Navigating emotions using grid cells

Do grid cells, which are a fundamental component of the brain's navigation system, support navigating emotional spaces? Performing single-cell recordings from the human amygdala while epilepsy patients implanted with intracranial depth electrodes encode and recall emotional images, we will identify grid cell activity tessellating the emotional space into equilateral triangles. Our results will reveal mechanistic insights into how humans navigate their emotions and will suggest grid cell dysfunction in the human amygdala as a new explanation for emotional disorders including depression.

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1. Research idea and context

The brain's navigation system is implemented by different specialized neurons, among which grid cells are of particularly high relevance. Grid cells fire at multiple locations tessellating the spatial environment into equilateral triangles (*Hafting et al., Nature, 2005*). Grid cells presumably constitute the neural basis of path integration (*Banino et al., Nature, 2018*), which is the ability to estimate one's current position based on knowledge about a previous position, time elapsed, movement direction, and movement speed. Theoretical models suggest that grid cells support not only spatial navigation, but also episodic memory (*Buzsáki & Moser, Nature Neuroscience, 2013*) and navigation in complex spaces (*Constantinescu et al., Science, 2016*). However, whether grid cells enable navigating (i.e., structuring and controlling) emotional spaces remains an open question.

Emotions are a core facet of human life. Every day we are confronted with a multitude of emotions, some of which we would like to grasp and keep, some of which we fear, avoid, or struggle with. Whereas authors, actors, and singers like James Joyce, Romy Schneider, and Luciano Pavarotti are famous for their ability to purposefully evoke multifaceted feelings in their audience, patients with emotional disorders (comprising mood disorders and anxiety disorders) are disabled in controlling their emotions. However, the neuronal basis of (not) being able to navigate emotions remains unknown. We hypothesize that grid cells provide a cognitive coordinate system that allows humans to organize their emotions.

Scientific classifications of emotions include the so-called circumplex model (*Russell, Journal of Personality and Social Psychology, 1980*) that arranges emotions in a two-dimensional space defined by the cardinal axes of "valence" (i.e., the degree of a positive or negative affective response that an experience evokes) and "arousal" (i.e., the intensity of the affective response that an experience evokes). Until now it has not been tested whether navigating this fundamental space of emotions is mechanistically implemented by the same cell types that constitute the brain's spatial navigation system. The proposed project will tackle this question via the rare opportunity of single-cell recordings from the human brain and elucidate whether grid cells tessellate emotional spaces with their unique firing pattern.

Identifying grid cells as a mechanism to successfully navigate emotions will (i) significantly expand our knowledge of grid cell functioning, (ii) provide a neuronal basis of how emotions are processed and structured by the human brain, and (iii) suggest grid cell dysfunction in the human amygdala as a new explanation for emotional disorders.

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2. Proposed solution or concept

Our research question whether grid cells exhibit their unique firing pattern in an emotional space will be operationalized by a new cognitive paradigm that epilepsy patients complete on a laptop while single-cell activity is measured via microwires. These microwires with a diameter of 40 µm extend from the tip of intracranial depth electrodes implanted into the patient's medial temporal lobe for diagnostic purposes. In particular, recordings will target the amygdala, whose role in emotion processing is established (*Phelps & LeDoux, Neuron, 2005*).

The cognitive paradigm uses emotional images that were previously rated by a large population according to the cardinal dimensions of valence and arousal (*Kurdi et al., Behavior Research Methods, 2017*). During an encoding phase, patients are presented with a series of images that they have to recall during a subsequent retrieval period (after a short distractor period; Fig. 1a). Patients will experience the paradigm as a memory task being uninformed about the two underlying dimensions of valence and arousal.

During data analysis, single-cell recordings will be examined via spike detection and sorting algorithms (*Quiroga et al., Neural Computation, 2004*). Spikes from single neurons will then be displayed as a function of valence and arousal in a two-dimensional space depending on the emotional images during which they occurred. Following grid cell analysis techniques from previous studies (*Jacobs et al., Nature Neuroscience, 2013*) we will identify grid cells tessellating the emotional space into equilateral triangles. The proposed solution is summarized in Fig. 1.

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3. Objective of the exploratory phase

The objectives of the exploratory phase are:

(1) Implementation and piloting of the new cognitive paradigm,
(2) Measurement of single-cell activity from the medial temporal lobe (particularly from the amygdala) of epilepsy patients implanted with microwires while they perform the paradigm,

(3) Data analysis to detect grid cells whose firing patterns tessellate the emotional space (spanned by the two dimensions of valence and arousal) into equilateral triangles.

4. Figures

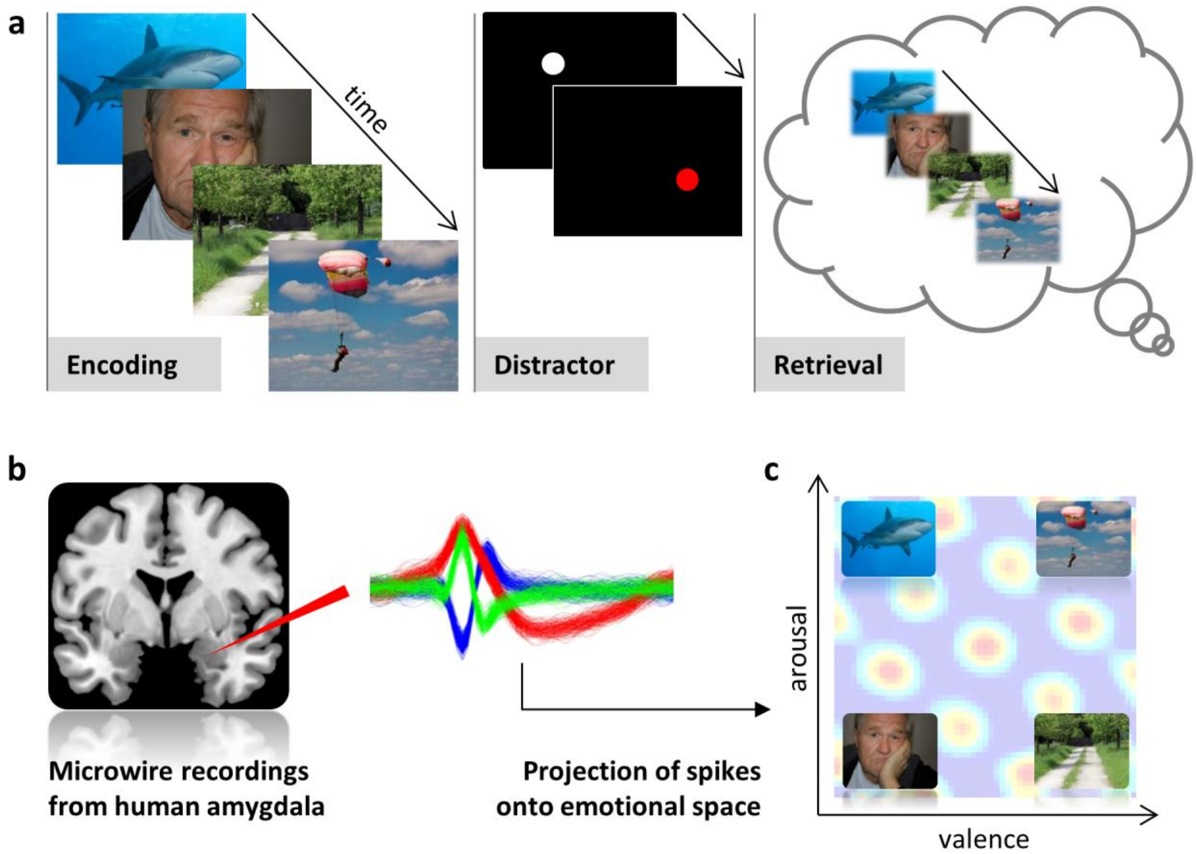

Fig. 1 | Proposed solution of the hypothesis that grid cells support navigating emotional spaces. a, Paradigm. During each trial of the cognitive paradigm, patients are first asked to encode a series of images ("encoding"). Afterward, patients complete a short distractor task during which they have to press a button whenever a red dot appears on the screen ("distractor"). Patients then have to freely recall the encoded images ("retrieval"). **b**, Microwire recordings and spike extraction. Microwires will be implanted into human medial temporal lobe (with the amygdala as specific target, which is located at the tip of the red triangle) to record activity from single neurons. During data analysis, spikes (from single-units and multi-units) are extracted using algorithms for spike detection and sorting (*Quiroga et al., Neural Computation, 2004*). **c**, Grid cell analysis. Since the images were previously rated with respect to valence and arousal, spikes occurring during specific images can be projected onto a two-dimensional emotional space (spanned by the two dimensions of valence and arousal). Firing fields of a given unit in the emotional space will be examined with regard to grid cell-properties.