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Robert F. Schmidt and William D. Willis

Hippocampus and Entorhinal Complex, Functional Imaging

Siri Leknes[3, 4] and Irene Tracey[3, 4]

(3) Pain Imaging Neuroscience (PaIN) Group, Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK

(4) Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, UK

Siri Leknes
Email: siri@fmrib.ox.ac.uk

Without Abstract

Synonyms

Entorhinal Cortex and Hippocampus, Functional Imaging; Parahippocampal Region, Neuroimaging

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Definition

The hippocampus is comprised of the dentate gyrus and the CA1, CA2 and CA3 pyramidal cell fields. The hippocampal formation consists of the hippocampus and the subiculum. The adjacent entorhinal, perirhinal, and parahippocampal cortices comprise the parahippocampal region (Fig. 1). These limbic subregions differ in their cellular organization and connectivity, but are commonly implicated in memory and emotion processing.

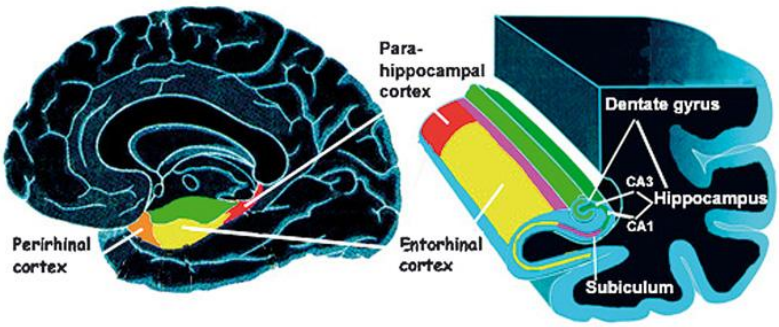

Figure 1 (left) Medial view of the human brain outlining the perirhinal cortex (orange); parahippocampal cortex (red); and entorhinal cortex (yellow). (right) Section of the temporal lobe showing the components of the hippocampal/entorhinal complex in some detail: the dentate gyrus (pale green); the CA1 and CA3 hippocampal fields (green) that make up the hippocampus proper; the subiculum (pink); the perirhinal cortex (orange); parahippocampal cortex (red); and entorhinal cortex (yellow).

The hippocampus lies at the end of a cortical processing hierarchy, and the entorhinal cortex is the major source of its cortical projections. Much of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive widespread projections from sensory and association areas in the frontal, temporal and parietal lobes (Squire et al. 2004).

Functional imaging is a general term used to describe methodologies that allow function to be located either spatially or temporally within the brain (and other organs). The methods are generally non-invasive and used for human studies; the term neuroimaging is often used when applied specifically to brain studies. Methods include functional magnetic resonance imaging (FMRI), positron emission tomography (PET), magneto-encephalography (MEG) and electro-encephalography (EEG). Unless otherwise stated, the studies discussed in this article are FMRI or PET studies of the brain.

Characteristics

Melzack and Casey (1968) proposed that the hippocampus and associated cortices participate in mediating the aversive drives and affective characteristics of pain perception. A wide range of animal studies support the notion that pain processing is a primary function of the hippocampal complex. Importantly, Dutar and colleagues (1985) demonstrated that septo-hippocampal neurons in rats respond directly to noxious peripheral stimulation. Similarly, functional imaging studies of pain perception have repeatedly reported a direct implication of areas within the hippocampus in the processing of nociceptive stimuli. Since nociceptive information is typically novel and of high priority, a direct role for the hippocampus in nociceptive processing is consistent with comparator theories of hippocampal function (e.g. McNaughton and Gray 2000). Comparator theory maintains that the hippocampus is involved in novelty detection and that its function is to compare actual and expected stimuli (i.e. stimuli registered in memory).

In an early PET study, Derbyshire and colleagues (1997) found hippocampal activation in response to mildly and moderately painful heat stimuli, when contrasted with warm, non-painful stimulation. Using very specific nociceptive stimuli (laser stimulation of A-δ fibers only) to subjects' left and right hands, Bingel and colleagues (2002) found bilateral activation of the amygdala and hippocampal complex. The receptive fields of hippocampal neurons are predominantly large and bilateral (Dutar et al. 1985). As other pain-related activation was lateralized, the authors suggested that the hippocampal activity reflected direct nociceptive projections to the hippocampus, perhaps revealing novelty detection (Bingel et al. 2002). Further, Ploghaus and colleagues (2001) found that pain modulation by drying stimulus temperature caused activation of a region of the hippocampus proper, consistent with a role of the hippocampus in pain intensity encoding (Fig. 2a).

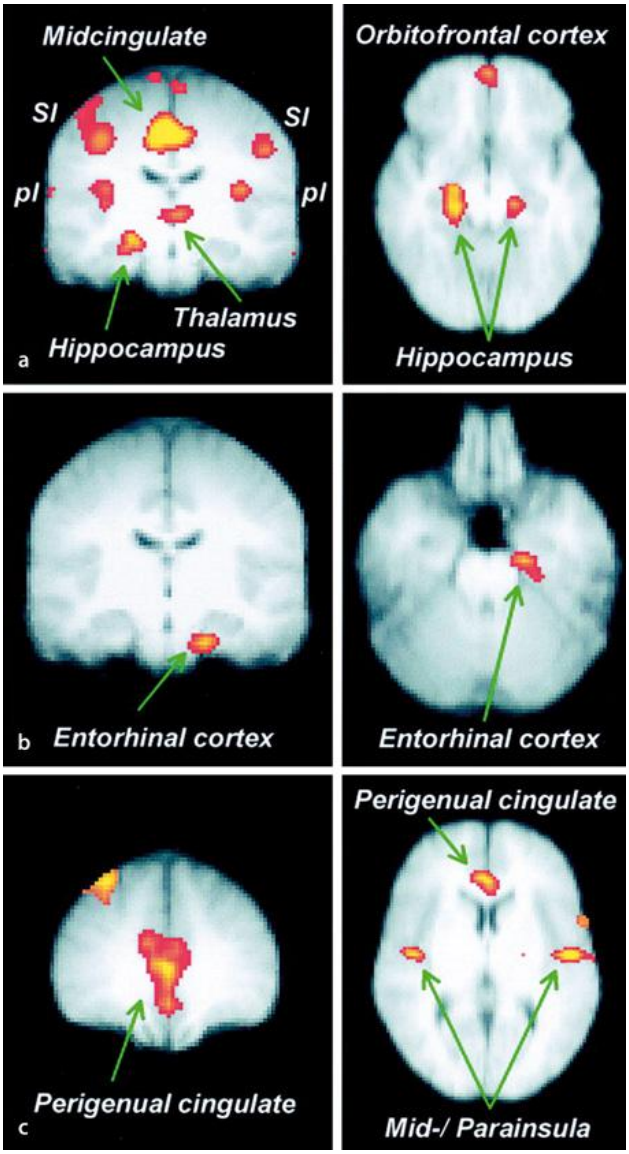

Figure 2 (a) Temperature-related activation increases in perceived pain: Bilateral S1, dorsal margin of posterior insula, thalamus, midcingulate and right hippocampus. (b) Anxiety-related activation increases in perceived pain associated with significant activation in left entorhinal cortex. (c) Activity in the perigenual cingulated and the mid- / para insula was significantly correlated with entorhinal FMRI signal during pain modulation by anxiety. Reproduced with permission from Ploghaus et al. 2001.

Nevertheless, the large majority of human functional imaging studies of pain do not report activation of regions within the hippocampus / entorhinal complex. There are several possible explanations for this discrepancy. The first concerns the signal to noise ratio. As the complex is a relatively small structure, the spatial resolution of conventional whole-brain imaging paradigms means that partial volume effects might occur and decrease signal to noise in this region. One caveat specific to functional imaging of this region is the implication of the hippocampus in the resting state network (Greicius and Menon 2004). PET and FMRI studies have suggested that the resting brain has a default mode of internal processing in which the hippocampus is a central component. In the neuroimaging of pain perception, nociceptive processing is commonly compared with baseline (rest) conditions. The hippocampus' involvement in resting state / baseline processing may mask out the activation of this region in such task-baseline comparisons if increased baseline activity reduces subsequent stimulation evoked responses and therefore could yield a false negative result. Another factor that may mask out activation of regions within the medial temporal lobe is the registration of individual brains onto a standard template for group comparison. Traditional techniques that optimize whole-brain alignment (e.g. aligning to the atlas of Talairach & Tournoux) do not

adequately account for variations in location and shape of medial temporal lobe structures (see Squire et al. 2004 for review).

Regions within the hippocampus / parahippocampal complex have been more consistently activated in studies where pain perception has been modulated by expectation and / or anxiety. It is clear that memory (which influences expectation) modulates pain perception. While certain expectation is associated with fear, uncertain expectation is associated with anxiety. For instance, a rat experiences fear when it must enter a space where a cat is present. Anxiety, on the other hand, corresponds to the state a rat is in when it must enter a space where a cat may or may not be present. While fear facilitates rapid reactions (fight or flight) and causes distraction and analgesia from the pain, anxiety is characterized by risk assessment behavior or behavioral inhibition (the rat hesitates to enter the space where a cat might be). This behavior is associated with increased somatic and environmental attention, which can lead to anxiety-driven hyperalgesia (McNaughton and Gray 2000).

Using FMRI to investigate the effects of expectation on pain perception, Ploghaus and colleagues (2000) found that areas in the hippocampal complex were activated during mismatches between expected and actual pain. Consistent with comparator theory, the same hippocampal regions were implicated in three different types of mismatch: when no pain was expected (novelty); when the nociceptive stimulus differed from expectation; and when the painful stimulus was unexpectedly omitted. In a subsequent study, Ploghaus and colleagues (2001) manipulated the certainty of expectation about impending nociceptive stimulation, to investigate its modulation on pain perception. This study examined the neural mechanism by which anxiety (uncertain expectation) causes increased pain perception (hyperalgesia), and contrasted it with the process by which a heightened nociceptive stimulation causes increased pain perception. The Gray-McNaughton theory proposes that the hippocampal formation responds to aversive events such as pain whenever they form part of a behavioral conflict, e.g. a conflict caused by uncertain expectation of pain. This conflict induces anxiety. Output from the comparator has two effects that underpin anxiety and behavioral inhibition. First, it tends to suppress both of the currently conflicting responses. Second, it increases the valence of the affectively negative associations of each of the conflicting goals (McNaughton and Gray 2000).

As predicted from theory, Ploghaus and colleagues reported activation of the entorhinal cortex during anxiety-driven hyperalgesia, but not during increased pain perception caused by augmented nociceptive input (Fig. 2b; Ploghaus et al. 2001). Studies of other (not anxiety-related) types of hyperalgesia typically report no significant activation of the hippocampus / parahippocampal region (e.g. Zambreanu et al. 2005). One exception is a recent FMRI study of drug modulation during pain (Borras et al. 2004). Naloxone, a predominantly μ opioid antagonist, was administered to naïve subjects in low doses. During rest (baseline) conditions where no stimulation was applied, regions in the hippocampal / entorhinal complex were activated more in the drug condition than during placebo. According to the Gray-McNaughton theory, the entorhinal cortex primes responses that are adaptive to an aversive input, such as the motor response necessary for escape from a threatening environment. Enhanced activation in this region after naloxone infusion indicates a change in basal activity, potentially lowering the threshold for activation of adaptive responses.

In line with this argument, differences between naloxone and placebo conditions during nociceptive processing were found in several areas within the

hippocampus / parahippocampal region. When pain ratings were matched across conditions, an area within the posterior parahippocampal gyrus was significantly more activated in the naloxone condition. Activation of the hippocampus proper to nociceptive stimulation in the drug condition compared to the placebo condition was found only when subjects rated the pain intensity higher in the naloxone condition (nociceptive stimuli were of equal intensity across conditions). This result adds further support for the role of the hippocampus proper in pain intensity encoding. In their study of anxiety-driven hyperalgesia, Ploghaus and colleagues (2001) found that the entorhinal cortex activation was predictive of activity in the perigenual cingulate and mid-insula (Fig. 2c). Corresponding regions of the cingulate and insular cortices were also implicated in naloxone-induced increases in pain perception (Borras et al. 2004). The authors concluded that the regions where activation by noxious heat was modulated by naloxone were the sites of action of endogenous opioid pathways involved in regulating the central nervous system response to aversive stimuli.

Some support for the involvement of the hippocampus / parahippocampal region in opioid regulation of the brain's response to nociceptive input comes from functional imaging studies of acupuncture. Several studies investigating brain responses to acupuncture in healthy, pain-free volunteers have reported deactivation of regions within the hippocampus / entorhinal complex (e.g. Napadow et al. 2005). A recent study examining the effects of acupuncture in chronic pain patients does not report involvement of the hippocampus or parahippocampal areas (Pariente et al. 2005), but this study did not include a contrast for deactivation of specific brain regions.

There can be little doubt that the role of the hippocampus / entorhinal complex in nociceptive processing and the generation of pain perception demands further investigation in both healthy volunteers and in clinical pain patients. So far, the functional imaging studies of pain reporting hippocampus / entorhinal complex activation have been whole-brain studies examining the effects of nociceptive stimulation on all regions of the brain. This contrasts with the neuroimaging literature on the role of the hippocampal complex in memory, where researchers have been able to focus solely on this narrow region of cortex, improving spatial resolution and avoiding registration caveats e.g. by employing partial-coverage imaging techniques (Fig. 3) (see also Squire et al. 2004). To disentangle the roles of the subregions within the hippocampus / entorhinal complex in nociceptive processing and pain perception, high-resolution studies of this region during pain, employing similar measures, are needed. Care must also be taken to optimize study design in order to avoid the masking out of nociceptive-related hippocampal activations by processing of the resting state network.

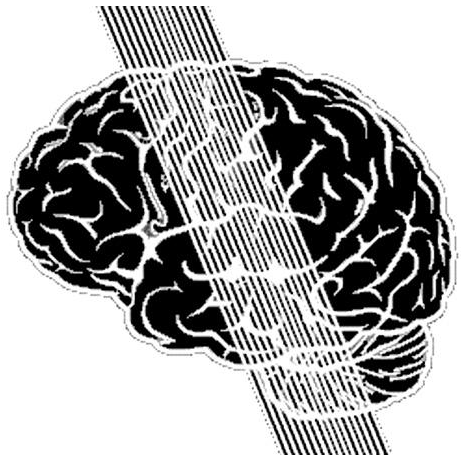

Figure 3 Visualization of slice positioning in a high-resolution, partial-coverage study of hippocampus / entorhinal complex function. By only covering a section of the brain, resolution can be improved significantly, and it may be possible to begin disentangling the function of small subregions within the hippocampus/parahippocampal complex for nociceptive processing and pain perception.

The role of hippocampus / entorhinal complex in clinical pain is still largely unknown. A study of patients suffering from irritable bowel syndrome (IBS) has recently shown involvement of hippocampus in pain processing in patients compared to healthy controls (Wilder-Smith et al. 2004). Given the known involvement of anxiety in irritable bowel syndrome, this result lends further support to the postulated involvement of the hippocampus / entorhinal complex in anxiety-driven increases of pain perception. Further, the hippocampus may form part of a system of central involvement that drives the visceral hypersensitivity of these patients. More studies of anxiety and hippocampus / entorhinal complex function in clinical pain should shed light on the importance of centrally generated pain and hyperalgesia.

In conclusion, converging evidence from human neuroimaging and animal studies points to a direct role for the hippocampus in the processing of nociceptive information such as pain intensity encoding. Areas within the hippocampus / entorhinal complex are involved in the comparison between actual and expected nociceptive stimuli, and play a role in anxiety-driven hyperalgesia. The increases in pain perception caused by uncertain expectation may be due to a modulation of the opiate system, as hinted at by a study investigating the effects of the μ opioid antagonist naloxone (Borras et al. 2004).

Table 1 Summary of functional imaging studies outlined here, listing stimulus type, neuroimaging technique and activations/deactivations in hippocampal/parahippocampal regions

Authors	Stimulus type		Hippocampus proper	Parahippocampal region
Derbyshire et al. 1997	Laser (heat nociception or warm)	PET	Nociceptive encoding	-
Ploghaus et al. 2000	Thermal (heat nociception or warm)	FMRI	Expectation related	Expectation related
Ploghaus et al. 2001	Thermal (heat nociception)	FMRI	Nociceptive encoding	Expectation related
Bingel et al. 2002	A-δ-specific laser	FMRI	Nociceptive encoding	-
Wilder-Smith et al. 2004	Rectal balloon distension and thermal (cold nociception)	FMRI	Patients more than controls	Patients more than controls
Borras et al. 2004	Thermal (heat nociception)	FMRI	Nociceptive encoding	May be related to shift in threshold for adaptive response
Greicius and Menon 2004	Visual (resting state examined)	FMRI	Resting state network	Resting state network
Napadow et al. 2005	Acupuncture in pain-free controls	FMRI	Deactivation	-

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