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Comment

The multi-instrumentalist hippocampus
Comment on "The quartet theory of human emotions: An integrative and neurofunctional model" by S. Koelsch et al.

Bryan A. Strange [a,b,*], Mar Yebra [a]

[a] *Laboratory for Clinical Neuroscience, Centre for Biomedical Technology, Technical University of Madrid, Spain*
[b] *Department of Neuroimaging, Reina Sofia Centre for Alzheimer's Research, Madrid, Spain*

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Characterizing the neural circuitry of emotion is important not only from a basic science perspective, but also for understanding how these circuits may malfunction in psychiatric disease. A fundamental question for affective neuroscience is whether there are specialised neuroanatomical areas, or "modules", dedicated to the processing of emotional stimuli. In their review, Koelsch and colleagues [1] argue for the existence of a quartet of neuroanatomically distinct cerebral systems involved in the generation of a specific class of affects. Intriguingly, all four systems (brainstem-, diencephalon-, hippocampus-, and orbitofrontal-centred) comprise brain areas whose role in emotional processing is in addition to mediating other specific aspects of cognition. One member of the quartet in which this is particularly apparent is the hippocampus, a structure known to be critical for episodic memory and navigation. If areas involved in emotion also mediate other brain functions, this raises an issue of whether these multiple functions are executed by segregated circuits within each structure – *i.e.*, a "module" for emotion residing in a sub-division of a brain structure – or whether these circuits are superimposed.

In the case of the hippocampus, it has been proposed that different functions may be segregated along its long axis: a ventral portion in rodents (analogous to anterior portions in humans [2]) is involved in emotion, whereas dorsal (posterior) hippocampus performs primarily cognitive functions, such as navigation and episodic memory [3]. This view is supported by evidence that the ventral hippocampus, but not the dorsal hippocampus, plays a role in mediating unconditioned fear behaviour [4,5], *e.g.*, ventral, but not dorsal, hippocampal lesions reduce defensive fear responses during exposure to the elevated plus maze (an unconditioned threatening environment [4]). Although this ventral-dorsal dichotomy of function has been revised [2] in light of observations that ventral hippocampus may play a similar role in spatial processing as the dorsal hippocampus, but at a larger spatial scale [6], whether both of these functions (spatial and unconditioned fear) rely on the same neuronal populations is currently unknown.

By contrast to this evidence for hippocampal involvement in fear behaviour, Koelsch et al. propose that the hippocampus is involved in attachment-related affects. This implies that this member of the affective quartet is playing (at

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* Corresponding author at: Laboratory for Clinical Neuroscience, Centre for Biomedical Technology, Technical University of Madrid, Campus de Montegancedo, Pozuelo de Alarcón, 28223, Spain.
E-mail address: bryan.strange@upm.es (B.A. Strange).

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least) two instruments – attachment and unconditioned fear – in addition to spatial and episodic memory. How these multiple functions are accommodated within the hippocampus might be explained by multiple anatomical and molecular factors which vary across the hippocampal long axis [2]. Of particular relevance to understanding the hippocampal role in the quartet theory of human emotion is the pattern of subcortical connectivity between hippocampus and hypothalamus. In rodent, different hippocampal regions along the longitudinal axis map topographically, via the lateral septum (LS), onto different hypothalamic regions [7]. A predominantly ventral hippocampal domain, just dorsal to the ventral tip, projects via rostral LS to hypothalamic medial zone nuclei [7]. Importantly, these nuclei, which include the anterior hypothalamic and ventromedial hypothalamic nuclei, form circuits involved not only in integrating innate defensive responses to environmental threats, but also in mediating reproductive and social agonistic behaviours [8]. Further studies are required to tease apart the hippocampal circuits involved in each behaviour, and whether other circuits exist to mediate the more positive emotions suggested by Koelsch et al. In this regard, it will be important to fully characterise the hippocampal projections to the paraventricular and supraoptic nuclei of the hypothalamus, as these nuclei mediate release of oxytocin, a hormone critical for the development of maternal behaviour [9] and pair bonding [10]. Whether these findings can then be extrapolated to accommodate a hippocampal role in feelings of joy and love, as suggested [1], is an interesting avenue for future research.

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