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Abstract

Risk assessment (RA) behavior is unusual in the context of survival circuits. An external object elicits eating, mating or fleeing; but conflict between internal approach and withdrawal tendencies elicits RA-specific behavior that scans the environment for new information to bring closure. Recently rodent and human threat responses have been compared using 'predators' that can be real (e.g. a tarantula), robot, virtual, or symbolic (with the last three rendered predatory by the use of shock). 'Quick and dirty' survival circuits in the periaqueductal grey, hypothalamus, and amygdala control external RA behaviour. These subcortical circuits activate, and are partially inhibited by, higher-order internal RA processes (anxiety, memory scanning, evaluation and sometimes-maladaptive rumination) in the ventral hippocampus and medial prefrontal cortex.

Keywords risk assessment; anxiety; goal conflict; periaqueductal grey; hypothalamus; amygdala; hippocampus; prefrontal cortex

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McN+Corr_Risk-Assess_HIGH_2017-12-08.docx [Highlights]

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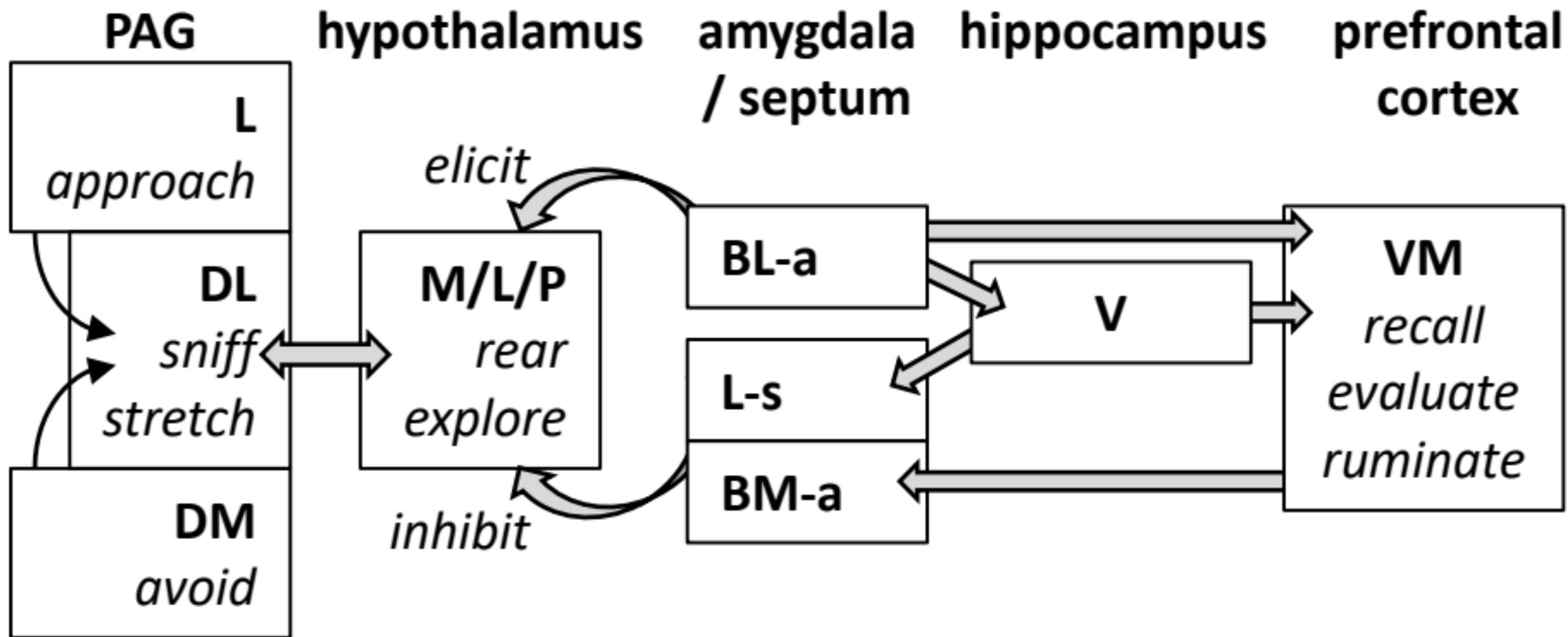
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Highlights:

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- Risk assessment is elicited by approach-avoidance conflict
- Periaqueductal grey and hypothalamus control urgent risk assessment behavior
- Amygdala, septum, and ventral hippocampus control complex risk assessment behavior
- Medial prefrontal cortex controls sophisticated internal risk assessment processes



SURVIVAL CIRCUITS AND RISK ASSESSMENT

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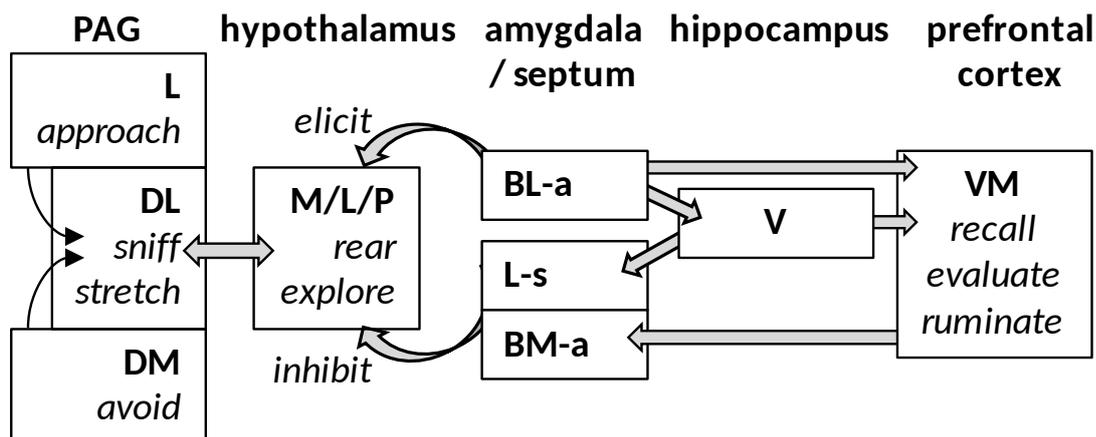
Abstract

Risk assessment (RA) behavior is unusual in the context of survival circuits. An external object elicits eating, mating or fleeing; but conflict between internal approach and withdrawal tendencies elicits RA-specific behavior that scans the environment for new information to bring closure. Recently rodent and human threat responses have been compared using 'predators' that can be real (e.g. a tarantula), robot, virtual, or symbolic (with the last three rendered predatory by the use of shock). 'Quick and dirty' survival circuits in the periaqueductal grey, hypothalamus, and amygdala control external RA behaviour. These subcortical circuits activate, and are partially inhibited by, higher-order internal RA processes (anxiety, memory scanning, evaluation and sometimes-maladaptive rumination) in the ventral hippocampus and medial prefrontal cortex.

[118/ 100-120 words]

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Graphical abstract (see also separate PDF file)



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Introduction

Our main text reviews reports (2015-2017) relating to “risk assessment” (RA) in the context of “survival circuits”. First, we provide some background context.

Survival circuits “instantiate functions that allow organisms to survive and thrive by detecting and responding to challenges and opportunities ... [e.g.] defense, maintenance of energy and nutritional supplies ... [they] and their adaptive functions *are conserved to a significant degree* across mammalian species, including humans” [1, p. 654, our emphasis]. They operate primarily at lower levels of neural processing, are not the substrate of conscious experience, and only partially overlap the control of ‘emotion’ [2]. Such “quick and dirty” [3] circuits produce characteristic RA-specific behaviors [4,5]. In rats, these include crouch-sniff and stretch-attend when threat is near; and rearing when threat is not so immediate. All RA behaviour functions to gain information from the environment.

With less proximal threat, RA processes shift internally (most obviously in humans): planning, scanning of memory [6*], and rumination/worry – but with high levels of rumination “appearing to represent a type of non-functional RA” [7**, section 2.2]. That is, worry does not add information from the world or from memory; and does not reduce threat. Internalised RA is embedded in complex ‘neuroeconomic’ processes [see 8]: “We routinely have to evaluate the relative risks and rewards associated with different options, choosing between potentially more profitable, but uncertain outcomes, and safer, yet more modest, rewards, such as when managing an investment portfolio”; with rats and humans both using prefrontal-amygdala-accumbens circuits in a dynamic competition between top-down and bottom-up processing [9, p. 2886]. Risk aversion can bias decisions, as can risk seeking, with bias sometimes reflecting evaluation failures within frontal circuits [10]; and risk modulates rhythmic activity in both frontal and posterior cortex [11]. As detailed below, the frontal areas involved in internal RA processes have bi-directional, co-ordinating, links with subcortical RA survival circuits, which are often driven by immediate input from the environment.

“Survival circuits are sensory-motor integrative devices that serve specific adaptive purposes, ... and they ... control behavioral responses and internal physiological adjustment that *help bring closure to the situation.*” [1, p. 655, our emphasis]. Tissue need can produce appetite and a search for an appetitive object. But, we are more often driven by incentive motivation – the object generates our desire [12]. With aversion, control by the object is more obvious. Proximity to, or contact with, such motivating objects (predator, food) elicits object-specific behaviors. At greater distance, behavior will be general rather than object-specific and can result from activation of subcortical survival circuits that control general approach to a positive goal and withdrawal from a negative goal, respectively [13*]. Such goal approach or goal withdrawal is an extension of object-specific behavior: lever pressing by a female rat to obtain a potent male [14] is an immediate precursor to lordosis and both are necessary for her achievement of the crucial (gene) survival behavior of copulation. Indeed, except with an unrestrained male rat, the female rat will always have to undertake general approach to obtain any of a wide range of desired objects – and so too with the human female.

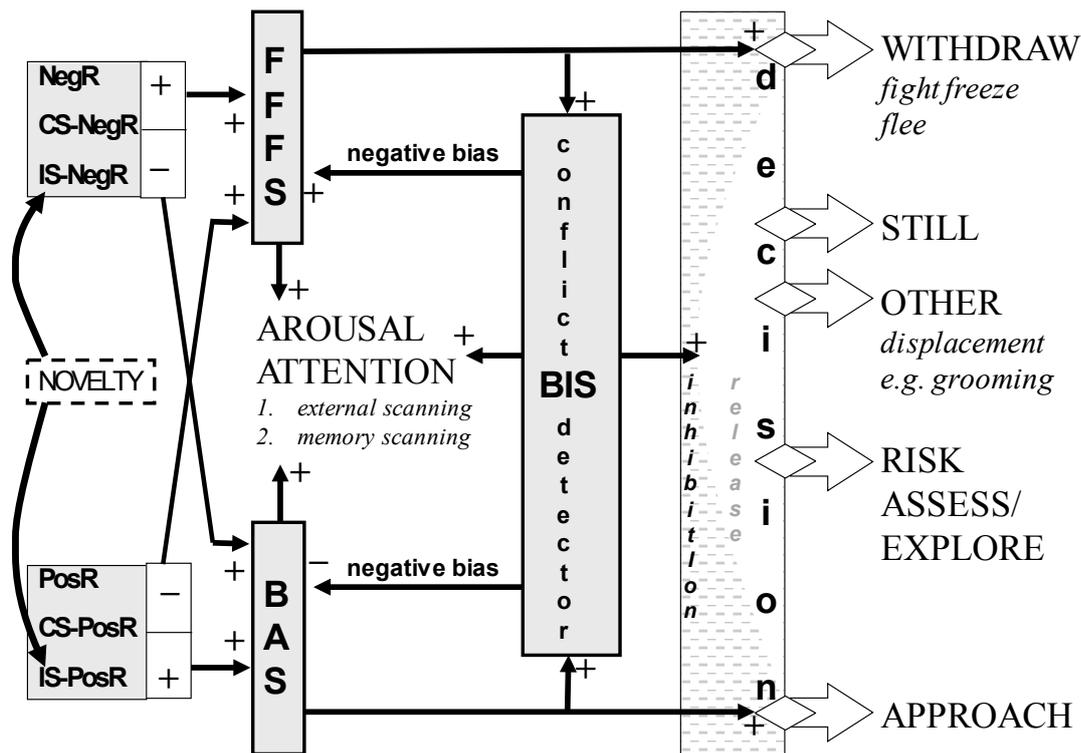


Fig. 1. Overall relation of goal approach (BAS), goal withdrawal (FFFS = fight, freeze, flee) and goal conflict (BIS = behavioral inhibition) systems. Inputs are classified as delivery (+) or omission (-) of primary positive reinforcers (PosR) or primary negative reinforcers (NegR) or conditional stimuli (CS) or innate stimuli (IS) that predict primary reinforcers. The BIS detects approach-withdrawal conflict and, when these are of similar strength, releases RA behaviors, including exploration, while inhibiting pre-potent approach and withdrawal. From [15].

RA behaviour arises in an unusual survival circuit. Risk is not an object like a predator or food. RA arises when the goal approach and goal withdrawal systems are in a conflict - detected by a third system (BIS, Fig. 1). Despite being neurally above the approach and withdrawal systems (which are above object-specific circuits), the BIS produces RA-specific behaviors. RA behaviour gathers, or makes salient, new positive or negative information and so brings closure from conflict. Closure will involve approach if safety is established; or, more usually, withdrawal (negative bias increases risk aversion, Fig. 1). This elicitation of RA-specific behaviours requires not only goal conflict, but also an intermediate 'defensive distance' [16-18] or immediacy of threat. When threat is close, defensive quiescence appears; when threat is far, RA is part of internal planning. We have previously mapped the hierarchy of passive defensive behavior to a hierarchy of neural structures [13*, 19, 20], locating the primary control of RA-specific behaviors in the ventrolateral periaqueductal grey and medial hypothalamus (Fig. 2), close to other survival circuits [21].

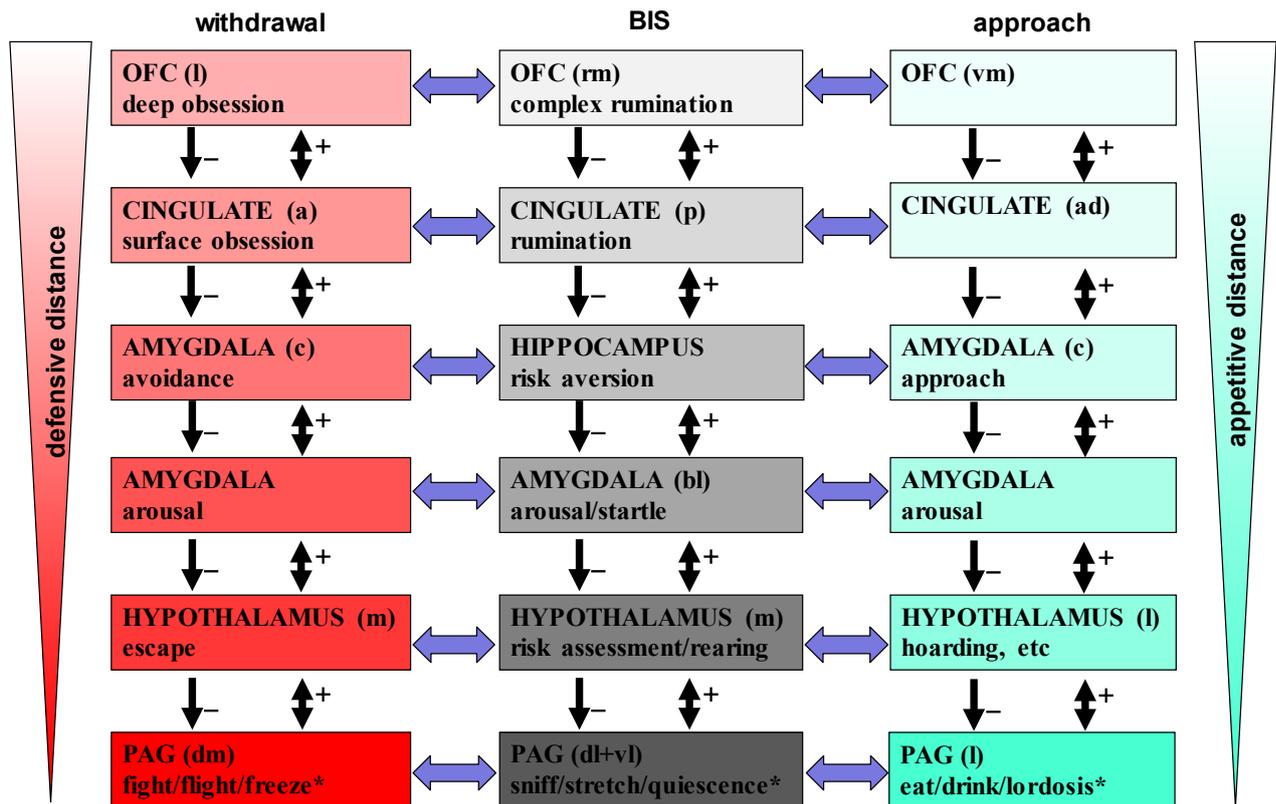


Fig. 2. Hierarchical organization of approach, withdrawal and behavioral inhibition (BIS) in terms of behavior and neural level. Lower levels process small defensive distances; higher levels process greater ones (i.e., negative events that are more distant in space or time). Activation tends to spread through the whole system (double-headed black arrows) but strong activation of a higher level (e.g., avoidance) inhibits (single-headed arrows) the behavioral output from (but not the activation of) lower levels (e.g., escape). * = static postures that achieve withdrawal, conflict resolution, or approach, respectively. Abbreviations: PAG = periaqueductal grey; OFC = orbital frontal cortex. [Adapted from 13*].

An important feature of the goal-conflict detection system in general (and of RA in particular) is sensitivity to benzodiazepines and other anxiolytic drugs (which affect neither approach nor withdrawal/fight/flight). This sensitivity gives us reason to see RA as functionally fundamental – the benzodiazepine receptor is phylogenetically old, appearing in bony fish [22], with a largely conserved functional role [23, p. 464]. Although our modern minds inhabit an “age of anxiety” that particularly engages our prefrontal cortex [24*], control of this anxiety is strongly linked to benzodiazepine receptors [25] implicating ancient survival circuits in key processes like RA [see also 7**].

Main text of review

Measuring Risk Assessment

As we have noted, RA is a response to a *lack of information* rather than to the presence of some explicit survival-related object. This makes its study difficult on two counts.

First, we cannot easily present a specific, explicit, eliciting stimulus; so most researchers measure RA incidentally or indirectly. RA is, therefore, best studied with neuroethology [26*]. Reliable elicitation of RA with a predator [27] has recently been extended to more controllable artificial predators [see 26*] and to more formal shock conditioning in rats [28*] and humans [29**].

Second, unlike approach and withdrawal, the specific type (coded by a trained observer) and intensity of RA behavior varies non-linearly with, e.g. threat level. Network analysis of behavior [e.g., 30] may help solve some of these problems. Recent translation of rodent RA paradigms to human scenarios, and video games, suggests that systematic manipulation of the ambiguity/uncertainty of threat is something to which “RA is exquisitely sensitive” [6*]; but escapability may also be important [28*]. Ecologically valid testing of variations in defensive distance, threat, and uncertainty in humans could also, therefore, involve quite simple stimulus presentation [e.g., 31*] but will need great care in its analysis.

Subcortical Risk Assessment Survival Circuits

The periaqueductal grey (PAG) appears to be the lowest level of integrated control of motivated responses (Fig. 2). The PAG has strong but complex clinical links with panic disorder; and is subject to top-down influences from prefrontal cortex (PFC), both directly, and via amygdala/hippocampus [32*,33**]. This is consistent with its association with very short defensive distance freezing/flight (Fig. 2) and control by the amygdala in the rat [34*]. PAG appears to control only the more proximal RA behaviors such as stretch-attend [35]. RA behavior elicited by avoidable contextual shock conditioning is associated with increased c-fos in the dorsomedial and lateral PAG [28*] – possibly due to concurrent activation of approach and avoidance (Fig. 2). In contrast, RA elicited by cat odour (or its context) is blocked by NMDA-receptor antagonist injections in the dorsolateral PAG [36; consistent with Fig. 2]. The serotonin system (its dorsal raphe component is embedded in the PAG) may be particularly important for the control of RA [7**].

Activation of the dorsomedial and lateral PAG during RA is accompanied by activation of the lateral hypothalamus and dorsal premammillary nucleus but not the hippocampal and septal areas that provide a major top-down input to the lateral hypothalamus [28*]. In addition to the lateral hypothalamus [37], the posterior hypothalamus may be involved in RA (in the form of novel object exploration) and may concurrently control the anxiety-related neuroendocrine stress response [38]. Consistent with the top-down control of the PAG by the amygdala in relation to freezing and flight, the basolateral amygdala appears to be involved in the generation of RA as measured by stretch-attend in the elevated plus-maze [39] and by the firing of one group of its cells during periods of hesitation or retreat, but not of escape [40*].

Subcortex-Cortex Interactions

We can expect (Fig. 2) bidirectional connections between any quick and dirty survival circuit and its slow and sophisticated cortical companion. Each should be able to activate the other and, when an appropriate sophisticated response is available, cortex should be able to inhibit the simplistic output from subcortex.

Interestingly, the key output from the amygdala in its control of PAG-based RA behavior is ascending: to medial PFC either directly [41] or relayed [42] via the ventral hippocampus [43,44]. This transfer, like many other processes [45*], depends on theta-frequency synchrony [42]. However, this theta-rhythmicity may be more related to the approach or withdrawal that follows RA than it is to RA itself [46]. Conversely, a distinct population of ventral hippocampal cells that targets the lateral septum rather than the medial PFC *inhibits* anxiety-related behavior, perhaps as a form of negative feedback [44]. In contrast to the positive role of the basolateral, the basomedial amygdala appears to mediate suppression by the ventromedial PFC of a wide range of fear- and anxiety-related responses [47**].

Recent imaging work with humans, using virtual predators, has distinguished between ‘reactive fear’ circuits (involving PAG and mid-cingulate cortex) controlling escape at short defensive distances and ‘cognitive fear’/anxiety circuits (involving hippocampus, posterior cingulate cortex, and ventromedial PFC) that control escape/strategic avoidance at long defensive distances [29**,48]. Given the use of long defensive distance, such strategic calculations likely reflect RA in the cognitive/neuroeconomic sense we mentioned earlier: clearly involving memory and operating well above the level of simple RA behavior controlled by highly conserved subcortical survival circuits. In particular, human cortical circuits appear to go well beyond the capacities of the survival circuits we share with other animals in their capacity for imagination/simulation of future threat, environmental/social reduction of threat, vicarious learning, and the use of reason to anticipate new threats – constituting a Survival Optimisation System [49**].

Models of Risk Assessment Circuits

We now have a detailed picture of the ascending control of RA [Fig. 3; 50*]. In this model, activation of PAG can engage the highest levels of internal processing and planning. However, quite simple RA behaviors that acquire more information from the environment may resolve even the most complex goal conflict. RA, as a whole, then is likely to involve interactions between ascending and descending circuits [47**]. The precise descending control of RA remains to be determined, but is likely to involve the same structures as does ascending control (compare Fig. 3 and Fig. 4).

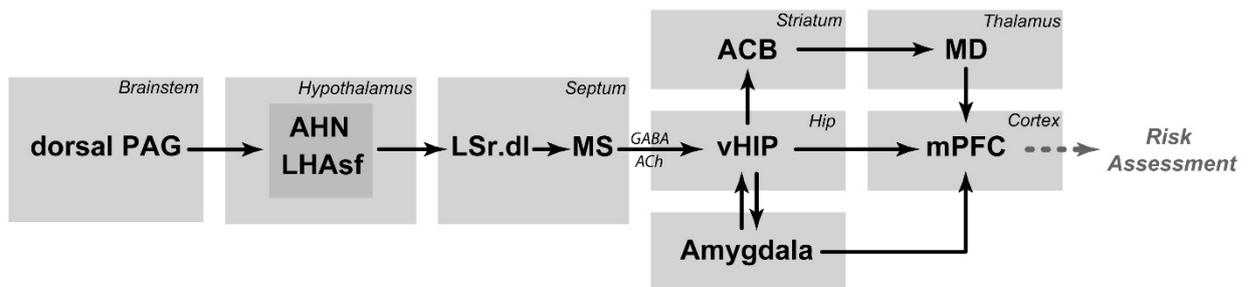


Fig. 3. The ascending control of risk assessment [from 50*; with permission].

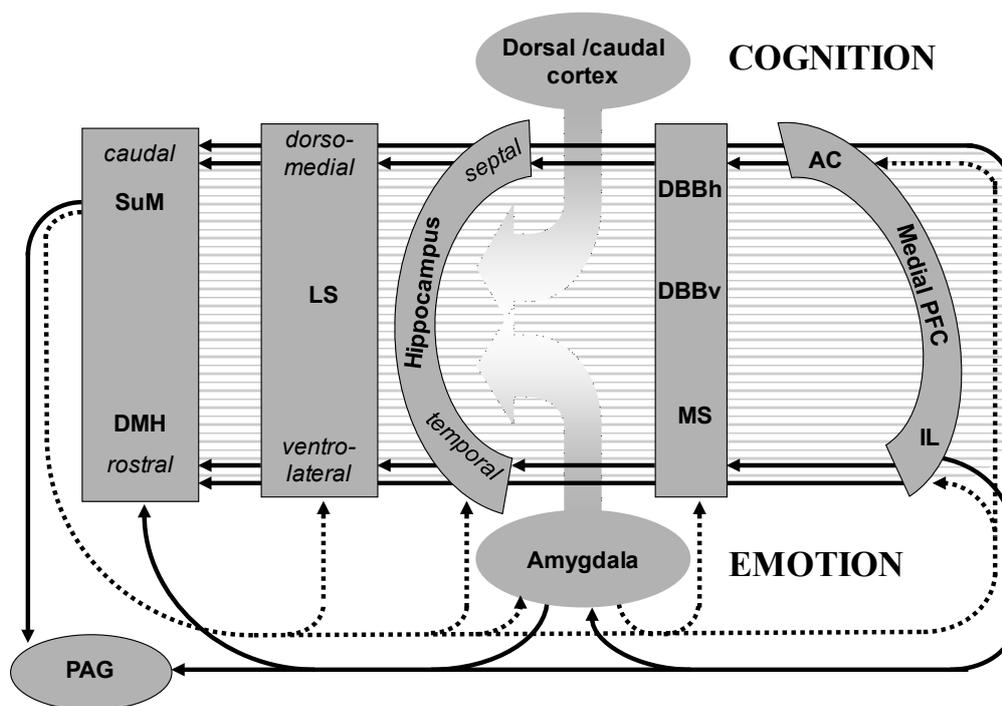


Fig. 4. Topographically organised descending control of goal-directed behaviour [adapted from 51].

Conclusions

Despite its key role in survival, there has been little direct study of ancient conserved RA survival circuits. The hope is that here, as more generally, the move towards “semi-realistic studies will allow ... a paradigm shift in experimental design, moving beyond the oversimplified methods uses in classical and instrumental conditioning, yet ... [with] tight control over conditions ... [and providing] a new window into the neural circuits that underlie fear and anxiety” [26*].

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References

1. LeDoux J: **Rethinking the Emotional Brain**. *Neuron* 2012, **73**:653-676.
2. LeDoux JE: **Coming to terms with fear**. *Proceedings of the National Academy of Sciences* 2014, **111**:2871-2878.
3. LeDoux JE: **Emotion, memory and the brain**. *Scientific American* 1994, **270**:50-59.
4. Blanchard DC, Blanchard RJ, Rodgers RJ: **Risk Assessment and animal models of anxiety**. In *Animal models in Psychopharmacology*. Edited by Olovier B, Mos J, Slangen JL: Birkhauser Verlag; 1991:117-134.
5. Blanchard DC, Griebel G, Pobbe R, Blanchard RJ: **Risk assessment as an evolved threat detection and analysis process**. *Neuroscience & Biobehavioral Reviews* 2011, **35**:991-998.
- *6. Blanchard DC: **Translating dynamic defense patterns from rodents to people**. *Neuroscience & Biobehavioral Reviews* 2017, **76**:22-28.
*up to the minute review of rodent-human translation of defense batteries, including RA, by the pre-eminent expert in this field.
- **7. Blanchard DC, Meyza K: **Risk assessment and serotonin: Animal models and human psychopathologies**. *Behavioural Brain Research* 2017, in press:DOI:10.1016/j.bbr.2017.1007.1008.
**a strong attempt to link RA in rodent models with rumination and other cognitive changes in human anxiety and depression psychopathology using serotonin manipulations as a translational tool.
8. Glimcher PW, Camerer CF, Fehr E, Poldrack RA: *Neuroeconomics: Decision making and the brain*. Amsterdam: Elsevier; 2009.
9. St. Onge JR, Stopper CM, Zahm DS, Floresco SB: **Separate Prefrontal-Subcortical Circuits Mediate Different Components of Risk-Based Decision Making**. *The Journal of Neuroscience* 2012, **32**:2886-2899.
10. Rudolf S, Preuschoff K, Weber B: **Neural Correlates of Anticipation Risk Reflect Risk Preferences**. *The Journal of Neuroscience* 2012, **32**:16683-16692.
11. Billeke P, Zamorano F, Cosmelli D, Aboitiz F: **Oscillatory Brain Activity Correlates with Risk Perception and Predicts Social Decisions**. *Cerebral Cortex* 2013, **23**:2872-2883.
12. Finlayson G, King N, Blundell JE: **Liking vs. wanting food: importance for human appetite control and weight regulation**. *Neuroscience & Biobehavioral Reviews* 2007, **31**:987-1002.
- *13. McNaughton N, DeYoung CG, Corr PJ: **Approach/avoidance**. In *Neuroimaging personality, social cognition and character*. Edited by Absher JR, Cloutier J: Elsevier; 2016:25-49.
*While not directly focussed on RA, this textbook chapter provides a comprehensive and up-to-date coverage of the key concepts relating to goals, approach, avoidance, conflict and the systems controlling them.
14. Bermant G: **Response Latencies of Female Rats during Sexual Intercourse**. *Science* 1961, **133**:1771-1773.
15. McNaughton N, Corr PJ: **Approach, avoidance, and their conflict: the problem of anchoring**. *Frontiers in Systems Neuroscience* 2014, **8**:A0124.
16. Blanchard RJ, Blanchard DC: **Antipredator defensive behaviors in a visible burrow system**. *Journal of Comparative Psychology* 1989, **103**:70-82.
17. Blanchard RJ, Blanchard DC: **An ethoexperimental analysis of defense, fear and anxiety**. In *Anxiety*. Edited by McNaughton N, Andrews G: Otago University Press; 1990:124-133.
18. Blanchard RJ, Flannelly KJ, Blanchard DC: **Defensive behaviors of laboratory and wild Rattus norvegicus**. *Journal of Comparative Psychology* 1986, **100**:101-107.
19. Gray JA, McNaughton N: *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System (2 ed.)*. Oxford: Oxford University Press; 2000.

20. McNaughton N, Corr PJ: **A two-dimensional neuropsychology of defense: Fear/anxiety and defensive distance.** *Neuroscience & Biobehavioral Reviews* 2004, **28**:285-305.
21. Sternson Scott M: **Hypothalamic Survival Circuits: Blueprints for Purposive Behaviors.** *Neuron* 2013, **77**:810-824.
22. Nielsen M, Braestrup C, Squires RF: **Evidence for a late evolutionary appearance of brain-specific benzodiazepine receptors: an investigation of 18 vertebrate and 5 invertebrate species.** *Brain Research* 1978, **141**:342-346.
23. Cloninger CR, Gilligan SB: **Neurogenetic mechanisms of learning: A phylogenetic perspective.** *Journal of Psychiatric Research* 1987, **21**:457-472.
- * 24. LeDoux J: *Anxious: The modern mind in the age of anxiety.* London: Oneworld Publications; 2015.
* recent detailed coverage of control of anxiety by the brain and its survival circuits; see particularly chapter 4, which includes discussion of subcortical involvement in processing of uncertainty and risk.
25. Tallman JF, Paul SM, Skolnick P, Gallager DW: **Receptors for the age of anxiety: pharmacology of the benzodiazepines.** *Science* 1980, **267**:274-281.
- * 26. Mobbs D, Kim JJ: **Neuroethological studies of fear, anxiety, and risky decision-making in rodents and humans.** *Current Opinion in Behavioral Sciences* 2015, **5**:8-15.
* presents the argument for controlled but ethological/realistic testing of threat in humans and rodents and comparison between the species; and provides a compact review of resultant analysis of survival circuits
27. Ribeiro-Barbosa ÉR, Canteras NS, Blanchard RJ, Blanchard DC: **An alternative experimental procedure for studying predator-related defensive responses.** *Neuroscience & Biobehavioral Reviews* 2005, **29**:1255-1263.
- * 28. Viellard J, Baldo MVC, Canteras NS: **Testing conditions in shock-based contextual fear conditioning influence both the behavioral responses and the activation of circuits potentially involved in contextual avoidance.** *Behavioural Brain Research* 2016, **315**:123-129.
* Interesting use of a more formal conditioning paradigm to elicit RA-specific behaviours (e.g. crouch-sniff, stretch-attend) in a controlled fashion and analysis of brain activation with c-fos that could easily be generalised to use in humans and fMRI.
- ** 29. Qi S, Sun J, Guo F, Daw N, Hassabis D, Mobbs D: **How Cognitive and Reactive Fear Circuits Optimize Escape Decisions in Humans.** *bioRxiv* 2017:DOI:10.1101/207936.
** direct test in humans of effects of defensive distance using virtual predators with different properties. Demonstrates an important separation between “reactive fear” circuits and “cognitive fear” circuits.
30. Suzuki Y, Imayoshi I: **Network analysis of exploratory behaviors of mice in a spatial learning and memory task.** *PLoS ONE* 2017, **12**:e0180789.
- * 31. Löw A, Weymar M, Hamm AO: **When Threat Is Near, Get Out of Here: Dynamics of Defensive Behavior During Freezing and Active Avoidance.** *Psychological Science* 2015, **26**:1706-1716.
* interesting for its use of a simple (circle/start) stimulus, linked to shock, in humans with size manipulated to simulate variations in distance
- * 32. Sobanski T, Wagner G: **Functional neuroanatomy in panic disorder: Status quo of the research.** *World Journal of Psychiatry* 2017, **7**:12-33.
* systematic up to date review of the functional anatomy of panic disorder, extending to the involvement of anxiety-related circuits
- ** 33. Tovote P, Fadok JP, Luthi A: **Neuronal circuits for fear and anxiety.** *Nature Reviews Neuroscience* 2015, **16**:317-331.

** Review of circuit-based analysis of fear, extinction, and anxiety networks with detailed circuit summary diagrams.

*34. Tovote P, Esposito MS, Botta P, Chaudun F, Fadok JP, Markovic M, Wolff SBE, Ramakrishnan C, Fenno L, Deisseroth K, et al.: **Midbrain circuits for defensive behaviour**. *Nature* 2016, **534**:206-212.

* detailed circuit analysis using cutting edge techniques demonstrating an amygdala-ventrolateral PAG-medulla system controlling freezing and allowing rapid switching between this and flight and emphasising the role of local circuits within PAG.

35. Bertoglio LJ, Zangrossi Jr H: **Involvement of dorsolateral periaqueductal gray N-methyl-D-aspartic acid glutamate receptors in the regulation of risk assessment and inhibitory avoidance behaviors in the rat elevated T-maze**. *Behavioural Pharmacology* 2006, **17**:589-596.

36. Souza RR, Carobrez AP: **Acquisition and expression of fear memories are distinctly modulated along the dorsolateral periaqueductal gray axis of rats exposed to predator odor**. *Behavioural Brain Research* 2016, **315**:160-167.

37. Rangel MJ, Jr., Baldo MV, Canteras NS, Hahn JD: **Evidence of a role for the lateral hypothalamic area juxtadorsomedial region (LHAjd) in defensive behaviors associated with social defeat**. *Frontiers in Systems Neuroscience* 2016, **10**:A0092.

38. Myers B, Carvalho-Netto E, Wick-Carlson D, Wu C, Naser S, Solomon MB, Ulrich-Lai YM, Herman JP: **GABAergic Signaling within a Limbic-Hypothalamic Circuit Integrates Social and Anxiety-Like Behavior with Stress Reactivity**. *Neuropsychopharmacology* 2015, **41**:1530-1539.

39. Sorregotti T, Cipriano AC, Cruz FC, Mascarenhas DC, Rodgers RJ, Nunes-de-Souza RL: **Amygdaloid involvement in the defensive behavior of mice exposed to the open elevated plus-maze**. *Behavioural Brain Research* 2017, **338**:159-165.

*40. Amir A, Lee S-C, Headley DB, Herzallah MM, Pare D: **Amygdala Signaling during Foraging in a Hazardous Environment**. *The Journal of Neuroscience* 2015, **35**:12994-13005.

* interesting for its use of a mechanical 'predator' to better control stimulus presentation within an ethological design.

41. Felix-Ortiz AC, Burgos-Robles A, Bhagat ND, Leppla CA, Tye KM: **Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex**. *Neuroscience* 2016, **321**:197-209.

42. Padilla-Coreano N, Bolkan SS, Pierce GM, Blackman DR, Hardin WD, Garcia-Garcia AL, Spellman TJ, Gordon JA: **Direct Ventral Hippocampal-Prefrontal Input Is Required for Anxiety-Related Neural Activity and Behavior**. *Neuron* 2016, **89**:857-866.

43. Felix-Ortiz AC, Beyeler A, Seo C, Leppla Christopher A, Wildes CP, Tye Kay M: **BLA to vHPC Inputs Modulate Anxiety-Related Behaviors**. *Neuron* 2013, **79**:658-664.

44. Parfitt GM, Nguyen R, Bang JY, Aqrabawi AJ, Tran MM, Seo DK, Richards BA, Kim JC: **Bidirectional Control of Anxiety-Related Behaviors in Mice: Role of Inputs Arising from the Ventral Hippocampus to the Lateral Septum and Medial Prefrontal Cortex**. *Neuropsychopharmacology* 2017, **42**:1715-1728.

*45. Korotkova T, Ponomarenko A, Monaghan CK, Poulter SL, Cacucci F, Wills T, Hasselmo ME, Lever C: **Reconciling the different faces of hippocampal theta: The role of theta oscillations in cognitive, emotional and innate behaviors**. *Neuroscience & Biobehavioral Reviews* 2017:DOI:10.1016/j.neubiorev.2017.1009.1004.

* up to date review of theta rhythmicity and its role in memory, locomotion and anxiety (but not explicitly mentioning RA). Important in showing that the links between theta and RA behaviour are not specific.

46. Jacinto LR, Cerqueira JJ, Sousa N: **Patterns of Theta Activity in Limbic Anxiety Circuit Preceding Exploratory Behavior in Approach-Avoidance Conflict**. *Frontiers in Behavioral Neuroscience* 2016, **10**:A0171.

47. Adhikari A, Lerner TN, Finkelstein J, Pak S, Jennings JH, Davidson TJ, Ferenczi E, Gunaydin LA, Mirzabekov JJ, Ye L, et al.: **Basomedial amygdala mediates top-down control of anxiety and fear. *Nature* 2015, **527**:179-185.

** While not directly focussed on RA, this paper uses cutting edge techniques to demonstrate control by ventromedial PFC of basomedial amygdala neurons that differentiate safe and unsafe environments producing output that decreases fear- and anxiety-related behaviour.

48. Rigoli F, Ewbank M, Dalgleish T, Calder A: **Threat visibility modulates the defensive brain circuit underlying fear and anxiety.** *Neuroscience Letters* 2016, **612**:7-13.

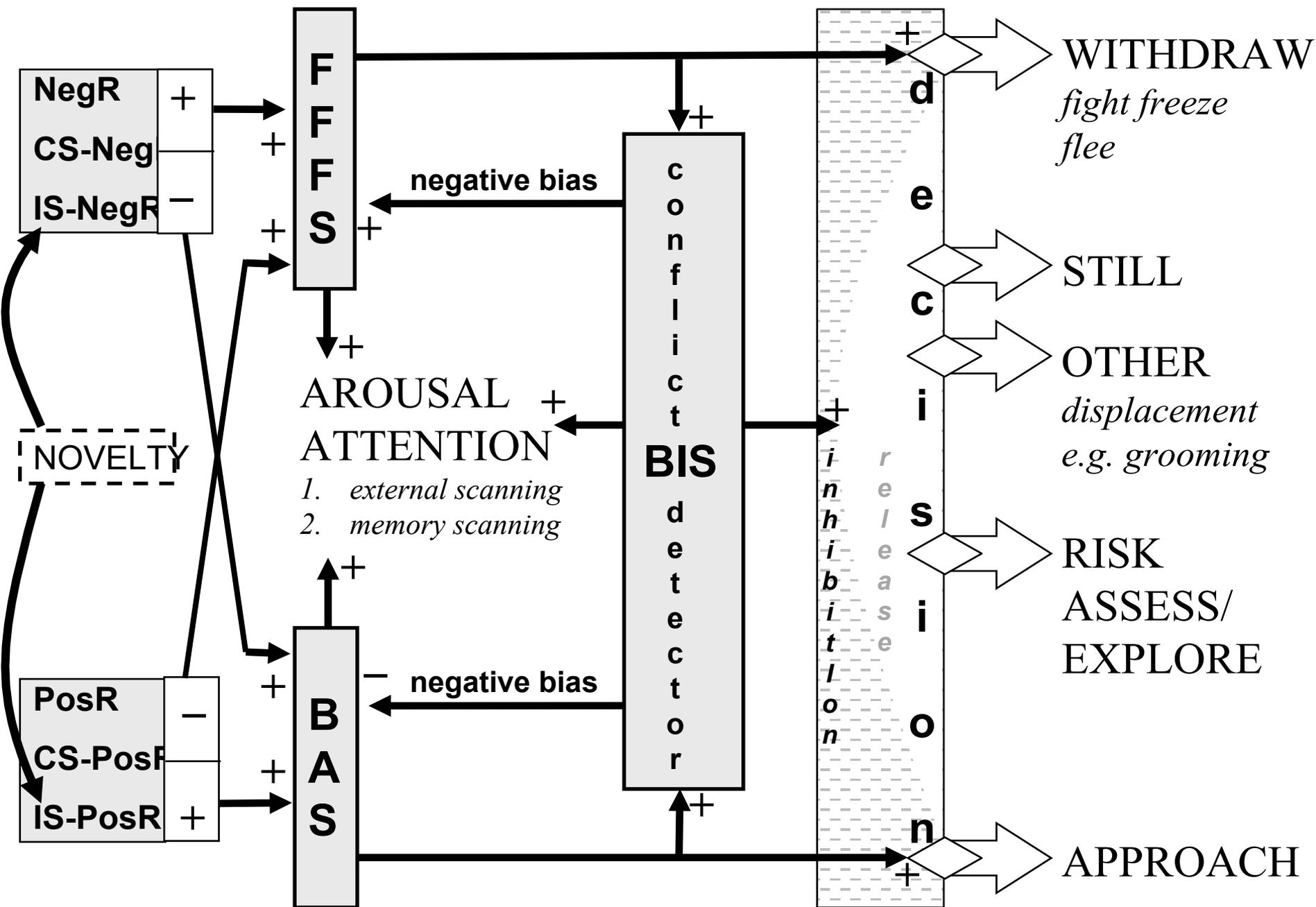
49. Mobbs D, Hagan CC, Dalgleish T, Silston B, Prevoost C: **The ecology of human fear: survival optimization and the nervous system. *Frontiers in Neuroscience* 2015, **9**:A055.

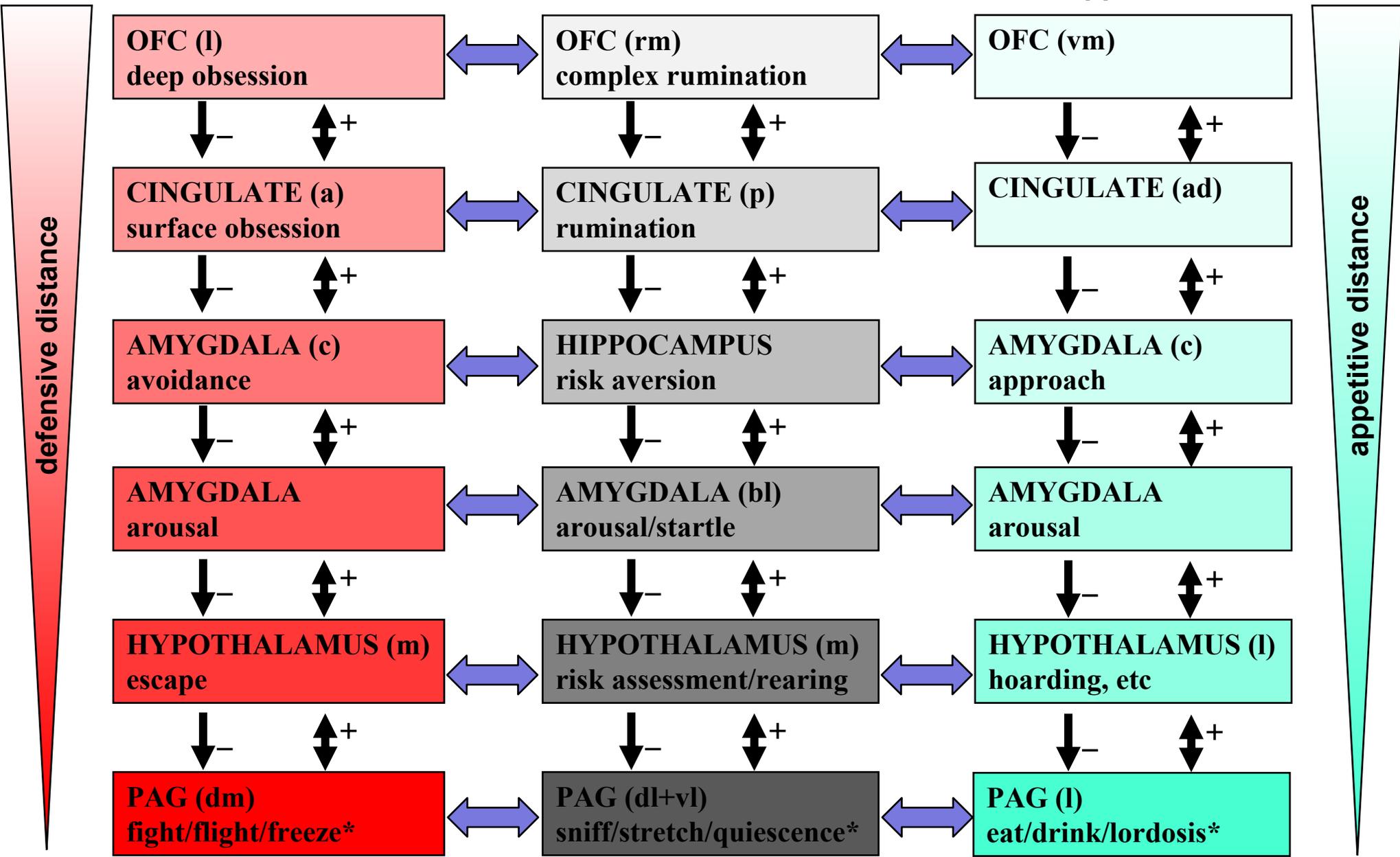
** Not directly focussed on RA but includes discussion of the role of predation risk and the nature of the systems that allow the prey to exercise some degree of control. The paper is particularly important for its presentation of a theory of a "Survival Optimisation System" to link lower level rodent-based survival circuit analysis with higher level work in humans.

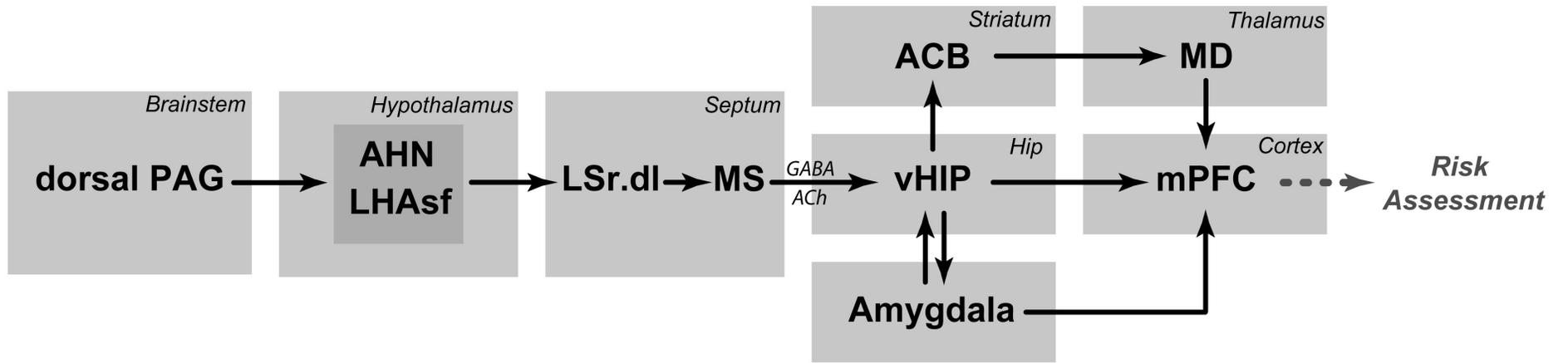
*50. Motta SC, Carobrez AP, Canteras NS: **The periaqueductal gray and primal emotional processing critical to influence complex defensive responses, fear learning and reward seeking.** *Neuroscience & Biobehavioral Reviews* 2017, **76**:39-47.

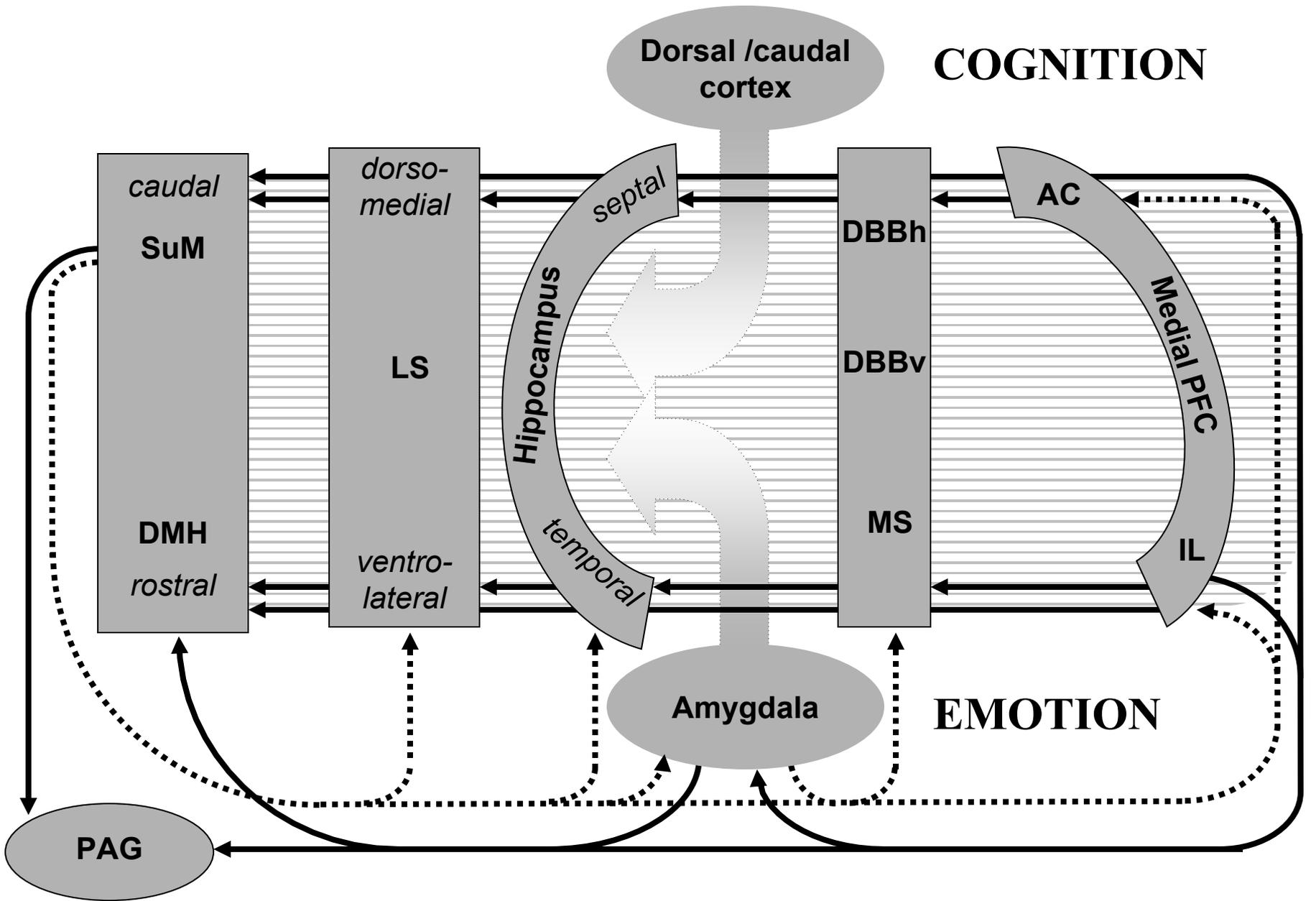
* up to date review of the interaction of the the different parts of the PAG with higher levels of the nervous system in the control of appetitive and aversive behaviour; with a set of detailed circuit diagrams.

51. Pan W, McNaughton N: **The supramammillary area: its organization, functions and relationship to the hippocampus.** *Progress in Neurobiology* 2004, **74**:127-166.









The authors declare no conflicts of interest