https://doi.org/10.1038/s41583-023-00703-y

Post-encounter freezing during approach–avoidance conflict: the role of the hippocampus

In their valuable Perspective article (Roelofs, K. & Dayan, P. Freezing revisited: coordinated autonomic and central optimization of threat coping. *Nat. Rev. Neurosci.* **23**, 568–580; 2022)[1], Roelofs and Dayan propose that complex cognitive processing occurs during the marked immobility ('freezing') that occurs "upon detection of a not-yet-attacking predator." They focus on autonomic control via amine neuromodulators and on the incomplete literature on brain circuits involved in both the inhibition of, and switch to, action. They emphasize the roles of the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), basolateral amygdala (BLA) and central amygdala (CeA), but mention the hippocampus only once, tangentially.

The hippocampus has long been argued[2] to be involved in the resolution of goal conflicts and thus in 'post-encounter' freezing and/or defensive quiescence, in contrast to 'circa-strike' freezing and/or fright. Post-encounter threat in humans and non-humans engages the ventral mPFC, ACC, ventral hippocampus (vHPC), amygdala and hypothalamus; and, when approach-avoidance conflict occurs, as during post-encounter threat, the vHPC plays a crucial arbitrator–comparator role to select between the available prepotent responses[2–6].

Two-way active avoidance (TWAA) paradigms generate a conflict between anxiolytic-insensitive active avoidance and anxiolytic-sensitive passive avoidance (that is, response inhibition), allowing the study of post-encounter threat responses[5]. In these tasks, rodents can learn to escape or avoid an aversive stimulus (the unconditioned stimulus (US)) that is preceded by a warning signal (the conditioned stimulus (CS)) by shuttling between opposite compartments within the experimental apparatus. A few initial CS–US pairings generate a post-encounter conflict in which approach is reduced by context- and CS-conditioned freezing (Fig. 1).

Context conditioning of avoidance depends on the vHPC[7], with activation of a circuit involving the vHPC, BLA and CeA leading initially (phase 1) to a predominant tendency towards Pavlovian conditioned freezing[5,6]. With further training, negative reinforcement — apparently mediated by decreased amygdala involvement, output from a circuit involving the vHPC, mPFC and nucleus accumbens (NAcc) and the release of behaviour controlled by the hypothalamus from inhibition by the vHPC — promotes a transition from freezing to US-elicited escape with some CS-elicited active avoidance (phase 2). Finally, there is a switch to action: goal-directed responses (escape or active avoidance) predominate with full activation of the vHPC–mPFC–NAcc and BLA–NAcc circuits (phase 3)[5,6].

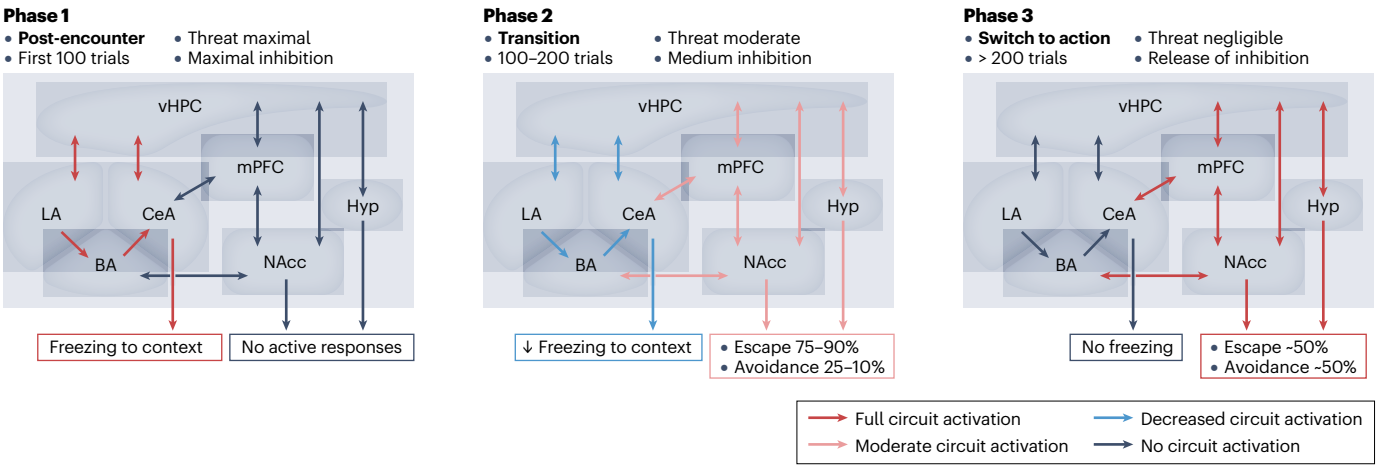

Fig. 1 | Changes in circuit activation across progressive phases of acquisition of two-way active avoidance. A simplified summary of the types of defensive response — including conditioned freezing, escape and active avoidance — that compete in each phase of acquisition of a two-way active avoidance (TWAA) instrumental task. Approximate (and qualitative) values shown are representative estimations from dozens of TWAA studies carried out with the 'high anxious' Roman low-avoidance rat line/strain during the past 30 years (reviewed elsewhere[10]). In all of these studies, each trial of TWAA acquisition consisted of a 10-s conditioned stimulus (CS, simultaneous presentation of a light and tone) followed by a 20-s scrambled footshock (the unconditioned stimulus (US)). The CS or US was terminated when the animal crossed to the opposite compartment, with crossing during the CS being considered an active avoidance response and crossing during the US an escape response. Freezing in TWAA conflicts with successful escape or avoidance. The drawings summarize the published experimental evidence of the neural regions and circuits responsible for the regulation (or control) of each of these types of defensive response across three phases of TWAA acquisition (reviewed elsewhere[5,6]). Phase 1, post-encounter, is the period of highest threat and inhibition or freezing, lasting for about 100 trials; phase 2, transition, is a period during which the perception of threat decreases and interference from inhibition or freezing decreases, lasting for about the next 100 trials; and phase 3, switch to action, is the period when successful TWAA has been achieved. BA, basal amygdala; CeA, central amygdala; Hyp, hypothalamus; LA, lateral amygdala; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; vHPC, ventral hippocampus.

In summary, the vHPC seems to be critically involved in all three TWAA phases and is therefore particularly important when we study different defensive responses across phases of threat imminence and the transitions among them. The vHPC is similarly involved in conditioned freezing in simpler post-encounter paradigms, such as extinction of context- or cue-conditioned fear in rodents or the presentation of a human intruder's profile to macaques[8,9].

The role of the vHPC in conflict arbitration within the model of autonomic–central function in post-encounter threat described by Roelofs and Dayan[1] is beyond our scope. However, the findings described above suggest that the vHPC should be included in this model, particularly given its high interconnectivity with regions that are crucial in this model, such as the mPFC, amygdala, NAcc, hypothalamus, ACC and periaqueductal grey[2,3].

There is a reply to this letter by Roelofs, K., Klaasson, F.H. & Dayan, P. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-023-00704-x (2023).

Alberto Fernández-Teruel [1] ✉ **& Neil McNaughton** [2] ✉

[1]Department of Psychiatry and Forensic Medicine, Faculty of Medicine and Institute of Neurosciences, Autonomous University of Barcelona, Barcelona, Spain. [2]Department of Psychology, University of Otago, Dunedin, New Zealand.

✉e-mail: albert.fernandez.teruel@uab.cat; neil.mcnaughton@otago.ac.nz

Published online: 9 May 2023

References

1. Roelofs, K. & Dayan, P. Freezing revisited: coordinated autonomic and central optimization of threat coping. *Nat. Rev. Neurosci.* **23**, 568–580 (2022).
2. McNaughton, N. & Corr, P. J. A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance. *Neurosci. Biobehav. Rev.* **28**, 285–305 (2004).
3. Mobbs, D., Headley, D. B., Ding, W. & Dayan, P. Space, time, and fear: survival computations along defensive circuits. *Trends Cogn. Sci.* **24**, 228–241 (2020).
4. Ito, R. & Lee, A. C. H. The role of the hippocampus in approach-avoidance conflict decision-making: Evidence from rodent and human studies. *Behav. Brain Res.* **313**, 345–357 (2016).
5. Fernández-Teruel, A. & Tobeña, A. Revisiting the role of anxiety in the initial acquisition of two-way active avoidance: pharmacological, behavioural and neuroanatomical convergence. *Neurosci. Biobehav. Rev.* **118**, 739–758 (2020).
6. Bryant, K. G. & Barker, J. M. Arbitration of approach-avoidance conflict by ventral hippocampus. *Front. Neurosci.* **14**, 615337 (2020).
7. Oleksiak, C. R. et al. Ventral hippocampus mediates the context-dependence of two-way signaled avoidance in male rats. *Neurobiol. Learn. Mem.* **183**, 107458 (2021).
8. Sotres-Bayon, F., Sierra-Mercado, D., Pardilla-Delgado, E. & Quirk, G. J. Gating of fear in prelimbic cortex by hippocampal and amygdala inputs. *Neuron* **76**, 804–812 (2012).
9. Shackman, A. J. et al. Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. *Proc. Natl Acad. Sci. USA* **110**, 6145–6150 (2013).
10. Fernández-Teruel, A. et al. Neurobehavioral and neurodevelopmental profiles of a heuristic genetic model of differential schizophrenia- and addiction-relevant features: the RHA vs. RLA rats. *Neurosci. Biobehav. Rev.* **131**, 597–617 (2021).

Acknowledgements

A. F.-T. receives support from the Ministerio de Ciencia e Innovación, project PID2020-114697GB-I00 (ref. AEI/10.13039/501100011033).

Competing interests

The authors declare no competing interests.