Large sectors of polymodal cortex project to the hippocampal formation via convergent input to the entorhinal cortex. The present study reports an additional access route, whereby several cortical areas project directly to CA1. These are parietal areas 7a and 7b, area TF medial to the occipitotemporal sulcus (OTS), and a restricted area in the lateral bank of the OTS that may be part of ventromedial area TE. These particular cortical areas are implicated in visuospatial processes; and their projection to and convergence within CA1 may be significant for the elaboration of ‘view fields’, for the postulated role of the hippocampal formation in topographic learning and memory, or for the snapshot identification of objects in the setting of complex visuospatial relationships. Convergence of vestibular and visual inputs (from areas 7b and 7a respectively) would support previous physiological findings that hippocampal neurons respond to combinations of whole-body motion and a view of the environment. The direct corticohippocampal connections are widely divergent, especially those from the temporal areas, which extend over much of the anteroposterior axis of the hippocampal main body. Divergent connections potentially influence large populations of CA1 pyramidal neurons, consistent with the suggestion that these neurons are involved in conjunction coding. The same region of ventromedial TE, besides the direct connections to CA1, also gives rise to direct projections to area V1, and may correspond to a functionally specialized subdivision, perhaps part of VTF.

Introduction
Both anatomical and functional evidence indicates a segregation of object and spatial processing through the cortical visual pathways and into temporal and parietal regions (associated, respectively, with object and spatial relationships: Ungerleider and Mishkin, 1982; Milner and Goodale, 1995). It is generally believed, however, that mechanisms of ‘cross-talk’ and convergence must also exist, and several sites of interconnectedness or convergence have in fact been identified; for example, parts of the intraparietal sulcus (Seltzer and Pandya, 1980; Webster et al., 1994), the superior temporal sulcus (Morel and Bullier, 1990; Baizer et al., 1991; Cusick, 1997), and the parahippocampal gyrus (Van Hoesen, 1982; Insausti et al., 1987; Suzuki and Amaral, 1994). Recent functional studies of the prefrontal cortex report a continued segregation of processing at the single neuron level (Wilson et al., 1993), although other investigations suggest that integrating responses may occur under some behavioral conditions (Rao et al., 1997).

Another key site of integration for object identity and location is the hippocampal formation. Lesion and imaging studies, as well as electrophysiological experiments, demonstrate involvement of the hippocampus in spatial perception, cognition and action (Burgess et al., 1997), in addition to its close association with memory-related processes. At the single unit level, ‘view fields’ have been identified, which combine information about position in space with information about objects that are in a given spatial position (Rolls, 1989; O’Mara et al., 1994).

The connectional basis of this integration is likely to involve in some measure corticohippocampal connections. The hippocampal formation is densely interconnected with large sectors of the cerebral cortex; and the general importance of these connections can be inferred by the devastating effects of cortico-hippocampal disconnection in disorders such as Alzheimer’s disease.

The principal cortical input source to the hippocampal formation is the entorhinal cortex (EC). The EC receives input from many cortical areas, directly or via multisynaptic relays through the parahippocampal gyrus. These include the parietal and temporal lobes (Van Hoesen, 1982; Amaral et al., 1983; Insausti et al., 1987; Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989; Andersen et al., 1990; Suzuki and Amaral, 1994; Saleem and Tanaka, 1996), so that the EC might well be a source of visual and spatial convergence. Layer II of the EC projects massively to the dentate gyrus, the first step in the well-established circuit that proceeds through CA3 and CA1 (Amaral and Witter, 1989; Witter et al., 1989). In addition, auxiliary corticohippocampal access routes link the EC directly to CA1 and CA3. The functional importance of auxiliary connections is suggested by the persistence of spatial selectivity in neurons of CA1 and CA3 after massive destruction of the granule cells of the dentate gyrus in rats (McNaughton et al., 1989).

In the primate, several reports have described a fourth corticohippocampal route whereby some ventromedial temporal areas project directly to CA1 (Yukie and Iwai, 1988; Shi et al., 1994; Wellman and Rockland, 1997; Saleem and Hashikawa, 1998). The present study confirms temporal cortical connections to CA1, further demonstrates that there are direct connections to CA1 from parietal areas 7a and 7b, and indicates that these latter partially converge with the temporal projection focus.

Materials and Methods
Eleven macaque monkeys received injections of anterograde tracers in different parts of the temporal (n = 6) or parietal lobe (n = 5). Surgery was carried out under sterile conditions on animals deeply anesthetized with barbiturate anesthesia (Nembutal 25 mg/kg, administered i.v., after a tranquilizing dose of ketamine, 11 mg/kg, i.m.). Procedures were in accordance with institutional and federal guidelines, as specified in approved Animal Care and Use Forms (University of Iowa). Cortical areas of interest were localized by direct visualization, subsequent to craniotomy and durotomy, in relation to sulcal landmarks. Ventromedial temporal areas were localized in relation to the occipitotemporal sulcus, after reduction of brain volume by i.v. injections of Mannitol.

The six monkeys in the temporal lobe series received iontophoretic injections of Phaseolus vulgaris leucoagglutinin [PHAL, Vector Labs, Burlingame, CA: 2.5% in 10.0 mM phosphate buffer (PB), 7 s on-off positive current cycle over 20 min]. The five monkeys in the parietal series received pressure injections of biotinylated dextran amine [BDA, Molecular Probes, Eugene, Oregon: 10% in 0.0125 M phosphate-buffered...
saline (PBS); 0.25–0.75 µl per injection]. Animals were allowed to recover and survived 14–21 days after injections. They were then re-anesthetized, given an overdose of Nembutal (75 mg/kg) and perfused transcardially, in sequence, with saline, 4% paraformaldehyde and chilled 0.1 M PB with
attachment. Injection sites were localized to specific cortical areas by transposed onto section outlines via a drawing tube microscope and, for bouton analysis, at 1000× under oil. Projection foci were shown in black, and P6, in broken outline). Six other injections (designated by a hollow outline) did not produce label in CA1. These injections were located in the superior parietal lobule (area 5), in the lower bank of the intraparietal sulcus (indicated by arrow), on the lateral portions of area TE, and more posteriorly in the ventromedial temporal lobe. AS, arcuate sulcus; CE, calcarine fissure; CS, central sulcus; IDS, inferior occipital sulcus; IPS, intraparietal sulcus; LS, lateral sulcus; LS, lunate sulcus; MDS, middle orbital sulcus; OTS, occipitotemporal sulcus; PS, principal sulcus; RS, rhinal sulcus; STS, superior temporal sulcus; TMAPS, temporal middle anterior sulcus; TMPS, temporal middle posterior sulcus.

Results
Of six brains with injections in various sectors of temporal cortex, direct projections to CA1 were found in the two with ventromedially placed injections: in areas TF (injection T7) and ventromedial TE (injection T5); see Materials and Methods and Figure 1. Injections confined to more lateral or more posterior temporal cortices did not result in projections to CA1 (Fig. 1). Injections placed in areas 7a (cases P5 and P6) or 7b (case P7) also resulted in direct projections, but two other injections, in the lower bank of the intraparietal sulcus and in area 5, did not (Fig. 1). In demonstrating these connections, the use of high-resolution tracers was important. Their superior sensitivity and resolution successfully demonstrated even relatively fine-caliber axons and structural features, which would be ambiguous at best with autoradiography or anterograde WGA-HRP.

The organization of temporal and parietal connections was similar in several respects. First, both terminated mainly in a superficial location near the hippocampal fissure in the stratum lacunosum-moleculare (Figs 2–4). This is the same termination zone that receives connections from the EC, and may partially coincide with subcortical afferents. Postsynaptic targets in this superficial position are most probably the distal apical dendrites of underlying pyramidal cells.

Second, the projection foci were of light to moderate density. Terminations in case T5 were densest, those in P5 and P7 intermediate in density, and those in T7 and P6 least dense. Terminations were sampled through the densest region and counted per 60 μm2 field at 1000× magnification. Resulting counts were 50–60 boutons per field for T5, ~30 boutons per field for P5 and P7, and <20 boutons per field for T7 and P6. In the mediolateral axis, projection foci in the parietal cases measured 0.4–0.6 mm; those in the temporal cases were slightly larger (0.7 mm). At their densest extent, foci in all cases formed a band 0.15 mm wide (Fig. 4). The actual number of axons is difficult to estimate with this technique, but may have been several hundred, at least for T5, P5 and P7. This impression is based on surveying the number of axon segments in the white matter subjacent to the projection focus at spaced intervals along its anterior, posterior and middle portions.

Third, both temporal and parietal terminations targeted the posterior portion of CA1, and appeared to converge in a similar location. The temporal foci were more extensive and continued over 10.0 mm through much of the anteroposterior axis of the hippocampal main body (Fig. 5). Parietal projections remained within the posterior 2.0 mm, despite the larger size of the injections in these cases (see Materials and Methods).

Fourth, both the temporal and parietal axons were fine in caliber (<1.0 μm in diameter), and studded with a mix of beaded and stalked specializations (Figs 2 and 3). These were predominately small, but there was a scattering of larger profiles (~2.0 μm in diameter).

Fifth, both sets of connections had terminal fields that
appeared to form elongated rather than clustered or spherical arbors. Terminal segments of 0.75 mm, aligned mediolaterally, were common in individual sections (Fig. 3); and serial reconstruction of temporal cortical axons demonstrated that these have large fields, extending 4–6 mm, mainly in the anteroposterior dimension (Shi et al., 1994).

**Discussion**

The present findings have several implications for the network architecture of corticohippocampal and corticocortical connectivity. Principally, they show that neurons in CA1 receive inputs from at least four cortical processing levels: direct monosynaptic input from specific temporal and parietal cortical areas; direct input from layer III of the EC; and two indirect inputs from the EC via its projections to the dentate gyrus and to CA3. Given the number of parallel routes between various cortical regions and the hippocampal formation, the idea of a unidirectional progression through the trisynaptic circuit, with the EC as an obligatory gatekeeper, may be only partially correct.

Some of the auxiliary pathways are directly reciprocal, but others are not. That is, neurons in CA1 both receive from and project to ventromedial temporal areas (Iwai and Yukie, 1988; Yukie and Iwai, 1988; Shi et al., 1994; Wellman and Rockland, 1997; Blatt and Rosene, 1998; Saleem and Hashikawa, 1998).
CA1 sends projections to orbital and medial frontal cortex (Barbas and Blatt, 1995), but has not been reported to receive direct projections back. CA1, as shown by our findings, receives projections from areas 7a and 7b, but has not been reported to send direct projections back (also unpublished observations based on retrograde tracer injections in areas 7a or 7b).

Direct temporal cortical connections to CA1 had previously been described after retrograde tracer injections within the hippocampus, although the exact localization of the cortical label has been controversial. Yukie and Iwai (1988) identified the projections as originating from area TE, but Suzuki and Amaral (1990) considered the field to be within the parahippocampal gyrus. Saleem and Hashikawa (1998) report direct connections to the hippocampal formation from the ventral part of anterior TE. Our results, especially injection T5, within the lateral bank of the OTS, support the interpretation of an origination from TE, although this may well be a functionally distinct subdivision. This is the same region that has been shown to send direct connections to primary visual cortex, by retrograde (Rockland and Van Hoesen, 1994) and anterograde techniques (Rockland and Drash, 1996). The suggestion that ventromedial and lateral temporal areas are functionally distinct has also been made from combined anatomical and behavioral evidence (Martin-Elkins and Horel, 1992).

**Temporal-parietal convergence**

Ventromedial temporal and posterior parietal areas are intricately linked through numerous corticocortical connections and, along with the dorsolateral prefrontal cortex, are considered to form a network involved in visuospatial processing and memory (Selemon and Goldman-Rakic, 1988). Functional coupling has been demonstrated between some inferior temporal and parietal regions by imaging experiments, in conditions in which perceptual learning of faces or objects might involve spatial attention, feature binding and memory recall (Dolan et al., 1997). The convergence of temporal and parietal connections in CA1 is consistent with recently postulated roles of the hippocampus in topographic learning (Maguire, 1997), dynamic aspects of spatial memory (‘topokinetic memory’: Berthoz, 1997), or the snapshot-like memory of objects in a complex scene (Gaffan and Hornak, 1997; Buckley and Gaffan, 1998). The convergence of vestibular and visual inputs (potentially from areas 7b and 7a respectively) is predicted from the physiological findings that hippocampal cells, believed to be pyramidal,
respond to whole-body motion, or to combinations of whole-body motion and a view of the environment (O’Mara et al., 1994).

Axonal divergence
Our findings provide further evidence that axonal divergence is an important feature in the functional architecture of the hippocampal formation. Other examples of divergence, as demonstrated at the level of single axons, are the projections from area TF to the EC, which can extend over 6–11 mm (Wellman and Rockland, 1997), the network of collaterals within CA3, and the Schaeffer collateral projections from CA3 to CA1 (Amaral and Witter, 1989; Li et al., 1994). The total projected axon length of a CA3 neuron has been estimated as 150–300 mm (Li et al., 1994). This divergent pattern is reminiscent of the distributed connections into olfactory cortex, cerebellar parallel fibers and feedback corticocortical connections in layer I. It contrasts with the spatially topographic mappings characteristic of the primary auditory, somatosensory and visual cortical systems.

Summary and Conclusions
Our results indicate that several temporal and parietal areas project directly to CA1 in a partially convergent manner. These connections add to the roster of multiple corticohippocampal pathways, and may contribute to visuospatial processes mediated by the hippocampus. The particular inferotemporal source locus in the OTS also gives rise to direct projections to area V1 (Rockland and Van Hoesen, 1994; Rockland and Drash, 1996; see also Sousa et al., 1991 in Cebus) and may correspond to a functionally specialized subdivision. It is in the general location of area ‘VTF’ (Boussaoud et al., 1991), but appears to be more anterior.

Notes
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Address correspondence to Kathleen S. Rockland, Department of Neurology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242–1053, USA. Email: rockland@blue.wecg.uiowa.edu.

References


