsistent with this notion, suggesting instead that MTL ERPs represent normal neurophysiological processes that occur in monkeys as well as in humans.

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