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Citation: McNaughton, N. & Corr, P. J. (2018). Survival circuits and risk assessment. *Current Opinion in Behavioral Sciences*, 24, pp. 14-20. doi: 10.1016/j.cobeha.2018.01.018

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SURVIVAL CIRCUITS AND RISK ASSESSMENT

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In *Survival Circuits* (ed) Prof. Dean Mobbs and Prof. Joe LeDoux

Special Issue of *Current Opinion in Behavioral Sciences*

Words: 1,970 [Aim approximately 2,000, excluding abstract and references]

References: 51 [Aim 50]

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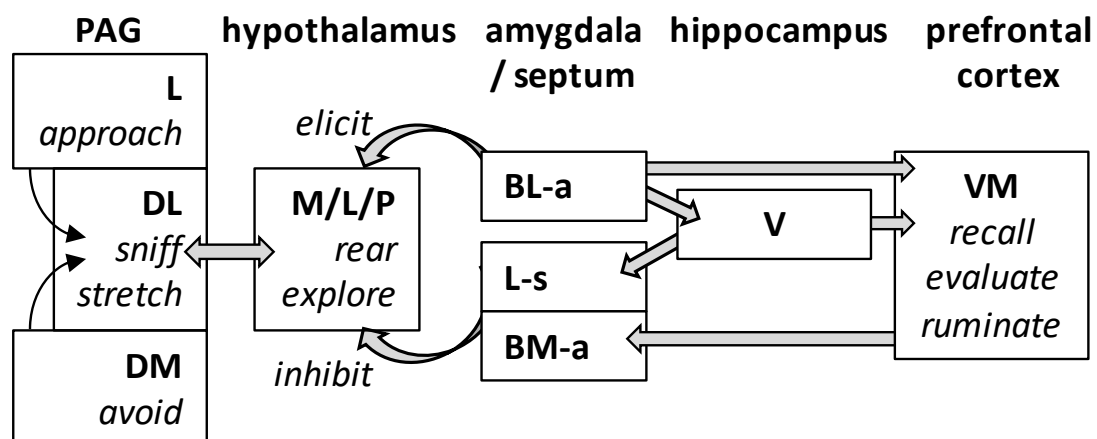
Abstract

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 behavior. 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]

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

Graphical abstract (see also separate PDF file)



Highlights:

- Risk assessment can be compared in humans and rodents with virtual predators
- 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

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 behavior functions to gain information from the environment.

With less proximal threat, RA processes shift from the gathering of new external information to (most obviously in humans) slow and sophisticated [3] re-processing of information internally: planning and scanning of memory [6*]. It may also involve rumination/worry – but with high levels of rumination “appearing to represent a type of non-functional RA” [7**, section 2.2]. Indeed, worry may not reflect RA at all, since it does not add information from the world or from memory; and does not function to resolve the response conflicts generated by 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]. Risk in the economic literature is tightly defined as the result of chance outcomes where the probabilities are known. Ambiguity is treated as distinct and arises when probabilities are not known. RA is likely to arise primarily when there is ambiguity [6*; see Blanchard this issue] or when behavioral strategies are being adapted in response to known probabilities. It would not be expected to occur once behavior has stabilised – that is, it has become habitual. 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, mate) elicits object-specific behaviors. At greater distance, behavior elicited by an object will not be object-specific (such as attack, eating or lordosis) but rather will result from activation of subcortical survival circuits that control general approach to any positive goal and withdrawal from any 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.

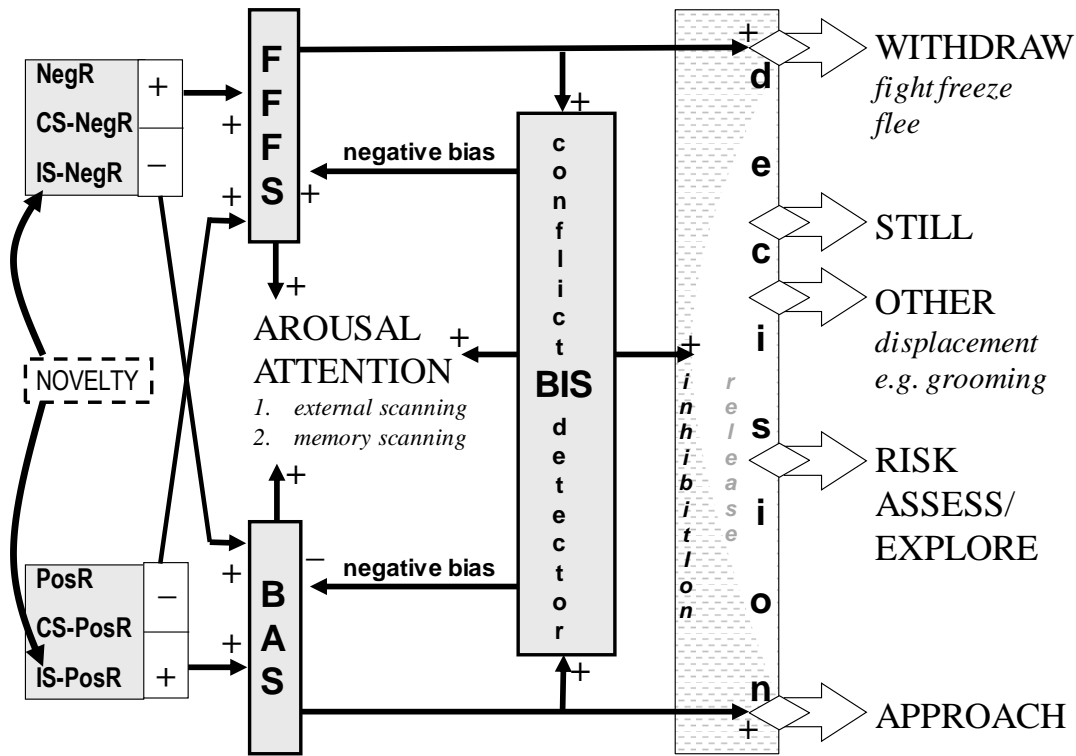


Fig. 1. Overall relation of goal approach (BAS), goal withdrawal (FFFS = fight, freeze, flee) and goal conflict (BIS = behavioral inhibition) systems. Inputs are classified as delivery (+) or omission (-) of primary positive reinforcers (PosR) or primary negative reinforcers (NegR) or conditional stimuli (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 behavior 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 conflict¹ – 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 behavior 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 behaviors 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-

¹ Approach can be produced by gain or the omission of loss; withdrawal can be produced by loss or the omission of gain. A choice to approach one of two alternatives automatically means omission of the consequences of the other. So approach/approach and avoidance/avoidance choice can elicit conflict, and RA, in the same way as approach/avoidance. Note that, in these situations, the words “reward” and “punishment” can be ambiguous [52].

specific behaviors in the ventrolateral periaqueductal grey and medial hypothalamus (Fig. 2), close to other survival circuits [21].

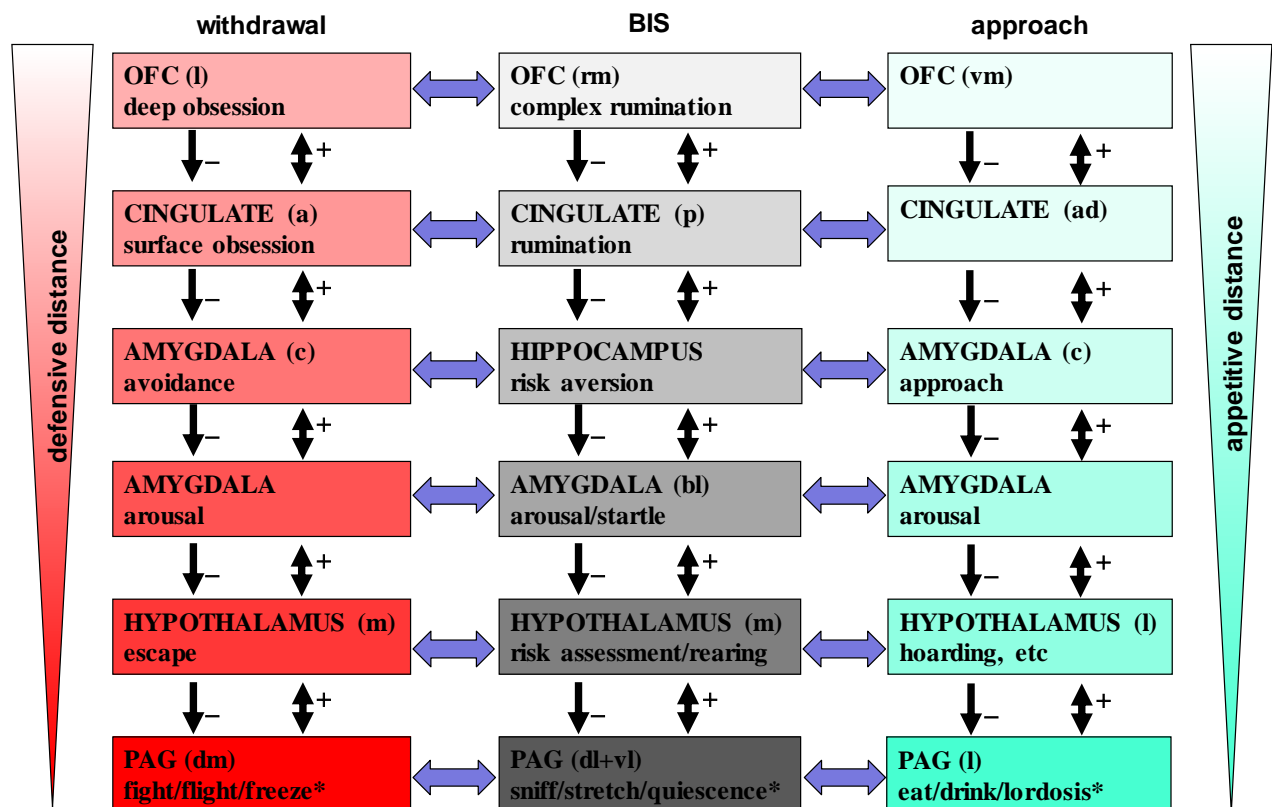


Fig. 2. Hierarchical organization of approach, withdrawal and behavioral inhibition (BIS) in terms of behavior and neural level. Lower levels process small defensive distances; higher levels process greater ones (i.e., negative events that are more distant in space or time). Activation tends to spread 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*].

In this context, it is important to realise that the PAG, while controlling simple forms of behavior, does so in a goal directed (not taxon or stimulus response [13]) fashion. Thus simple RA behavior could be elicited by moderate co-activation of PAG areas controlling conflicting goals. As with direct prefrontal influences on panic simple RA behaviors could be elicited where neocortically-detected uncertainty simply requires additional external information for its resolution. Conversely, conflicting simple PAG activations could elicit higher order, neocortical, RA processes.

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, for example, 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*] – emphasising that RA is a response to a lack of explicit stimulus information rather than a response to an explicit stimulus; 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 preammillary 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).

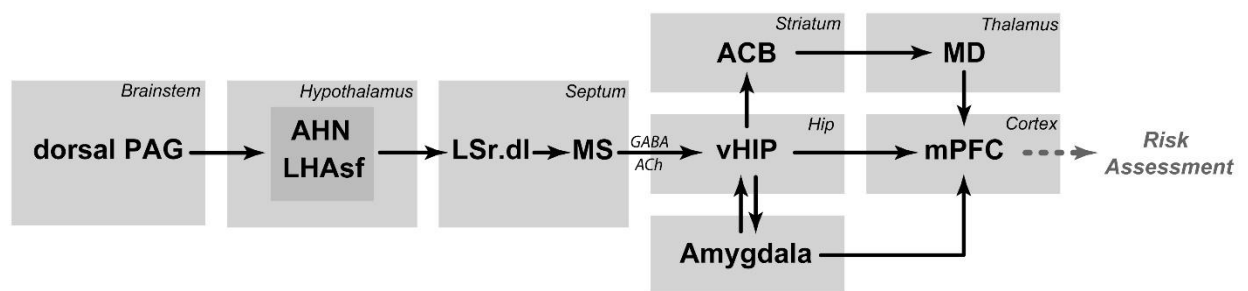


Fig. 3. The ascending control of risk assessment [from 50*; with permission].

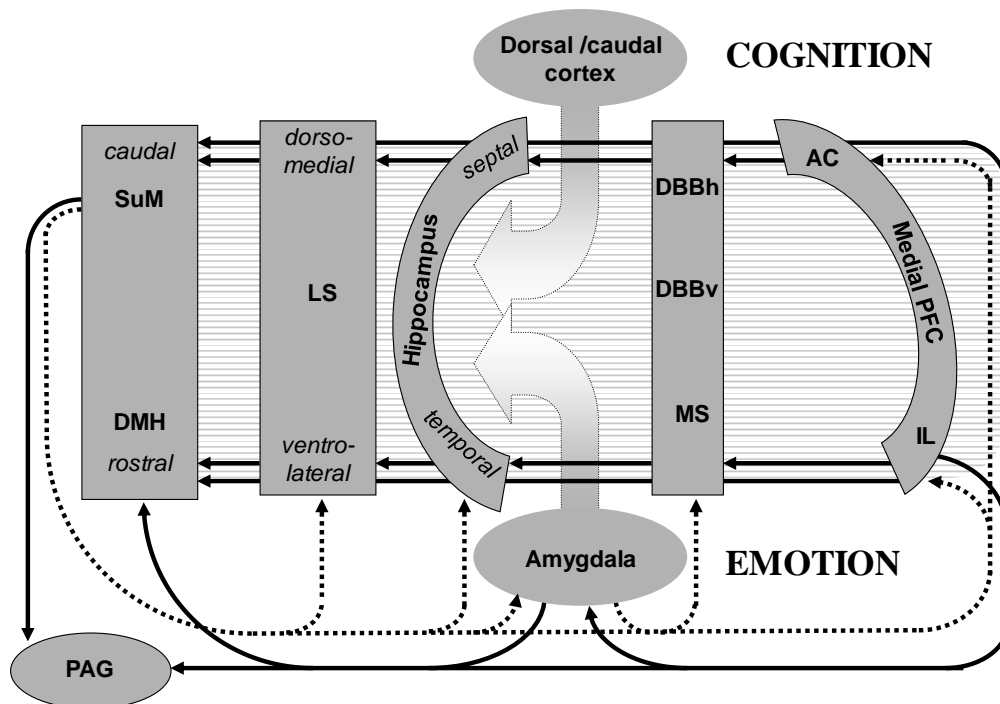


Fig. 4. Topographically organised descending control of goal-directed behavior [adapted from 51].

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*].

Acknowledgements

We would like to thank Carlos Silva, and Hélio Zangrossi Jr for comment on this article.

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