

## INTERACTIONS AMONG THE MEDIAL PREFRONTAL CORTEX, HIPPOCAMPUS AND MIDLINE THALAMUS IN EMOTIONAL AND COGNITIVE PROCESSING IN THE RAT

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**Abstract**—The medial prefrontal cortex (mPFC) participates in several higher order functions including selective attention, visceromotor control, decision making and goal-directed behaviors. We discuss the role of the infralimbic cortex (IL) in visceromotor control and the prelimbic cortex (PL) in cognition and their interactions in goal-directed behaviors in the rat. The PL strongly interconnects with a relatively small group of structures that, like PL, subserve cognition, and together have been designated the ‘PL circuit.’ These structures primarily include the hippocampus, insular cortex, nucleus accumbens, basolateral nucleus of the amygdala, the mediodorsal and reuniens nuclei of the thalamus and the ventral tegmental area of the midbrain. Lesions of each of these structures, like those of PL, produce deficits in delayed response tasks and memory. The PL (and ventral anterior cingulate cortex) (AC) of rats is ideally positioned to integrate current and past information, including its affective qualities, and act on it through its projections to the ventral striatum/ventral pallidum. We further discuss the role of nucleus reuniens of thalamus as a major interface between the mPFC and the hippocampus, and as a prominent source of afferent limbic information to the mPFC and hippocampus. We suggest that the IL of rats is functionally homologous to the orbitomedial cortex of primates and the prelimbic (and ventral AC) cortex to the lateral/dorsolateral cortex of primates, and that the IL/PL complex of rats exerts significant control over emotional and cognitive aspects of goal-directed behavior. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** infralimbic cortex, prelimbic cortex, nucleus reuniens, hippocampus, memory, working memory.

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**Abbreviations:** AC, anterior cingulate cortex; ACC, nucleus accumbens; ACTH, adrenocorticotropic hormone; AGm, medial agranular (frontal) cortex; BLA, basolateral nucleus of amygdala; BST, bed nucleus of the stria terminalis; CEA, central nucleus of the amygdala; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FEF, frontal eye fields; HF, hippocampal formation; ICA, intercalated nucleus of the amygdala; IL, infralimbic cortex; LTD, long term depression; LTP, long term potentiation; MD, mediodorsal nucleus of thalamus; M1, primary motor cortex; mPFC, medial prefrontal cortex; NTS, nucleus of the solitary tract; OMPFC, orbitomedial prefrontal cortex; PAG, periaqueductal gray; PFC, prefrontal cortex; PHA-L, *Phaseolus vulgaris* leucoagglutinin; PL, prelimbic cortex; PPF, paired pulse facilitation; PT, paratenial nucleus; PV, paraventricular nucleus; RAM, radial arm maze; RE, nucleus reuniens of thalamus; SNc, substantia nigra-pars compacta; VTA, ventral tegmental area; WM, working memory.

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doi:10.1016/j.neuroscience.2006.06.027

It is well recognized that the prefrontal cortex (PFC) participates in several higher order functions including selective attention, visceromotor control, working memory (WM), decision making and goal-directed behavior.

The present review focuses on the role of ventral regions of the rat medial prefrontal cortex (mPFC) in the integration of emotional and cognitive aspects of behavior. We discuss: (1) anatomical/functional differences between dorsal and ventral regions of the mPFC; (2) anatomical differences between the infralimbic (IL) and prelimbic (PL) cortices; (3) possible functional homologues between the PFC of rats and primates; (4) anatomical loops between the hippocampus and mPFC via nucleus reuniens (RE) of the midline thalamus; (5) physiological actions of the hippocampus on the mPFC; (6) physiological effects of RE on the hippocampus; (7) RE as a major source of limbic information for the hippocampus and mPFC; (8) the role of the IL in visceromotor control and the prelimbic cortex in limbic/cognitive functions; and (9) interactions between RE, the hippocampus and IL/PL in emotion/cognition. We suggest that the IL of rats is primarily involved in visceromotor functions, homologous to the orbitomedial cortex of primates, and the PL (and ventral anterior cingulate, AC) is involved in limbic/cognitive activity, homologous to the lateral/dorsolateral cortex of primates, and that the IL/PL complex of rats exerts significant control over emotional and cognitive aspects of behavior.

### Functional and anatomical differences between the dorsal and ventral mPFC of rats

The mPFC of rats consists of four main divisions which from dorsal to ventral are the medial agranular (AGm) (or medial precentral), the AC (dorsal and ventral divisions), the PL and the IL (Berendse and Groenewegen, 1991; Ray and Price, 1992; Price, 1995; Swanson, 1998; Öngür and Price, 2000; Heidbreder and Groenewegen, 2003). The various subdivisions of the mPFC appear to serve separate and distinct functions. For instance, dorsal regions of mPFC (AGm and AC) have been linked to various motor behaviors, while ventral regions of mPFC (PL and IL) have been associated with diverse emotional, cognitive, and mnemonic processes (Heidbreder and Groenewegen, 2003).

Early reports in rats showed that stimulation of AGm/AC generated eye movements (Hall and Lindholm, 1974; Donoghue and Wise, 1982), which together with the demonstration that AGm/AC projects to oculomotor sites (Beckstead, 1979; Hardy and Leichnetz, 1981; Neafsey

et al., 1986a; Leichnetz and Gonzalo-Ruiz, 1987; Leichnetz et al., 1987; Reep et al., 1987; Stuesse and Newman, 1990), led to the proposal that AGm/AC of rats was equivalent to the frontal eye fields (FEF) of primates (Leonard, 1969; Reep et al., 1984, 1987; Leichnetz and Gonzalo-Ruiz, 1987; Guandalini, 1998). Subsequent studies confirmed AGm involvement in eye movement control, and further showed that AGm stimulation produced other types of movements including those of the vibrissa, head and hindlimbs (Neafsey and Sievert, 1982; Sanderson et al., 1984; Sinnamon and Galer, 1984; Gioanni and Lamarche, 1985; Neafsey et al., 1986a). Accordingly, it has been variously proposed that the AGm/AC of rats is homologous to the FEF, supplementary motor and premotor cortices of primates (Neafsey et al., 1986a; Reep et al., 1987, 1990; Passingham et al., 1988; Conde et al., 1995).

In contrast to motor-associated properties of the dorsal mPFC, the ventral mPFC (IL and PL) has been functionally linked to the limbic system. As will be discussed, the IL profoundly influences visceral/autonomic activity. IL stimulation produces changes in respiration, gastrointestinal motility, heart rate and blood pressure (Terreberry and Neafsey, 1983; Burns and Wyss, 1985; Hurley-Gius and Neafsey, 1986; Verberne et al., 1987; Hardy and Holmes, 1988) and has been viewed as a visceromotor center (Hurley-Gius and Neafsey, 1986; Neafsey, 1990). PL, on the other hand, has been directly implicated in cognitive processes. PL lesions produce pronounced deficits in delayed response tasks (Brito and Brito, 1990; Seamans et al., 1995; Delatour and Gisquet-Verrier, 1996, 1999, 2000; Floresco et al., 1997; Ragozzino et al., 1998; Dalley et al., 2004) similar to those seen with lesions of the lateral PFC of primates (Kolb, 1984; Goldman-Rakic, 1987, 1994; Groenewegen and Uylings, 2000).

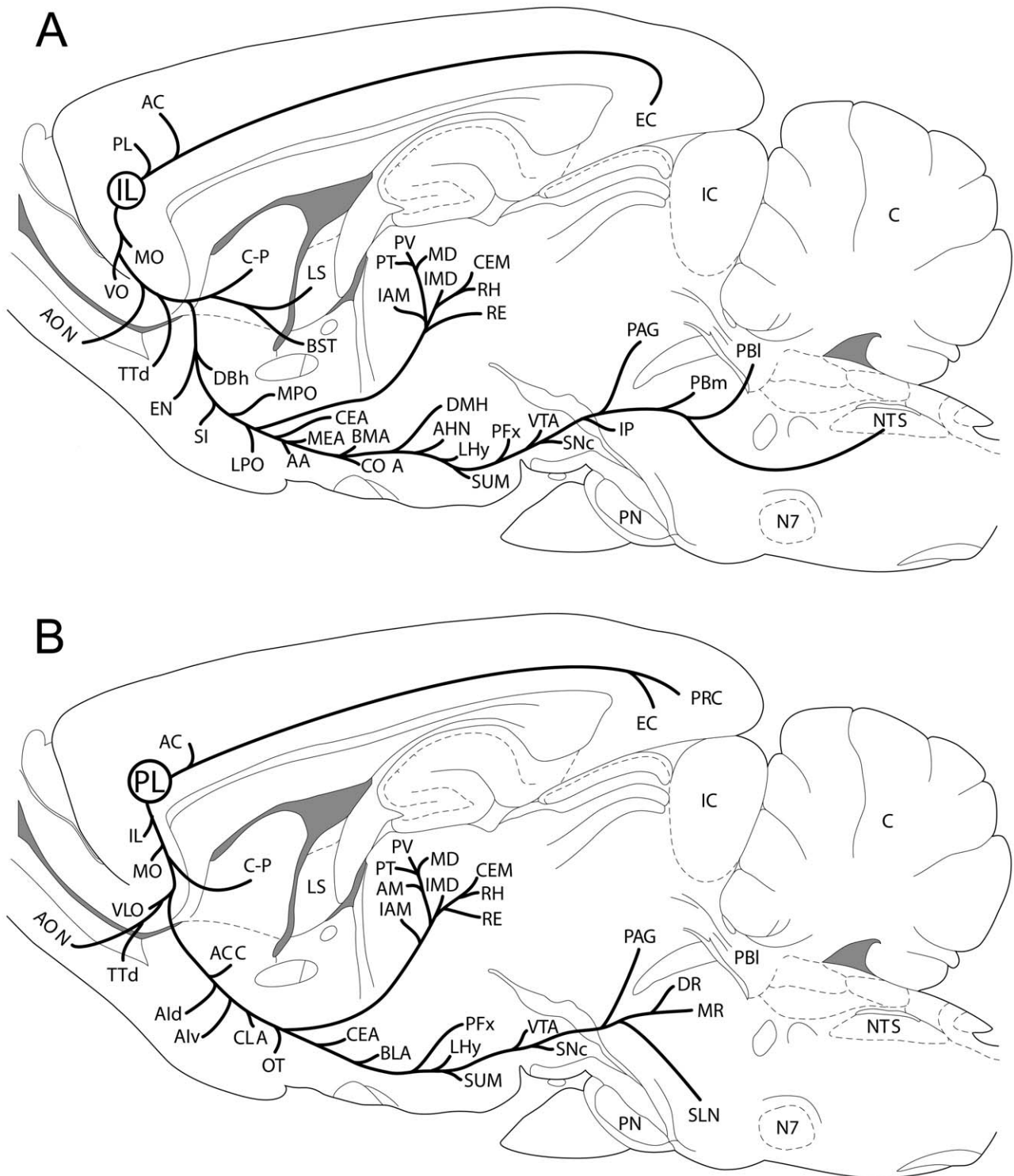
As would be expected by a functional differentiation, there are distinct anatomical differences between dorsal and ventral regions of the mPFC. Specifically, the dorsal mPFC, particularly AGm, distributes to sensori-motor regions of the brain including motor and somatosensory cortices, dorsal striatum, ventral and lateral nuclei of thalamus, tectum/pretectum and the brainstem reticular formation, but essentially avoids 'limbic' regions of the forebrain and hindbrain (Reep et al., 1984, 1990, 2003; Conde et al., 1995; Guandalini, 1998; Reep and Corwin, 1999; Cheatwood et al., 2003; Voorn et al., 2004; Gabbott et al., 2005). By contrast, the ventral mPFC (IL/PL) strongly connects with limbic structures prominently including other regions of 'limbic' cortex, bed nucleus of the stria terminalis (BST), nucleus accumbens (ACC), amygdala, midline thalamus and widespread regions of the hypothalamus and brainstem (Room et al., 1985; Sesack et al., 1989; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan et al., 1994; Conde et al., 1995; Chiba et al., 2001; Vertes, 2002, 2004; Gabbott et al., 2003, 2005). In addition, the hippocampus (ventral CA1 and subiculum) projects to IL/PL but not to the dorsal mPFC (Jay and Witter, 1991; Laroche et al., 2000; Vertes et al., 2002).

### Differential projections of the infralimbic and prelimbic cortices

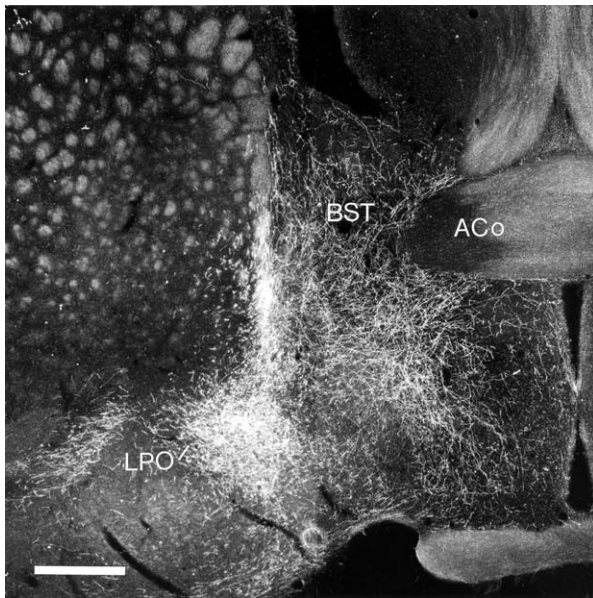
In a recent comparison of IL and PL projections in the rat, we showed that, with a few exceptions, PL and IL distribute differently throughout the brain (Vertes, 2004). These differential patterns of projections are summarized in Fig. 1. As illustrated (Fig. 1), IL distributes significantly to: (1) neighboring regions of the orbitofrontal cortex including the medial and lateral orbital cortices, PL and AC; (2) anterior piriform cortex, dorsal and ventral taenia tecta, and anterior olfactory nucleus of the olfactory forebrain; (3) medial and lateral preoptic areas, substantia innominata, BST, lateral septum and horizontal limb of diagonal band nucleus of the basal forebrain; (4) the medial, basomedial, cortical and central nuclei of the amygdala; (5) the midline thalamus; (6) dorsomedial, lateral, perifornical, posterior, and supramammillary nuclei of the hypothalamus; and (7) the substantia nigra-pars compacta (SNc), periaqueductal gray (PAG), parabrachial nucleus and nucleus of the solitary tract (NTS) of the brainstem. Fig. 2 shows dense terminal labeling in BST and the medial and lateral preoptic areas following a *Phaseolus vulgaris* leucoagglutinin (PHA-L) injection in IL (Vertes, 2004).

With respect to IL modulation of visceral functions, IL distributes to sites that directly affect autonomic/visceromotor activity including the parabrachial nucleus, NTS and the intermediolateral cell column of the spinal cord, as well as to several structures that project to, and influence, autonomic nuclei of the brainstem/spinal cord (Cechetto and Saper, 1990; Neafsey et al., 1986b; Neafsey, 1990; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan and Powell, 1993; Verberne and Owens, 1998; Vertes, 2004; Gabbott et al., 2005). The latter includes the medial and lateral preoptic areas, BST, central nucleus of the amygdala (CEA), and the lateral and posterior hypothalamus (Saper et al., 1976, 1979; Hopkins and Holstege, 1978; Schwaber et al., 1982; Veening et al., 1984; Moga and Gray, 1985; Grove, 1988; Moga et al., 1989, 1990a,b; Loewy, 1991; Rizvi et al., 1991, 1992, 1996; Allen and Cechetto, 1992; Vertes and Crane, 1996; Petrovich and Swanson, 1997; Murphy et al., 1999; Floyd et al., 2001). This indicates direct as well as indirect IL actions on a network of interconnected nuclei subserving autonomic/visceral control.

By contrast with IL, the PL sends few projections to 'visceral-related sites' of the forebrain and brainstem (Fig. 1). Main PL targets are: (1) the orbitofrontal, anterior piriform, agranular insular (dorsal and ventral divisions) and entorhinal cortices; (2) the anterior olfactory nucleus and dorsal taenia tecta of the olfactory forebrain; (3) medial parts of the dorsal striatum, the ACC (core and shell), olfactory tubercle, and the claustrum of the basal forebrain; (4) the midline thalamus; (5) the basolateral nucleus of the amygdala (BLA); and (6) the ventral tegmental area (VTA), SNc, PAG, supramammillary nucleus (Vertes and Crane, 1997) and the dorsal and median raphe nuclei of the brainstem (Fig. 1)(Vertes, 2004). Fig. 3 depicts dense terminal labeling in the anterior part of the ACC, the olfac-



**Fig. 1.** Schematic sagittal sections summarizing the main projection sites of the IL (A) and PL (B). Note that IL projections are much more widespread than PL projections, particularly to the basal forebrain, amygdala and hypothalamus. Sections are modified from the rat atlas of Paxinos and Watson (1986). For illustrative purposes several sagittal planes are collapsed onto single sagittal sections. Abbreviations: AA, anterior area of amygdala; AHN, anterior nucleus of hypothalamus; AI,d,v, agranular insular cortex, dorsal, ventral divisions; AM, anteromedial nucleus of thalamus; AON, anterior olfactory nucleus; BMA, basomedial nucleus of amygdala; C, cerebellum; CEM, central medial nucleus of thalamus; CLA, claustrum; COA, cortical nucleus of amygdala; C-P, caudate/putamen; DBh, nucleus of the diagonal band, horizontal limb; DMH, dorsomedial nucleus of hypothalamus; DR, dorsal raphe nucleus; EN, endopiriform nucleus; IAM, interanteromedial nucleus of thalamus; IC, inferior colliculus; IMD, intermediodorsal nucleus of thalamus; IP, interpeduncular nucleus; LH, lateral hypothalamic area; LPO, lateral preoptic area; LS, lateral septal nucleus; MEA, medial nucleus of amygdala; MO, medial orbital cortex; MPO, medial preoptic area; MR, median raphe nucleus; N7, facial nucleus; NTS, nucleus tractus solitarius; PAG, parabrachial nucleus, medial and lateral divisions; Pfx, perifornical region of hypothalamus; PN, nucleus of pons; PRC, perirhinal cortex; RH, rhomboid nucleus of thalamus; SI, substantia innominata; SLN, suprallemniscal nucleus (B9); SUM, supramammillary nucleus; TTd, taenia tecta, dorsal part; VLO, ventral lateral orbital cortex; VO, ventral orbital cortex. Reprinted from Vertes (2004).



**Fig. 2.** Darkfield photomicrograph of a transverse section through the forebrain showing patterns of labeling in the basal forebrain produced by an injection in the IL. Note dense terminal labeling in the BST, the ventral part of the lateral preoptic area (LPO), and the medially adjacent medial preoptic area. Abbreviation: ACo, anterior commissure. Scale bar=600  $\mu$ m. Reprinted from Vertes (2004).

tory tubercle and the dorsal agranular insular cortex following a PHA-L injection in PL (Vertes, 2004).

Consistent with findings in rats (Sesack et al., 1989; Vertes, 2004), an early report on cats (Room et al., 1985) demonstrated pronounced PL projections to the ACC, and further noted that the PL to ACC projection was the first leg of a cortical loop involving PL, that is, a loop “from the prelimbic area via the ventral striatum, ventral pallidum, and the mediodorsal nucleus back to the prelimbic area.” This system of connections, or the ‘PL circuit’ (Alexander et al., 1990; Groenewegen et al., 1990), has subsequently been elaborated to include several additional structures which in addition to PL, ACC, ventral pallidum and mediodorsal nucleus of thalamus (MD), include the insular cortex, hippocampus, claustrum, BLA, paraventricular (PV) and RE of thalamus, and the VTA of the midbrain (McDonald, 1987, 1991; Witter et al., 1988; Groenewegen, 1988; Cassell et al., 1989; Sesack et al., 1989; Zahm, 1989; Berendse and Groenewegen, 1990; Kita and Kitai, 1990; Berendse and Groenewegen, 1991; Heimer et al., 1991; Jay and Witter, 1991; Kuroda and Price, 1991; Ray and Price, 1992; Groenewegen et al., 1993, 1999; Brog et al., 1993; Miyamoto and Jinnai, 1994; Shinonaga et al., 1994; Moga et al., 1995; Wright and Groenewegen, 1995; Bacon et al., 1996; Carr and Sesack, 1996; McDonald et al., 1996; Wright et al., 1996; Zahm et al., 1996; Maurice et al., 1997; O’Donnell et al., 1997; Mulder et al., 1998; Vertes, 2002, 2004; Gabbott et al., 2003; Pare, 2003; Jasmin et al., 2004).

As will be discussed, this extended PL circuitry, consisting of a main loop through ventral striopallidal–thalamo-cortical circuits, with additional interconnections with the

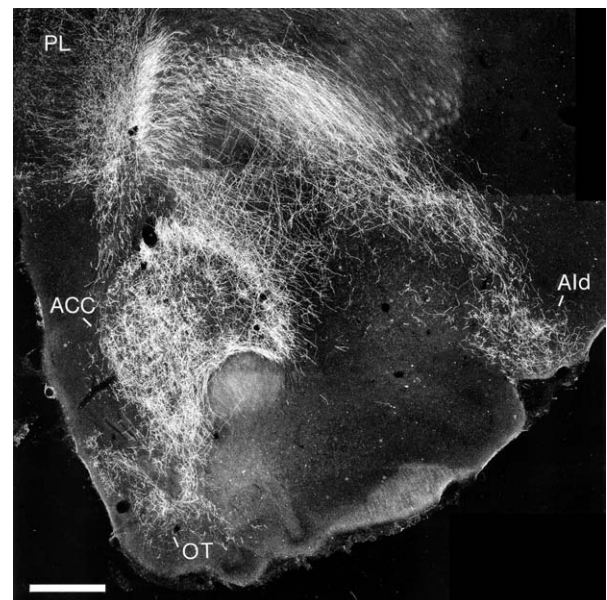
insular cortex, hippocampus, claustrum, BLA of amygdala, PV and RE of the midline thalamus, and SNc/VTA of the midbrain, appears to represent an important circuitry involved in cognitive processing.

In summary, IL and PL project differentially throughout the brain (Fig. 1). IL predominantly distributes to autonomic/visceral-related sites, supporting its role in visceromotor activity. PL (and ventral AC) primarily projects to limbic sites associated with cognitive behaviors, supporting its role in cognitive/mnemonic functions.

#### mPFC of rats: possible homologies to the PFC of primates

The PFC of primates consists of three major divisions: orbital, medial and lateral parts (Fuster, 2001). The orbital and medial divisions serve well-recognized roles in emotional behavior and the dorsolateral prefrontal cortex (or lateral) (DLPFC) in ‘executive’ functions of the PFC (Barbas, 1995, 2000a; Öngür and Price, 2000; Fuster, 2001).

The connections of the orbitomedial PFC (OMPFC) and DLPFC support respective roles in emotional and executive behaviors. The OMPFC receives direct and indirect input from all sensory modalities and distributes to autonomic/visceral sites of the amygdala, diencephalon and brainstem. Specifically, the OMPFC receives afferents from all sensory cortices (Morecraft et al., 1992; Barbas, 1993; Carmichael and Price, 1995b), and information reaching it mainly originates from second and third order sensory processing regions that largely code global rather than specific attributes of a stimulus. For in-



**Fig. 3.** Darkfield photomicrograph of a transverse section through the rostral forebrain showing labeling contralaterally in the forebrain produced by an injection in the PL. Note dense collection of ventrolaterally-oriented labeled fibers terminally bound for the dorsal agranular insular cortex (Ald). Note also massive labeling throughout the extent of the anterior pole of ACC as well as significant labeling in the ventrally adjacent olfactory tubercle (OT). Scale bar=600  $\mu$ m. Reprinted from Vertes (2004).

stance, several reports have shown that auditory projections to OMPFC arise from auditory association areas of the superior temporal gyrus (rostral parabelt region) (Barbas et al., 1999; Hackett et al., 1999; Romanski et al., 1999) which contains ‘broadly tuned’ cells that respond maximally to complex species-specific vocalizations (Rauschecker et al., 1995; Kosaki et al., 1997).

Price and co-workers (Öngür and Price, 2000) have subdivided the OMPFC into two networks with differing connections and functions: medial and orbital PFC networks. The medial network includes regions on the medial wall of the PFC and a few orbital areas, while the orbital network consists of most of the orbital cortex as well as the insular cortex. With respect to sensory inputs to the OMPFC, they report that the caudal part of the orbital PFC receives cortical afferents from all sensory modalities and this information, in turn, converges on the rostral orbital cortex which accordingly represents a multisensory integration zone (Carmichael et al., 1994; Carmichael and Price, 1995b). By contrast with orbital network, the medial network receives few direct sensory projections (Carmichael and Price, 1995b).

In addition to direct sensory input from sensory cortices, the OMPFC receives indirect multisensory information from the amygdala, mainly via basal groups of the amygdala (Turner et al., 1980; Porrino et al., 1981; Amaral and Price, 1984; Barbas and De Olmos, 1990; Carmichael and Price, 1995a; Ghashghaei and Barbas, 2002), and from the MD (Porrino et al., 1981; Aggleton and Mishkin, 1984; Russchen et al., 1987).

As would be expected from its role in emotional behavior, the OMPFC also receives substantial input from the limbic forebrain, particularly pronounced from the amygdala, ventral striatum (ACC), hippocampus and parahippocampal cortex. Ventral striatal afferents are routed through the ventral pallidum (and substantia nigra, pars reticulata) to the MD and then to OMPFC (Goldman-Rakic and Porrino, 1985; Ilinsky et al., 1985; Barbas et al., 1991; Ray and Price, 1993; Ferry et al., 2000; McFarland and Haber, 2002; Haber, 2003). The hippocampus (CA1 and subiculum) and parahippocampal gyrus are prominent sources of direct projections to the OMPFC (Barbas and Blatt, 1995; Carmichael and Price, 1995a; Bachevalier et al., 1997; Barbas et al., 1999; Insausti and Munoz, 2001; Lavenex et al., 2002; Kondo et al., 2003; Munoz and Insausti, 2005). Hippocampal/parahippocampal fibers distribute more heavily to the medial than to the orbital PFC, and within both regions predominantly target the caudal OMPFC (Insausti and Munoz, 2001; Barbas et al., 1999; Munoz and Insausti, 2005).

The convergence of multisensory and limbic information at the OMPFC suggests that the OMPFC is important for assessing the significance of complex stimuli, or as Barbas (2000b) recently observed the OMPFC may act an “environmental integrator” serving to “capture the emotional significance of events.”

The OMPFC receives multimodal information and also acts on it; that is, directly influences emotional behavior through descending projections to autonomic/visceral sites

of the hypothalamus and brainstem. Öngür and Price (2000) contend that orbital PFC predominantly serves as a multimodal sensory receiving network, whereas the medial PFC represents a visceromotor (or emotomotor) system.

The OMPFC has been shown to project to several visceral-related sites, as follows: the BST, medial preoptic area, central and basal nuclei of amygdala, the anterior, medial, lateral and posterior hypothalamus and the dorso-lateral PAG and lateral parabrachial nucleus of the brainstem (An et al., 1998; Öngür et al., 1998; Rempel-Clower and Barbas, 1998; Freedman et al., 2000; Chiba et al., 2001; Ghashghaei and Barbas, 2002; Barbas et al., 2003). By contrast, however, with the IL of other species (Terberry and Neafsey, 1983, 1987; Sesack et al., 1989; Hurley et al., 1991; Buchanan et al., 1994; Vertes, 2004), the medial PFC (or area 25) of primates does not appear to directly innervate regions of the lower brainstem and spinal cord that directly affect the viscera, such as the ventrolateral medulla, NTS, and intermediolateral cell column of the spinal cord (Freedman et al., 2000). Accordingly, Freedman et al. (2000) observed that the MPFC of monkeys, like non-primates, can be regarded as a visceromotor region but effects on the autonomic system “are likely to be less direct than in nonprimates.”

The specific details of OMPFC projections to autonomic/visceral sites continue to be elaborated. For example, Barbas et al. (2003) recently described two pathways for the excitatory actions of the OMPFC on amygdalar–hypothalamic circuitry: one originating in the orbital PFC and the other in the medial PFC. The orbital system consists of excitatory projections from the OPFC to intercalated nuclei of the amygdala (ICAs). ICAs inhibit the central nucleus of amygdala which, in turn, inhibits (or disinhibits) hypothalamic nuclei to produce net excitatory effects. The medial PFC exerts excitatory actions on the hypothalamus both through direct projections to the hypothalamus, and indirectly through an (excitatory) relay in the BLA.

In sum, a wealth of evidence indicates that the OMPFC of primates serves a critical role in emotional behavior; that is, an integrated multisensory/viscerosensory and emotomotor/visceromotor network.

### Lateral/DLPFC

As well recognized, the lateral/dorsolateral prefrontal cortex of primates participates in several higher order processes which collectively have been referred to as ‘executive functions’ of the DLPFC. As discussed, critical to its functioning is the ability of the DLPFC to hold and manipulate information over short delays for intended actions or WM (Baddeley, 1986; Repovs and Baddeley, 2006). In monkeys, the PFC region responsible for WM is mainly located in the caudal DLPFC, around the principal sulcus, and includes Brodmann’s areas 46, 8, 9 and 47/12 (Fuster, 2001).

Unlike the OMPFC, the DLPFC primarily receives sensory information from early stages of cortical sensory processing, involved in coding detailed aspects of the sensory environment (Barbas and Mesulam, 1985; Barbas, 1988; Petrides and Pandya, 1988; Preuss and Goldman-Rakic,

1989; Distler et al., 1993; Webster et al., 1994; Schall et al., 1995; Hackett et al., 1999; Kaas et al., 1999; Romanski et al., 1999; Barbas, 2000b). For example, the DLPFC receives input from regions of the auditory cortex that respond to pure tones (caudal parabelt area), as opposed to areas processing complex auditory stimuli that project to the OMPFC (Leinonen et al., 1980; Hikosaka et al., 1988; Hackett et al., 1999).

In a similar manner, the efferent projections of DLPFC are predominantly directed to somatomotor structures of the cortex, striatum, and brainstem (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994; Petrides and Pandya, 1999, 2002; Tehovnik et al., 2000; McFarland and Haber, 2002; Haber, 2003; Luppino et al., 2003; Takada et al., 2004; Miyachi et al., 2005; Hoshi, 2006). As noted by Takada et al. (2004), this suggests that information from the DLPFC (or area 46) “is transmitted to motor related areas of the frontal lobe and converted into motor signals to perform an organized set of voluntary movements.”

Although the precise routes whereby the DLPFC influences the motor cortex (M1) in motor control remains to be fully determined, it clearly represents a multisynaptic network with relays through various frontal (motor) areas including the premotor cortex, presupplementary and supplementary motor regions, and the cingulate motor area. Specifically, using a combination of anterograde and retrograde tracers, Takada et al. (2004) recently described a network of connections for forelimb movement: (1) from the DLPFC (area 46) to the premotor cortex (dorsal and ventral parts of the rostral division); (2) from the premotor cortex to the pre-supplementary and cingulate motor areas; and (3) from there to M1. This supports earlier findings showing that the DLPFC distributes heavily to the forelimb region of the premotor cortex (Luppino et al., 2003). Subcortically, the DLPFC projects to the dorsal (motor) but not to the ventral (limbic) striatum and indirectly, via the striatum, pallidum and substantia nigra, to parts of the thalamus (ventral anterior and ventral lateral and lateral MD) that supply the M1 (Joel and Weiner, 1994; Barbas et al., 1991; Rouiller et al., 1999; McFarland and Haber, 2002; Middleton and Strick, 2002; Erickson and Lewis, 2004; Xiao and Barbas, 2004).

Finally, unlike the OMPFC, the DLPFC receives few, if any, projections from the amygdala (Barbas and De Olmos, 1990) and hippocampus/parahippocampal cortex (Barbas et al., 1999; Insausti and Munoz, 2001; Munoz and Insausti, 2005), and distributes sparsely to visceral-related sites of the forebrain and brainstem (An et al., 1998; Öngür et al., 1998; Rempel-Clower and Barbas, 1998). The DLPFC, nonetheless, has direct access to limbic (emotional/cognitive) information through pronounced OMPFC projections to the DLPFC (Barbas and Pandya, 1989). This is presumably critical for an integrated (somatomotor/emotomotor) DLPFC response to environmental events (Barbas, 1995, 2000a).

In summary, the orbitomedial and DLPFC of primates are respectively involved in emotional and ‘executive’ functions. As developed below, we suggest that the IL of rats

may be functionally homologous to the OMPFC of primates and the PL (and ventral AC) homologous to the DLPFC of primates, and that the IL/PL complex of rats, like the OMPFC/DLPFC of primates, exerts significant control over emotional and cognitive aspects of behavior.

### **Hippocampal–mPFC–midline thalamic circuitry in the rat: possible role in mnemonic functions**

*Hippocampal–mPFC–RE–HF circuitry.* The hippocampus and mPFC serve well-recognized roles in mnemonic functions. The precise manner in which these two structures interact to process memory remains to be determined. It is clear, however, that there are strong interconnections between the hippocampus and mPFC, in part, mediated through the RE of the midline thalamus.

Several reports in various species have demonstrated pronounced projections from the hippocampal formation (HF) to the mPFC (Swanson, 1981; Irle and Markowitsch, 1982; Cavada et al., 1983; Goldman-Rakic et al., 1984; Ferino et al., 1987; Jay et al., 1989; van Groen and Wyss, 1990; Jay and Witter, 1991; Carr and Sesack, 1996). In rats, hippocampal efferents to the mPFC arise from temporal aspects of CA1 and the subiculum and terminate in a restricted region of the ventral mPFC, including the medial orbital area, IL and PL (Jay et al., 1989; Jay and Witter, 1991). There are no projections from CA2/CA3 or the dentate gyrus to the mPFC (Jay and Witter, 1991). HF fibers form asymmetric synapses with pyramidal cells of mPFC (Carr and Sesack, 1996) and exert excitatory actions on them (Ferino et al., 1987; Laroche et al., 1990, 2000; Jay et al., 1995).

Despite well-documented hippocampal projections to mPFC, there are essentially no return projections from the mPFC to the HF (Beckstead, 1979; Goldman-Rakic et al., 1984; Room et al., 1985; Reep et al., 1987; Sesack et al., 1989; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan et al., 1994). Addressing this, Laroche et al. (2000) recently stated that: “Unlike other neocortical areas such as the perirhinal or entorhinal cortices, which are reciprocally connected to the hippocampus (Witter et al., 1989), area CA1 and the subiculum do not, in return, receive direct projections from the prefrontal cortex in the rat.”

*Nucleus reuniens: relay between the mPFC and hippocampus.* The RE lies ventrally on the midline, dorsal to the third ventricle and ventral to the rhomboid nucleus of thalamus, and extends longitudinally, virtually throughout the thalamus (Swanson, 1998). RE is the largest of the midline nuclei of the thalamus. RE is the major source of thalamic afferents to the hippocampus and parahippocampal cortical structures (Herkenham 1978; Wyss et al., 1979; Riley and Moore, 1981; Room and Groenewegen, 1986; Yanagihara et al., 1987; Su and Bentivoglio, 1990; Wouterlood et al., 1990; Wouterlood, 1991; Dolleman-Van der Weel and Witter, 1996; Bokor et al., 2002). RE distributes densely to CA1 of Ammon’s horn, the ventral subiculum, and the medial and lateral entorhinal cortex (EC), and moderately to the dorsal subiculum and parasubiculum (Su and Bentivoglio, 1990; Wouter-

lood et al., 1990; Wouterlood, 1991; Bokor et al., 2002; Vertes et al., 2006). There are essentially no RE projections to the dentate gyrus or to CA3. RE fibers form asymmetric (excitatory) contacts predominantly on distal dendrites of pyramidal cells in stratum lacunosum-moleculare of CA1 (Wouterlood et al., 1990).

In a recent examination of projections from the mPFC to the thalamus, with a concentration on RE (Vertes, 2002), we showed that the ventral mPFC (IL, PL and ventral AC) virtually exclusively targets midline/medial structures of the thalamus, including the paratenial (PT), PV, interanteromedial, anteromedial, intermediodorsal, MD, RE and central medial nuclei. By contrast, the dorsal mPFC (AGm and dorsal AC) distributes over a much wider region of the thalamus, to some midline groups, but primarily to the intralaminar (central lateral, paracentral, central medial nuclei, parafascicular), ventral (ventromedial and ventrolateral) and lateral (ventral anterolateral, lateral dorsal and lateral posterior) nuclei of thalamus. All four divisions of the mPFC project heavily to RE; the ventral (IL/PL) mPFC more strongly than the dorsal mPFC.

The pattern of distribution of prelimbic fibers to the thalamus is schematically illustrated in Fig. 4. As depicted, labeling is restricted to midline nuclei of thalamus and within the midline is particularly dense within mediodorsal nucleus (mainly medial MD) and RE throughout the extent of the thalamus. At the rostral thalamus (Fig. 4A–C), labeling spreads dorsoventrally throughout the midline, whereas at the caudal thalamus (Fig. 4D–G) labeling is essentially localized to the PV and mediodorsal nuclei, dorsally, and RE, ventrally. As illustrated in Fig. 5, labeling was pronounced within the PV, PT and RE at the rostral thalamus, stronger ipsilaterally than contralaterally.

In the absence of direct mPFC projections to hippocampus and EC, the findings that IL/PL projects strongly to RE (Vertes, 2002, 2004), coupled with the demonstration that RE is the major (or virtually sole) thalamic input to the hippocampus, suggests that RE is a critical relay in the transfer of information from mPFC to the hippocampus. This system of connections (mPFC–RE–hippocampus) would appear to be the primary route from the prefrontal cortex to the hippocampus, and accordingly would complete an important loop between the hippocampus and mPFC; that is, a loop from HF to IL/PL and then to RE and back to the hippocampus: CA1/subiculum→IL/PL→RE→CA1/subiculum.

*Physiological interactions of structures of the HF→IL/PL→RE→HF loop.* With respect to physiological interactions of nodes of the hippocampal-prefrontal-thalamic loop, the physiological effects of HF on the mPFC have been well characterized, whereas other parts of the loop have been less well described (RE→HF) or remain to be examined (mPFC→RE).

Although hippocampal fibers innervating the mPFC terminate on both pyramidal cells and interneurons of IL/PL (Carr and Sesack, 1996; Gabbott et al., 2002), they predominantly form excitatory contacts with dendritic spines of pyramidal cells (Jay et al., 1992). Consistent with this

profile, low amplitude stimulation of HF activates pyramidal cells of the mPFC at monosynaptic latencies (Ferino et al., 1987; Laroche et al., 1990). Laroche et al. (1990) demonstrated that approximately 40% of PL cells were excited by hippocampal stimulation at short (monosynaptic) latencies. In like manner, Degenetis et al. (2003) reported that single pulse stimulation of the hippocampus induced early (mean latency, 14.6 ms) EPSPs in 91% (106/116) of intracellularly recorded pyramidal cells of PL of rats. The EPSPs were followed by prolonged IPSPs presumably involving recurrent inhibitory actions on pyramidal cells.

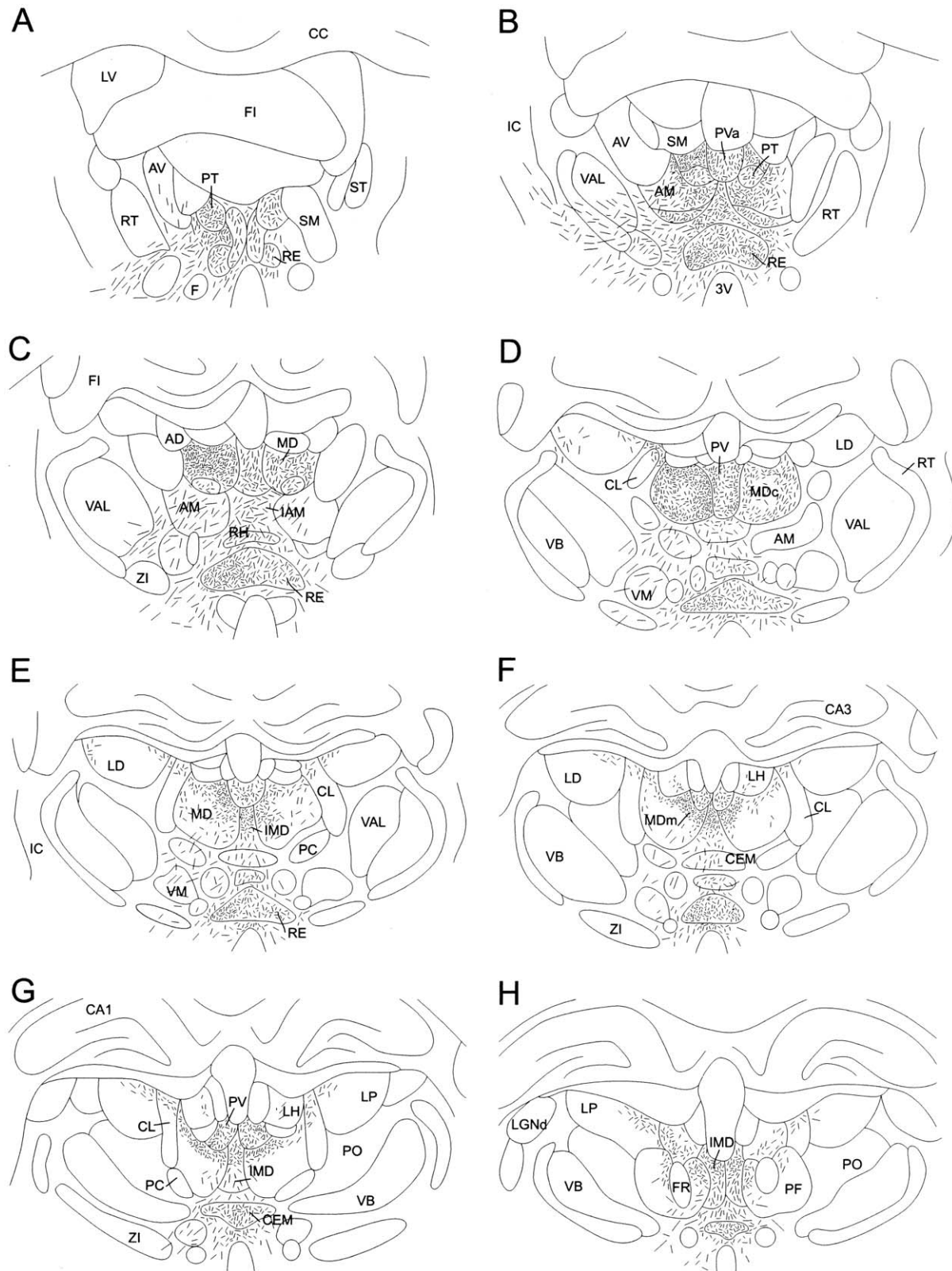
Hippocampal stimulation also produces persistent changes at the mPFC: paired pulse facilitation (PPF) and long term potentiation (LTP). Paired stimulation of HF gives rise to short lasting facilitatory actions (PPF) on single units, field potentials (Laroche et al., 1990; Mulder et al., 1997) and monosynaptically-elicited EPSPs (Degenetis et al., 2003) at IL/PL, whereas tetanic stimulation produces a rapidly-induced and stable LTP at PL in both anesthetized (Laroche et al., 1990) and behaving rats (Jay et al., 1996). Based on their findings of persistent changes at PL with HF stimulation, Degenetis et al. (2003) concluded: “the hippocampal-prefrontal network can participate in the formation and consolidation of memories.” Finally, long term depression (LTD) (Takita et al., 1999) and depotentiation (i.e. reversal of LTP) (Burette et al., 1997) have been demonstrated at mPFC with low frequency HF stimulation. In summary, the hippocampus exerts pronounced modulatory actions at the mPFC; that is, monosynaptic excitation of IL/PL cells as well as enduring changes: PPF, LTP, LTD and depotentiation.

Although RE has long been recognized a major input to the hippocampus (Herkenham, 1978), few studies have examined the physiological effects of RE on the hippocampus. Two recent reports have shown, however, that RE exerts significant excitatory actions at CA1 of the hippocampus (Dollemann-Van der Weel et al., 1997; Bertram and Zhang, 1999).

Dollemann-Van der Weel et al. (1997) reported that RE stimulation produced large negative-going field potentials at stratum lacunosum-moleculare of CA1 of the hippocampus indicative of a prominent depolarizing actions on distal apical dendrites of CA1 pyramidal cells, as well as a marked facilitation (PPF) of evoked responses at CA1. They proposed that RE may “exert a persistent influence on the state of pyramidal cell excitability, depolarizing cells close to threshold for activation by other excitatory inputs.”

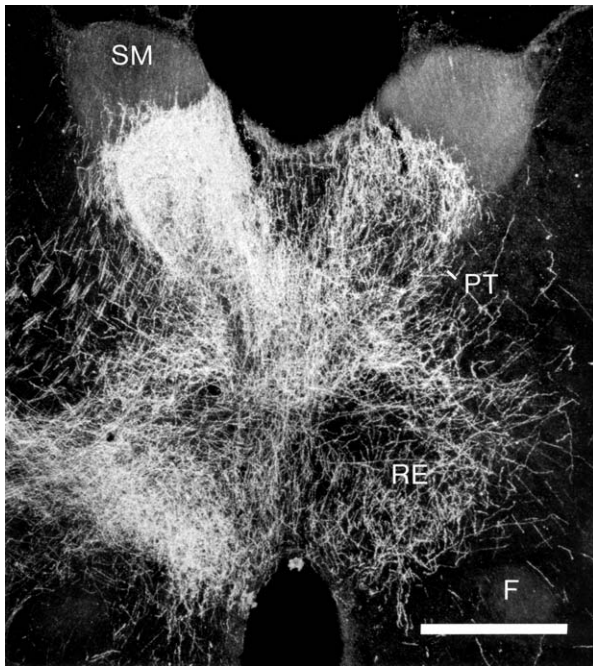
Consistent with this, Bertram and Zhang (1999) compared the effects of RE and CA3 stimulation on population responses (field EPSPs and spikes) at CA1, and reported that RE actions on CA1 were equivalent to, and in some cases considerably greater than, those of CA3 on CA1. They concluded that the RE projection to the hippocampus “allows for the direct and powerful excitation of the CA1 region. This thalamohippocampal connection bypasses the trisynaptic/commissural pathway that has been thought to be the exclusive excitatory drive to CA1.”

As discussed, IL and PL project heavily to the RE of thalamus (Vertes, 2002, 2004). To our knowledge, however, the physiological actions of the mPFC on RE have



**Fig. 4.** Schematic representation of selected sections through the diencephalon depicting labeling present in the thalamus produced by a PHA-L injection in the PL. Sections aligned rostral to caudal (A–H). Abbreviations: AD, anterodorsal nucleus; AM, anteromedial nucleus; AV, anteroventral nucleus; CA1, CA3, CA1, CA3 fields of Ammon's horn; CC, corpus callosum; CEM, central medial nucleus; CL, central lateral nucleus; F, fornix; FI, fimbria of hippocampal formation; FR, fasciculus retroflexus; IAM, interanteromedial nucleus; IC, internal capsule; IMD, intermediodorsal nucleus; LGNd, lateral geniculate nucleus, dorsal division; LH, lateral habenula; LD, lateral dorsal nucleus; LP, lateral posterior nucleus; LV, lateral ventricle; MD,c,m, mediodorsal nucleus, central, medial divisions; PC, paracentral nucleus; PF, parafascicular nucleus; PO, posterior nucleus; PV,a, paraventricular nucleus; anterior division; RH, rhomboid nucleus; RT, reticular nucleus; SM, stria medullaris; ST, stria terminalis; VAL, ventral anterior-lateral complex; VB, ventrobasal complex; VM, ventromedial nucleus; ZI, zona incerta; 3V, third ventricle. Reprinted from Vertes (2002).





**Fig. 5.** Darkfield photomicrograph of a transverse section through the rostral diencephalon showing patterns of labeling at the rostral thalamus produced by a PHA-L injection in the PL. Note pronounced labeling in the PT dorsally and RE ventrally, stronger ipsilaterally (left side) than contralaterally. Abbreviations: F, fornix; SM, stria medullaris. Scale bar=500  $\mu$ m. Reprinted from Vertes (2002).

not been described. We have recently found, however, that IL/PL fibers form asymmetric (excitatory) synapses (mainly on dendritic spines) with RE neurons projecting to the hippocampus (Vertes et al., submitted for publication). These findings, together with the demonstration that RE exerts excitatory effects on the hippocampus (Dolleman-Van der Weel et al., 1997; Bertram and Zhang, 1999) and EC (Zhang and Bertram, 2002) suggest that IL/PL, indirectly through RE, may activate the hippocampus/EC. In effect, this system of connections (IL/PL $\rightarrow$ RE $\rightarrow$ HF) may represent an important return route for the actions of the hippocampus on the mPFC (Laroche et al., 2000).

#### **RE: prominent source of limbic afferent information to the hippocampus and IL/PL**

Although the hippocampus receives a diverse array of information, there are few direct routes to the hippocampus. Excluding monoaminergic afferents, direct sources of input are primarily restricted to the EC, medial septum, basal nucleus of amygdala, supramammillary nucleus and RE (Witter and Amaral, 2004).

In like manner, the mPFC receives relatively limited input (from all sources) and surprisingly little from 'limbic' regions of the brain. For instance, using retrograde techniques, Conde et al. (1995) described few projections from limbic/limbic-related structures of the forebrain and brainstem to mPFC in rats (see their Table 2, p. 572). Specifically, relatively large retrograde tracer injections encompassing PL, IL, and the dorsal peduncular area, gave rise

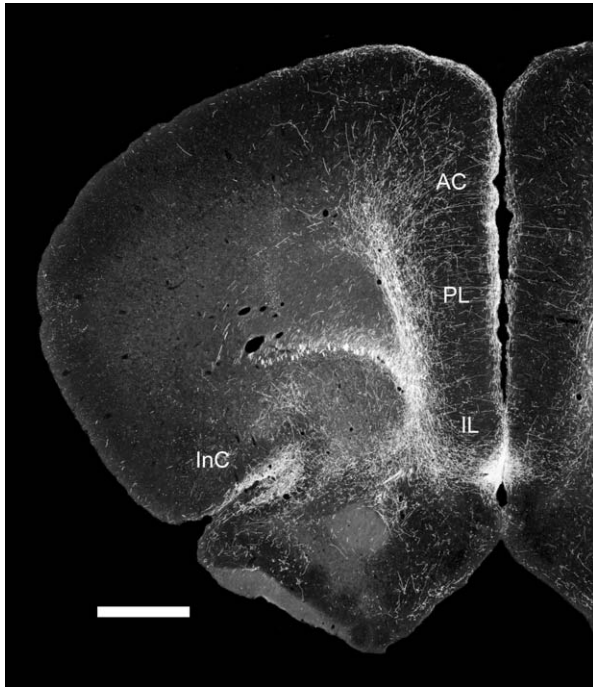
to few labeled cells in the septum, medial basal forebrain, hypothalamus, and with some exceptions, the brainstem. This contrasted with significant afferents to the mPFC from other regions of the cortex and from the thalamus. Although labeling was heavy in the BLA, it was essentially limited to this cell group of the amygdala. Consistent with this, we also observed only minor 'limbic' subcortical projections to the mPFC (Vertes et al., 2002).

A significant indirect source of limbic information to the mPFC is the insular cortex (Yasui et al., 1991; Shi and Cassell, 1998; Gabbott et al., 2003). The insular cortex receives visceral sensory information, projects to the ventral PFC (Conde et al., 1995; Shi and Cassell, 1998; Gabbott et al., 2003; Hoover and Vertes, 2005), and is thought to relay visceral sensory information to visceromotor regions of the mPFC (Yasui et al., 1991).

With few direct or indirect limbic afferents to the mPFC, 'limbic' information may primarily reach the mPFC (and the HF) through midline nuclei of the thalamus, or RE (McKenna and Vertes, 2004; Viana Di Prisco and Vertes, 2006). In this regard, we recently examined afferent projections to RE in the rat and showed that RE receives a diverse and widely distributed set of afferents, mainly from limbic/limbic-associated structures (McKenna and Vertes, 2004).

RE receives pronounced projections from several cortical and subcortical sites (McKenna and Vertes, 2004). They include: (1) the orbitomedial, insular, ectorhinal, perirhinal and retrosplenial cortices; (2) CA1/subiculum of hippocampus; (3) the claustrum, lateral septum, substantia innominata and lateral preoptic nucleus of the basal forebrain; (4) the medial, basomedial and cortical nuclei of amygdala; (5) the PV and lateral geniculate nuclei of thalamus; (6) the zona incerta; (7) the anterior, ventromedial, lateral, posterior, supramammillary and dorsal premammillary nuclei of the hypothalamus; and (8) the VTA, PAG, medial and posterior pretectal nuclei, nucleus of posterior commissure (NPC), superior colliculus, precommissural nucleus, parabrachial nucleus, laterodorsal and pedunculo-pontine tegmental nuclei, nucleus incertus, and the dorsal and median raphe nuclei of the brainstem.

Although RE projections to HF have been well documented, those to other sites have been much less studied. Using PHA-L, we recently examined the efferent projections of the RE and rhomboid nuclei of the midline thalamus (Vertes et al., 2006). Although the input to RE is diverse and widespread (McKenna and Vertes, 2004), RE was found to project to fairly restricted sites of the brain, which in addition to HF, mainly includes the orbitomedial prefrontal and parahippocampal cortices. This is consistent with earlier descriptions (Herkenham, 1978; Ohtake and Yamada, 1989; Wouterlood et al., 1990; Wouterlood, 1991; Conde et al., 1995; Reep et al., 1996; Risold et al., 1997; Reep and Corwin, 1999; Bokor et al., 2002; Van der Werf et al., 2002). The photomicrograph of Fig. 6 shows a dense concentration of labeled fibers in IL and PL following a PHA-L injection in RE. In essence, then, RE appears to be a critical site for the convergence of limbic/limbic-related information from widespread sources and its subsequent trans-



**Fig. 6.** Darkfield photomicrograph through the rostral forebrain depicting patterns of labeling in the mPFC produced by a PHA-L injection in the RE of the thalamus. Note particularly dense labeling in inner layers of the infralimbic and prelimbic cortices. Abbreviation: InC, insular cortex.

fer to its main targets: the hippocampus/parahippocampal cortex and the orbitomedial prefrontal cortex.

#### **IL: visceral motor cortex**

As discussed, the IL of the mPFC exerts a pronounced influence on visceral/autonomic activity through direct and indirect projections to autonomic sites of the brainstem and spinal cord. IL is viewed as 'visceral motor cortex' (Hurley-Gius and Neafsey, 1986; Neafsey, 1990).

Although findings conflict, the actions of IL on target structures seem to be mainly excitatory. For instance, Powell et al. (1994) demonstrated that IL stimulation in awake rabbits produced increases in heart rate and blood pressure and a reduction in gastric motility, all sympathetic-mediated responses. In like manner, IL lesions were found to block increases in heart rate, respiration, ultrasonic vocalizations and freezing behavior to conditional emotional stimuli in behaving rats (Fryszak and Neafsey, 1991, 1994).

By contrast, however, several studies report that IL (or ventral mPFC) stimulation produces the opposite effect on the viscera; that is, depressor rather than pressor responses (Hardy and Holmes, 1988; Hardy and Mack, 1990; Verberne, 1996; Owens et al., 1999; Owens and Verberne, 2001). Although the reason(s) for these differences remains unclear, one possibility is that they may involve the use of anesthetized compared to non-anesthetized animals. Specifically, most (but not all) studies demonstrating pressor effects with IL stimulation have been

done with non-anesthetized animals (Burns and Wyss, 1985; Powell et al., 1994; Tavares et al., 2004), whereas reports showing depressor effects involve anesthetized animals (Hardy and Holmes, 1988; Hardy and Mack, 1990; Verberne, 1996; Owens et al., 1999; Owens and Verberne, 2001). The same applies to the effects of mPFC injections of excitatory amino acids on cardiovascular responses in rats. Verberne (1996) reported that microinjections of the L-glutamate into the mPFC of anesthetized rats produced depressor responses, whereas Resstel and Correa (2005) showed that L-glutamate injections into PL/IL of unanesthetized rats generated long lasting, dose related, pressor responses and tachycardia. Finally, Tavares et al. (2004) recently compared the effects of mPFC stimulation in anesthetized and non-anesthetized rats, showing the former (anesthetized) produced depressor responses and the latter (awake) pressor responses.

As expected from its actions on viscera, the ventral mPFC reportedly serves an important regulatory role in such behaviors as conditioned fear (and fear extinction), anxiety and stress. For example, several studies have described marked *c-fos* expression in the ventral mPFC during exposure to various stressors or to anxiety-inducing (anxiogenic) situations (Cullinan et al., 1995; Figueiredo et al., 2002, 2003; Ostrander et al., 2003).

Although results vary, it seems (somewhat paradoxically) that, on balance, lesions of the ventral mPFC (IL/PL) produce *increased* levels of fear, anxiety and stress, rather than the expected opposite. Specifically, ventral mPFC lesions reportedly produce (1) increases in 'fear' in both natural and experimental settings (Holson, 1986a,b; Morgan et al., 1993); (2) enhanced levels of general anxiety to novel or stressful conditions (Silva et al., 1986; Jaskiw and Weinberger, 1990); (3) increased release adrenocorticotrophic hormone (ACTH) or corticosterone to psychological or physical stressors (Diorio et al., 1993; Crane et al., 2003; Figueiredo et al., 2003); and (4) marked deficits in fear extinction, presumably reflecting the inability of animals to suppress fear to a stimulus that no longer signals danger (Morgan et al., 1993; Morrow et al., 1999; Quirk et al., 2000; Milad and Quirk, 2002).

If, as described, IL exerts excitatory actions on autonomic/visceral structures, IL lesions might be expected to reduce sympathetic tone and possibly suppress ACTH/corticosterone release, thereby decreasing fear/anxiety/stress and presumably improving performance in tasks benefitting by those reductions. Perhaps, a likely explanation for the results that ventral mPFC lesions can, in some circumstances, enhance visceral activity and produce increased levels of fear/anxiety is that the ventral mPFC contains regions that both excite and inhibit the viscera (and/or the hypothalamic–pituitary–adrenal axis), and depending on the site and extent of lesions (or stimulation), one of the two effects would predominate.

With regard to this possibility, we suggest that dorsal and ventral regions of the ventral mPFC may exert opposite effects on visceral activity; that is, IL may 'activate' the viscera through direct excitatory actions on autonomic/

visceral structures, whereas PL (and ventral AC) may 'suppress' visceral activity mainly through inhibitory actions on IL. Supporting this, [Fryszak and Neafsey \(1994\)](#) described increases in heart rate and blood pressure with dorsal mPFC lesions, and decreases with ventral mPFC lesions. Similarly, [Powell et al. \(1994\)](#) showed that stimulation dorsally in the mPFC (AC/PL) produced depressor responses and bradycardia, while IL stimulation yielded pressor responses and tachycardia.

In addition, a close examination of previously discussed studies reporting that mPFC lesions produced increases in fear/anxiety and stress shows that most of the lesions were located dorsally in the mPFC (PL/AC) or spanned PL/AC and IL; few were restricted to IL. One of the few reports ([Jinks and McGregor, 1997](#)) to systematically compare the effects of PL and IL stimulation on emotional behaviors described significant differences between the two sites. According to the authors ([Jinks and McGregor, 1997](#)), the aim of their report was to "discriminate the functional roles of the infralimbic and prelimbic subregions of the MPC. To our knowledge, a functional dissociation between these two regions has not been hitherto attempted since previous studies reporting effects of 'ventral MPC' lesions have typically destroyed both regions." They showed that rats with PL lesions spent significantly less time in the center of an open field or on exposed arms of an elevated plus maze, indicating heightened levels of anxiety. By contrast, rats with IL lesions (but importantly not those with PL lesions) showed reduced levels of fear/anxiety on a passive avoidance task; that is, compared with controls, IL-lesioned rats more readily stepped down to a previously electrified grid. Although at odds with the authors' interpretation of their findings ([Jinks and McGregor, 1997](#)), we suggest that IL lesions suppressed fear by dampening of excitatory drive to autonomic/visceral structures, whereas PL lesions enhanced fear/anxiety mainly by reducing inhibitory influences on IL.

The foregoing mechanism is one among several ways in which IL and PL could interact to modulate visceral activity and 'visceral-related behaviors.' Alternatively, [Quirk and colleagues \(Milad et al., 2006; Vidal-Gonzalez et al., 2006\)](#) recently described opposing IL and PL actions in fear extinction mediated through the amygdala. They had previously demonstrated ([Milad and Quirk, 2002; Milad et al., 2006](#)) that the ventral mPFC serves a twofold role in fear extinction: it retains information that fearful events are no longer fearful (retention of fear extinction), and acts on visceral structures to reduce fear (expression of fear extinction). They recently showed that conditioned stimuli (tones) paired with IL stimulation decreased fear (strengthened fear extinction), while those paired with PL stimulation increased fear (impaired fear extinction) ([Vidal-Gonzalez et al., 2006](#)). They indicated that the "opposite effects of PL and IL microstimulation suggest that these mPFC subterritories target different brain regions important for fear expression" ([Vidal-Gonzalez et al., 2006](#)). Regarding anatomical substrates for these effects, PL projects to the BLA, and BLA, in turn, exerts excitatory effects on the CEA to enhance fear, whereas IL projects to GABAergic inter-

calated groups of amygdala which inhibit CEA to reduce fear ([Vertes, 2004; Berretta et al., 2005; Likhtik et al., 2005](#)).

In summary, a number of reports have demonstrated that ventral regions of the mPFC affect several measures of emotional responding in rats. We suggest that the dorsal mPFC (primarily PL) exerts a modulatory influence on IL in visceromotor control. In effect, PL may serve to dampen IL activity in situations requiring precise movements/actions, despite elements of danger, whereas PL might augment IL activity in threatening situations demanding immediate and global responses: fight or flight.

### **PL: limbic–cognitive functions**

As indicated, the mPFC participates in several higher order processes including selective attention, WM, decision making, and goal-directed behaviors ([Goldman-Rakic, 1987, 1994; Fuster, 1989, 2001; Kolb, 1984, 1990; Petrides, 1995, 1998; Barbas, 2000a,b; Öngür and Price, 2000](#)). By contrast with visceromotor functions of IL, recent evidence indicates that the PL of rats is directly involved in limbic/cognitive functions, homologous to the DLPFC of primates ([Laroche et al., 2000](#)). A function commonly associated with the prefrontal cortex, and one extensively examined, is WM; that is, the temporary storage and utilization of information over short intervals ([Baddeley, 1986; Goldman-Rakic, 1987, 1995; Fuster, 2001; Repovs and Baddeley, 2006](#)).

As well documented, lesions of the dorsolateral prefrontal cortex of monkeys disrupt performance on delayed response tasks ([Goldman and Rosvold, 1970; Passingham, 1975; Mishkin and Manning, 1978; Funahashi et al., 1993; Petrides, 2000; Fuster, 2001](#)), and DLPFC cells maintain elevated rates of discharge during the delay period of delayed response tasks ([Niki, 1974; Kojima and Goldman-Rakic, 1982; Quintana et al., 1988; Funahashi et al., 1989; Miller et al., 1996; Chafee and Goldman-Rakic, 1998; Romo et al., 1999; Sawaguchi and Yamane, 1999](#)).

The mPFC of rats has also been shown to serve a critical role in tasks requiring the maintenance of information over time, including delayed alternation ([Larsen and Divac, 1978; Silva et al., 1986; van Haaren et al., 1988; Brito and Brito, 1990; Bubser and Schmidt, 1990; Kesner et al., 1996; Delatour and Gisquet-Verrier, 1996, 1999](#)) and delayed matching and nonmatching to sample tasks ([Shaw and Aggleton 1993; Kolb et al., 1994; Granon et al., 1994; Broersen et al., 1995; Seamans et al., 1995; Harrison and Mair, 1996; Young et al., 1996; Porter and Mair, 1997](#)). The reversible or irreversible inactivation of the ventral mPFC, generally restricted to PL and ventral AC, produces marked deficits in delayed response tasks involving short or long delays ([Brito and Brito, 1990; Seamans et al., 1995; Delatour and Gisquet-Verrier, 1996, 1999, 2000; Floresco et al., 1997; Fritts et al., 1998; Ragozzino et al., 1998, 2002; Izaki et al., 2001; Lee and Kesner, 2003; Dalley et al., 2004; Di Pietro et al., 2004](#)). Further, cells of the mPFC in rats, like those of primates, show sustained activity during the delay period of delay

tasks (Orlov et al., 1988; Batuev et al., 1990; Baeg et al., 2003).

The fairly unique ability of the PFC to hold and manipulate information over short delays undoubtedly contributes to its role in higher order processing such as decision making or goal directed behavior (Baddeley, 1986, 1998; Fuster, 2001; Wang et al., 2006). These functions generally depend upon the ability to retain information in temporary buffers, where it can be assessed (or repeatedly reassessed) with respect to immediate sensory stimuli, past events and possible future actions, for goal directed behaviors (Wang, 2001). Fuster (2001) characterized WM as “related to the need to retain information for an impending action that is in some way dependent on that information.” As such, it is clear that the ‘executive functions’ of the mPFC depend on the integration of information from various sources representing sensory attributes (sensorimotor association areas), value (limbic structures), and early and recent history (hippocampal/parahippocampal cortices).

In this regard, a number of reports in rats have described the contribution of limbic and hippocampal inputs to the ventral mPFC (or PL/AC) in mnemonic and executive functions of the mPFC. Phillips and co-workers (Seamans et al., 1995) initially demonstrated that the bilateral inactivation of PL in rats produced marked deficits in a delayed, but not in a non-delayed, version of a spatial radial arm maze (RAM) task, and subsequently that virtually identical effects (degree and pattern) were observed on this task by disconnecting the hippocampus from PL (Floresco et al., 1997). They viewed the dysfunction as one of ‘prospective coding,’ or the inability of rats to use information acquired before the delay to plan, program or guide behavior. Subsequent reports have similarly demonstrated that blocking connections from the hippocampus to the ventral PFC (PL/ventral AC) disrupts performance on delayed-response tasks (Floresco et al., 1999; Aujla and Beninger, 2001). Floresco et al. (1997) characterized the role of HF inputs to the PL in PL-mediated behaviors as follows: “the neural circuit linking the hippocampus and PFC provides an essential pathway by which spatial information can be integrated into the cognitive and motor planning processes mediated by the PFC.”

While hippocampal–prefrontal connections appear critical for the integration of the past (HF) with the present (and possibly the future), the hippocampal input to mPFC is seemingly not responsible for the affective component of experience which is obviously essential for goal directed behaviors. Instead, this element appears to arise from subcortical limbic structures, mainly, VTA, BLA of amygdala, and the midline thalamus.

Using the same disconnection procedure wherein different structures are temporarily inactivated on opposite sides of the brain, Seamans et al. (1998) showed that the simultaneous blockade of hippocampal inputs to PL and dopamine ( $D_1$ ) receptors at PL disrupted performance on delayed, but not on non-delayed, versions of the RAM task. Regarding the possible role of dopamine in hippocampal–prefrontal interactions, Seamans et al. (1998) suggested that: “ $D_1$  receptors in the PFC may modulate

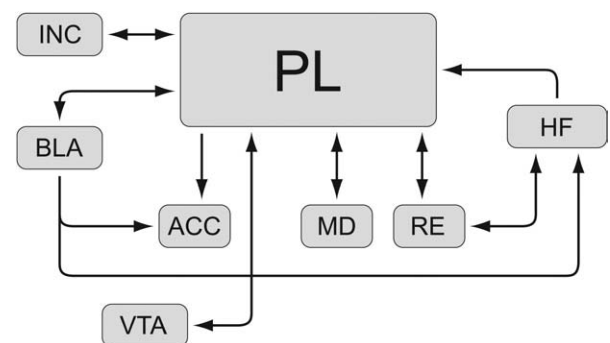
the transfer of spatial information from the hippocampus to the PFC at a time when a prospective series of response must be organized and executed.”

In a continuing analysis of the circuitry involved in mPFC functions, Floresco et al. (1999) demonstrated that inactivation of the MD nucleus of the thalamus also disrupts performance on delayed response tasks. Incorporating this finding with previous results, they described a putative network for WM in rats. The network consists of afferents to PL from VTA, MD and the hippocampus, mediating signal amplification (VTA), stimulus significance (MD) and spatial/contextual information (HF), respectively, and outputs from PL to the ventral striatum and ventral pallidum. In effect, a putative PL network involved in the short term manipulation of information for directed actions (see their Fig. 6, p. 11069).

Although this scheme incorporates some of the elements of the previously described ‘PL circuit’ (see earlier description and Fig. 1), other important links to PL were not included, namely, the BLA, the insular cortex, the claustrum, and significantly, the RE of thalamus. Fig. 7 represents a revised ‘PL circuit’ putatively responsible for higher order functions of PL/ventral AC in rats. The precise role of each of these structures (and their interactions) in WM and goal-directed behaviors remains to be fully determined.

The potential involvement, however, of most of the foregoing structures in memory/WM gains support from the demonstration that their manipulation (like PL/AC itself) affects delayed response tasks, or WM. For instance, alterations of ACC (Floresco et al., 1999), ventral pallidum (Kalivas et al., 2001), BLA (Barros et al., 2002; Pare, 2003; Roozendaal et al., 2004), MD (Harrison and Mair, 1996; Floresco et al., 1999; Romanides et al., 1999; Kalivas et al., 2001), RE (Cain and Boon, 2004) or VTA (Seamans et al., 1998; Seamans and Yang, 2004) have been shown to disrupt tasks requiring WM.

If, as suggested, affective/motivational and spatial/contextual information converge at PL for goal-directed ac-



**Fig. 7.** The extended ‘PL circuit’ putatively responsible for limbic–cognitive functions of the mPFC of rats. The output of PL is fairly limited and restricted to structures identified as serving a role in cognition and memory. These include the insular cortex (INC), ACC, BLA, the midline thalamus (mediodorsal nucleus and RE) and the hippocampus. The projections of PL to the hippocampus are indirect mainly through RE. With the exception of ACC, PL receives projections from each of its major targets. All interconnections among structures of the PL circuit are not shown.

tions, this might be reflected in the activity of prelimbic neurons. In this regard, Poucet and colleagues (Poucet et al., 2004; Hok et al., 2005) recently described an interesting type of cell in PL that putatively combines 'motivational' and spatial properties. Specifically, rats were trained to run to a specific location on a cylinder (trigger zone), and if done successfully, food pellets were delivered from a feeder positioned elsewhere in the cylinder (landing zone). The food pellets, dispensed from the feeder, fell randomly throughout the cylinder, and were hence consumed in different parts of the cylinder. The latter was done to dissociate goal value (i.e. trigger zone) from reward value (i.e. eating of the pellet). Hok et al. (2005) reported that 25% of PL/IL cells fired selectively in the two locations signaling impending reward; namely, the trigger zone and the landing zone. These cells appeared to encode value plus place, and as such may be crucial for goal-directed actions of PL. According to Hok et al. (2005), "PL/IL neurons have properties expected of cells encoding spatial goals, a key component necessary for computing optimal paths in the environment."

## CONCLUSIONS

In summary, the IL projects to autonomic/visceral-related sites, supporting its role in visceromotor activity, whereas PL/ventral AC primarily projects to limbic-related sites that reportedly affect cognition (Vertes, 2004; Gabbott et al., 2005). It is obviously the case, however, that complex goal-directed behaviors entail an integration of visceral and cognitive elements. It seems likely that this integration may largely occur at the level of mPFC involving interactions between IL and PL. In the rat, then, the IL/PL–ventral AC complex may exert significant control over emotional–cognitive aspects of behavior. To conclude, the mPFC of rats appears functionally homologous to a fairly widespread region of the prefrontal/frontal cortex of primates subserving motor, emotional and cognitive elements of behavior; that is, the dorsal mPFC appears homologous to the supplementary/premotor area, the PL/ventral AC to the lateral/DLPFC, and IL to the orbitomedial cortex of primates.

*Acknowledgments*—Grant sponsor; NIMH; grant numbers: MH63519 and MH01476.

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(Accepted 16 June 2006)  
(Available online 2 August 2006)