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Review

Tuning to the significant: Neural and genetic processes underlying affective enhancement of visual perception and memory

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HIGHLIGHTS

- Emotionally arousing events reach awareness more easily than more mundane events.
- Emotionally salient events are also perceived and remembered more vividly.
- We present the Biased Attention via Norepinephrine (BANE) model of affect-biased attention (ABA).
- BANE draws on genetic, neuromodulatory, neural and behavioural evidence to account for ABA.

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ABSTRACT

Emotionally arousing events reach awareness more easily and evoke greater visual cortex activation than more mundane events. Recent studies have shown that they are also perceived more vividly and that emotionally enhanced perceptual vividness predicts memory vividness. We propose that affect-biased attention (ABA) – selective attention to emotionally salient events – is an endogenous attentional system tuned by an individual's history of reward and punishment. We present the Biased Attention via Norepinephrine (BANE) model, which unifies genetic, neuromodulatory, neural and behavioural evidence to account for ABA. We review evidence supporting BANE's proposal that a key mechanism of ABA is locus coeruleus–norepinephrine (LC–NE) activity, which interacts with activity in hubs of affective salience networks to modulate visual cortex activation and heighten the subjective vividness of emotionally salient stimuli. We further review literature on biased competition and look at initial evidence for its potential as a neural mechanism behind ABA. We also review evidence supporting the role of the LC–NE system as a driving force of ABA. Finally, we review individual differences in ABA and memory including differences in sensitivity to stimulus category and valence. We focus on differences arising from a variant of the *ADRA2b* gene, which codes for the alpha2b adrenoreceptor as a way of investigating influences of NE availability on ABA in humans.

Contents

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1. Introduction

Emotionally arousing events are experienced with a heightened vividness, and emotionally compelling objects in the environment capture the eye as we navigate the world. It is, of course, well known that we continuously filter incoming sensory information, selectively allocating attention to what is important to us and suppressing distracting or irrelevant information. Yet the neural processes involved in attentional biases towards affectively significant aspects of the world remain relatively underspecified.

There is a well-established literature documenting the tension between 'top-down' and 'bottom-up' processes in modulating attention (for review see [1]). In this literature, 'top-down' refers to effortful attentional processes mediated by frontoparietal attentional networks and tuned to short-term goals, whereas 'bottom-up' refers to attentional capture by 'objectively' salient stimuli such as bright colours, motion, and high contrast [2–4].

Alongside other challenges to the original top-down/bottom-up distinction [5–7], we have argued that attention is also modulated by longer-term subjective goals of increasing pleasure and avoiding pain [8]. Such long-term goals can tune visual attention habitually to emotionally significant, or *affectively salient*, stimuli such as an attractive person, an angry face, or a gruesome scene. Based on observations that the amygdala and other brain regions key in tagging salience modulate visual cortex activation in a manner similar to the way frontoparietal regions do [9] we propose that *affect-biased attention* (ABA), which tunes visual attention to affectively salient stimuli, is distinct from both 'classic' executive top-town and bottom-up visual attention, and is at least in part circumscribed by a different set of neural mechanisms (see also [18]). In this paper we will propose the Biased Attention via Norepinephrine model (BANE), a multilevel model incorporating neuromodulatory, genetic, imaging and behavioural levels of analysis implicated in affective biasing of attention and memory. BANE focuses on the influence of noradrenergic processes on activation patterns in hubs of the 'anterior affective system' [10], including the amygdala and orbitofrontal cortex, which in turn modulate activity in other brain regions implicated in affect-biased visual attention and memory. This system is responsible for directing attention to and heightening the subjective vividness of perceived emotional events, which in turn enhances memory vividness. In this paper we will review evidence for BANE, arguing that affect biased attention can modulate visual cortex activity in a manner distinct from – although at times overlapping and/or interacting with – the frontoparietal executive network.

We will first review literature on ABA, and will then discuss potential neural mechanisms underlying ABA, particularly biased competition, which facilitates the influence of frontoparietal networks on the visual cortices in selective attention. We will further review recent evidence that biased competition may underlie ABA as well. We will then look at the role of norepinephrine (NE) and the locus coeruleus (LC) of the brainstem in ABA and memory. NE is produced by LC neurons, which have widespread projections throughout the brain [11], and facilitates processing of salient events [12–14]. We will then review evidence about individual differences in ABA and memory, focusing on individual differences arising from a common variant of the *ADRA2b* gene coding for the alpha2b adrenoreceptor, which influences extracellular NE availability. Finally we will present the BANE model in detail based on the evidence previously discussed.

2. Terminology

Before we examine the literature, let us first clarify the key terms used in this paper. *Salience* is defined as the quality by which an aspect of the environment stands out relative to its surroundings due, perhaps, to its visual features (visual salience) or the goals of the perceiver. For example, something may be visually salient because it is high in contrast or brightly coloured or high in motion in comparison with its surroundings. Because salience is a somewhat circular term – some items catch our attention because they are salient, and are salient because their qualities catch our attention – we use the term in a manner that is descriptive rather than explanatory. As such, it can be a useful concept in that it allows us to examine the properties that determine salience in a given context. *Affective salience* is the tendency of an item to stand out relative to its neighbours due to an association between its semantic meaning and a history of emotional arousal [8]. *Affect-biased attention* (ABA) is attention biased towards stimuli that are affectively salient because they have a developmental history of pain and pleasure, approach and avoidance.

We have claimed that in affect-biased attention, motivational goals tune affective control settings, habitual 'mental sets' that are shaped by one's history of emotionally arousing experiences [8]. We suggest that, over time, affective control settings come to be applied reflexively. Thus, whereas we may be tuned to stimuli that are visually salient because evolution has tuned us to attend to moving or high contrast aspects of the environment, we may be similarly tuned to affectively salient stimuli because of our history of emotional experience with them.

Building on the modulation hypothesis of McGaugh, Cahill and colleagues [15,16], BANE proposes that ABA influences emotional enhancement of memory. According to the modulation hypothesis, the effects of arousal on initial memory formation, or *encoding*, interact with the influence of arousal on longer-term memory *consolidation* processes to bias memory for emotionally salient events. To *encode* an event is to process the relevant sensory information into a unified, coherent construct so that it may be remembered. *Consolidation* is divided into short- and long-term processes. The former is a set of molecular processes required for the creation and change of synaptic connections and occurs during the hours after the experience [17]. Long-term consolidation is the set of processes responsible for large-scale reorganization of neural memory systems [17].

3. Caveat

Previous research has uncovered two functionally independent attentional systems in the cortex: a dorsal-frontoparietal network involved in top-down selection of stimuli and responses which

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involves the intraparietal cortex and superior frontal cortex and a right-lateralized ventral-frontoparietal network sensitive to the bottom-up salience of stimuli and which is centred on the temporoparietal cortex and inferior frontal cortex [2]. BANE is a model of the ABA system. Though Corbetta and Shulman [2] state that the ventral system is responsible for detecting behaviourally relevant stimuli, we should note that the ABA system is distinct from the right ventral-frontoparietal attentional system because it is responsible for directing attention to stimuli with an individual history of reward and punishment. In contrast, Corbetta and Shulman's right ventral frontoparietal system orients attention to objectively visually salient, task relevant and unexpected stimuli (although some regions, such as lateral intraparietal cortex (LIP), may be key nodes in both affective salience and bottom-up salience systems).

4. Affective salience enhances visual perception and memory

There is an extensive body of literature on ABA and its neural correlates, including how ABA interacts with classically defined top-down and bottom-up attentional systems, and a full review is beyond the scope of this paper (for reviews see [18,19]). In this paper, following a brief overview of background research establishing prioritized processing of affective salience, and a review of our own work revealing emotional enhancement of perceptual and mnemonic vividness, we will focus on noradrenergic contributions to ABA as illustrated by select studies.

A large body of research has shown that affectively salient stimuli elicit enhanced behavioural and neural processing compared to more neutral stimuli. Emotional stimuli capture attention more easily when they are at the threshold of awareness [20] and when several stimuli are in competition for attention [21,22]. We are also more easily distracted by affectively salient stimuli when focusing on another task [23,24]. Finally, we generally have better memory for emotional than mundane events [25–29] (but see [30,31]).

At the neural level, affective salience has been strongly linked to increased activity in sensory cortices. Neuroimaging studies have shown that affectively salient images evoke greater visual cortex activation than mundane ones [32–36], an effect that is paralleled for affectively salient sounds in auditory cortex [37–39]. This effect is found for social stimuli as well as emotionally arousing scenes: Face-specific regions of the fusiform cortex have been found to show greater fMRI activation for fearful than neutral faces even when processing facial expression is not part of the task [40–42]. Such enhanced activation of fusiform cortex is also associated with better detection of emotional faces [43,44].

Affectively salient stimuli also evoke enhanced event-related potentials (ERPs) at both early and late latencies, suggesting both rapid and extended prioritization of salient aspects of the world [45,46]. Importantly, enhanced activity for affectively salient stimuli has been observed in very early ERP components which are also sensitive to classic 'top-down' attention. These include the C1 [47,48] a very early ERP generated by the striate cortex reflecting low-level visual features, and the P1 [49], a component primarily indexing extrastriate cortex activity [50]. Although there is still some controversy about the latency at which affective salient effects can be observed, these finding suggest that very early visual cortex activation is sensitive to predictions/expectations related to prior learning about affective salience.

One line of our own research has focused on enhanced perceptual encoding of affectively salient stimuli as a marker of affectively tuned attentional sets. An experimental paradigm that has been useful in indexing affective biases in attention is an emotional variant of the attentional blink (AB) paradigm. In classic AB studies, two target words are presented among a series of distractor stimuli

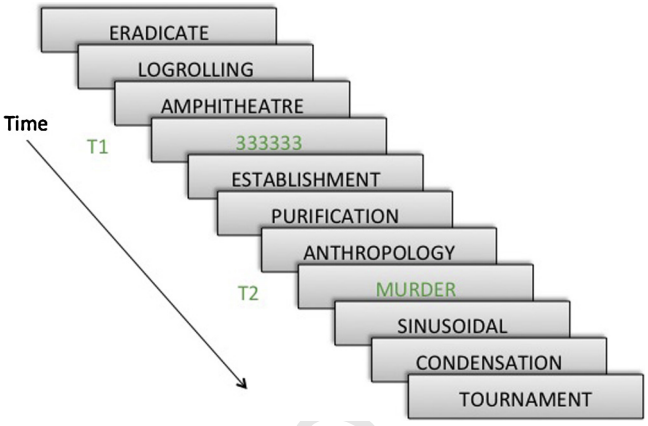

Fig. 1. Diagram of a dual-target rapid serial visual presentation (RSVP) task used to measure the attentional blink. Participants were instructed to ignore words appearing in black and to report the identity of the targets appearing in green. The time lag between the first (T1) and second (T2) target was varied. When T2 is presented within 500 ms of T1, the attentional blink typically occurs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(Fig. 1). The attentional 'blink' itself is a phenomenon where participants are typically unable to report a target stimulus when it is presented within ~500 ms of a previous target in a rapid stream of stimuli. According to one interpretation of the AB, the blink reflects a failure to switch attentional sets from those tuned to the category of the T1 stimulus to those tuned to the T2 stimulus if it appears too quickly after T1, resulting in impaired perceptual awareness [51]. Anderson [22] used a version of the AB paradigm to examine whether emotionally salient T2 stimuli are less subject to the attentional blink than neutral stimuli. The first experiment compared AB for negatively valenced high-arousal words (e.g. "rape"), negatively valenced low-arousal words (e.g. "hurt"), and neutral words (e.g. "rule"). Results showed that negatively valenced high-arousal words had a significantly smaller blink effect than negatively valenced low-arousal words, which themselves had a smaller AB effect than neutral words. Thus, emotionally salient and negatively valenced words were easier to detect than neutral words or, in other words, that there was an emotional "sparing" of the blink for such words. The second study showed that this effect applied to positively valenced target words as well, implying that what is important for detection of the stimuli is emotional arousal rather than valence. A further series of experiments ruled out potential confounds for the sparing of emotional words. In conclusion, these experiments revealed that when attentional resources are limited, emotionally salient stimuli are perceived more easily than neutral stimuli – a finding that may reflect more resilient attentional filters for affectively salient stimuli.

4.1. Affective salience enhances the subjective quality of perception and memory

Another line of our research has focused on enhanced subjective experience of perceptual and mnemonic vividness for affectively salient stimuli. While it was established that emotional events are typically (though not always) better remembered than mundane ones [52–54], it was not known whether emotional events are remembered more vividly because they are experienced as more vivid in the first place. To investigate whether emotional salience influences the subjective experience of perceptual vividness, we employed an emotional version of a classic magnitude estimation paradigm from psychophysics experiments of the 1950s [55,56]. In a classic magnitude estimation task, participants are presented with a stimulus (e.g. a light or a tone) and are asked to

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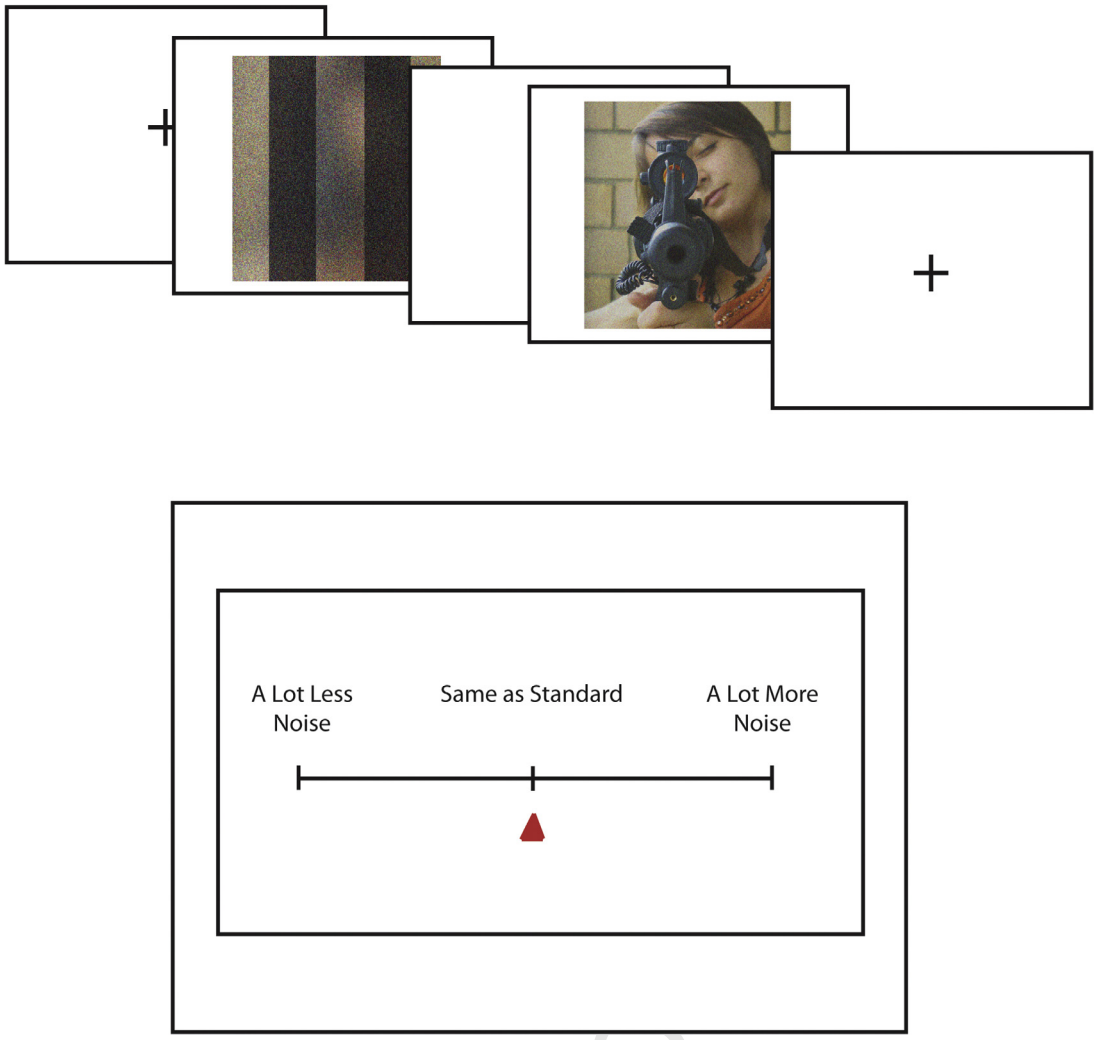

Fig. 2. Task design for Noise Estimation experiment. A standard, created by phase scrambling the target image, was overlaid with 15% noise. The standard was followed by the target image overlaid with 10%, 15%, or 20% noise. Following image offset, participants moved a cursor on a scale to indicated NE for the image relative to the standard from "a lot less noise" to "same as standard" to "a lot more noise."

compare the magnitude of the stimulus to a standard presented at a constant magnitude. In our adaptation, emotionally salient and neutral images, which were equated for contrast and luminance, were overlaid with one of three levels of Gaussian visual noise and standards were created for each image by scrambling the image so its contents were not recognizable and overlaying a standard level of noise (Fig. 2). Participants were asked to judge the proportion of noisiness of each image relative to a standard [57]. This design allowed us to look at the subjective vividness of affectively salient relative to neutral images measured as the signal of the underlying image relative to the overlaid noise. Results showed that participants were very accurate in estimating objective levels of noise. Crucially, both positive and negative arousing images were perceived as less noisy, or more perceptually vivid, than neutral images. Even after controlling for the objective characteristics of each image, participants still rated positive and negative images as containing lower levels of noise, suggesting that affectively salient images are subjectively experienced as more vivid than mundane ones. Moreover, when we created a direct measure of perceptual vividness by calculating the inverse of the noise estimation ratings (NE^{-1}, a measure of how clearly or vividly the image signal underneath the noise was perceived), we found that, image by image, perceptual vividness predicted ratings of emotional salience. This relationship remained after controlling for computational measures of objective visual salience, such as colour, image complexity, and a composite measure of visual salience [58,59], indicating that affective and objective salience make dissociable contributions to perceived vividness. We refer to this influence of emotional salience on perceptual vividness as emotionally enhanced vividness (EEV).

Several control studies were performed to rule out confounding explanations. To eliminate the possibility that noise ratings were driven by differential deployment of overt attention, we used eye tracking to control for differences in looking patterns. We found that emotional salience did predict patterns of overt attention, with more fixations for affectively salient images; however, emotional salience predicted perceptual vividness after controlling for number of fixations, and fixations did not statistically mediate emotional salience. Thus, deployment of overt attention did not account for the influence of affective salience on noise estimation ratings. The main effect of affective salience on noise estimation ratings was sustained in experiments using grayscale images, images with lower levels of noise and a single presentation of each image, indicating that greater perceived vividness for affectively salient images is not affected by image colour or differential effects arising from repetition of emotional images; rather, it is due to the emotional content of the images themselves (Fig. 3).

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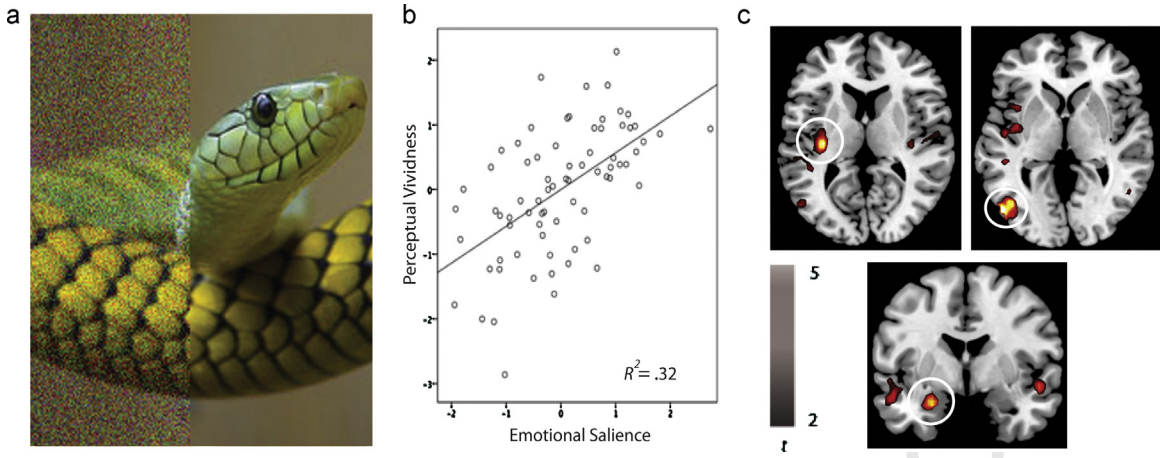

Fig. 3. Noise estimation results. Arousing images were psychophysically scaled to contain less noise, i.e. were perceived as more perceptually vivid, despite equal levels of objective noise. The right side of the image illustrates a 15% decrement in noise level from the left. (b) Image by image, emotional salience predicted perceptual vividness after controlling for objective salience related to low-level featural characteristics of the image. (c) fMRI activation parametrically modulated by emotionally enhanced vividness in left insula (left), LOC (right), and amygdala (bottom).

To see if the behavioural phenomenon of EEV reflected relatively rapid perceptual processes rather than later conceptual evaluative processes, we further examined the time course of ERP activity following presentation of the images. We focused on the postsensory P2, an early- to mid-latency positive peak measured at occipital electrodes and implicated in object discrimination and enhanced attention to affectively salient images [60,61]. We found that P2 amplitude was greatest for the least noisy images and importantly, that there was an effect of affective salience, with larger P2 amplitudes for negative and positive versus neutral images. That P2 amplitudes reflected objective perceptual vividness and subjective affective salience suggests that EEV involves relatively rapid perceptual processing and that emotionally salient images are perceived in the manner of objectively clearer images. This corresponds with the behavioural data indicating that participants perceive emotional images more vividly.

Finally, we employed fMRI to examine potential modulatory sources of EEV, to determine whether emotionally enhanced perception reflected enhanced visual cortex activation, and to examine the relation between amygdala and visual cortex activation in relation to EEV. We found that activations in the left amygdala as well as left lateral occipital cortex (LOC), which plays a role in object discrimination [62–64], and a region of left dorsal posterior insula thought to function as primary interoceptive cortex [65,66], modulated NE^{-1} for emotional images. Further analyses of co-activation (PPI) found correlated activity between amygdala and visual cortex for affectively salient but not for neutral images. Statistically, amygdala activation mediated the influence of LOC and posterior insula on EEV. These findings can be interpreted as reflecting the role of the amygdala in tagging affective salience, which in turn may enhance both the experience of seeing (reflected in LOC activation) and gut feeling (reflected by posterior insula activation). Finally, activation in parietal and frontal regions which function as hubs in executive attentional networks was negatively correlated with NE^{-1} suggesting that in this task there was a trade-off between executive attentional activity and amygdala-mediated modulation of ABA.

In short, we found that emotional salience modulates the subjective visual experience of seeing an image. Moreover, our results suggest that emotional salience modulates object-based attention, making a subjectively salient object appear more objectively salient. In this case, the amygdala, a hub of the anterior affective system, accounted for enhanced visual cortex activation linked to EEV in a manner that is consistent with the hypothesis that anterior affective networks modulate visual cortex activation similarly to, but dissociable from, frontoparietal networks. This result converges with electrophysiological findings that both affective salience [47] and state [67,68] modulate visual processing independently but similarly to executive top-down attention. Moreover, there was a tradeoff between activation in anterior affective networks and frontoparietal networks associated with top-down executive attention. Thus, in terms of executive attention, our results indicate that participants were not just attending more to affectively salient images – they were attending differently.

A second line of interest concerned whether EEV at the time of encoding was related to memory vividness. Previous studies have demonstrated that affectively salient images are typically better recollected than neutral ones (e.g. [53] but see [69]). More specifically, participants show greater memory for the goal-related and emotionally salient aspects of images [70,71]. These effects may be due to differences at the time of perceptual processing between emotionally salient and neutral images. Emotional events are encoded more easily [22,32,44,72] and enhanced memory of emotional images is associated with increased amygdala activation [73,74] and high-level visual cortex activation [75,76] at the time of encoding.

To test whether perceptual vividness at the time of encoding predicts memory vividness we employed two memory tasks: a cued recall task and a recognition memory task [57]. The cued recall study was performed 45 min after the completion of the noise estimation task. Participants were given one-word cues that corresponded to one of the pictures seen in the noise estimation task and asked to provide a written description of the picture in as much detail as possible. Descriptions were rated for number of details recalled from correctly remembered images, including thoughts and emotions associated with the image. Participants recalled more details about affectively salient than neutral images, and inverse noise estimation was correlated with number of details recalled as well as associated thoughts and emotions. Thus, although participants were not more likely to recall an emotional image than a neutral one, it appears that the vividness with which we view emotionally salient images modulates memory vividness as well.

In the recognition memory task, participants returned one week after performing the noise estimation task. They were shown all of the images from the original task as well as unfamiliar images matched for emotional salience, scene content and objective image characteristics. Participants were asked to rate each image as old or new and to rate the vividness of the memory. Again, NE^{-1}

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significantly predicted memory vividness after controlling for objective salience. Thus EEV contributes to some of the vividness of emotional memory, though it is likely that post encoding consolidation processes play a further role in memory vividness as well [77,78]. fMRI findings further revealed that the same regions of amygdala and LOC that modulated EEV modulated subsequent ratings of recognition memory vividness [79]; however memory vividness was uniquely modulated by additional activity in hippocampal and parahippocampal regions. These findings suggest shared neural substrates for the influence of emotional salience on perceptual and mnemonic vividness, with amygdala and visual cortex activation at encoding contributing to the experience of both perception and subsequent memory. However, memory vividness is also predicted by unique patterns of neural activity.

In summary, the noise estimation studies showed that affective salience contributes not only to ease of detecting an image but also to the quality of one's visual experience. Thus, not only do emotional images grab attention more easily, but we also see them more clearly. Affective salience is a distinct source of perceptual vividness – contributing to an image's vividness in a manner additional to the image's objective visual characteristics. The enhanced perceptual vividness of emotional images is due to rapid perceptual processing rather than later conceptual processing. Furthermore, the enhanced processing received by affectively salient images at the time of perception trickles down to impact memory processes. The vividness of an image during perception and the emotional salience of an image both contribute to the vividness of an image in memory.

Thus, a large body of research has established that affectively salient stimuli enjoy prioritized attention and perceptual encoding, and elicit rapid and prioritized sensory enhancement. Our own findings have established that they also enhance the vividness of subjective perceptual experience, which in turn predicts memory vividness. Current research questions involve specifying in greater detail which aspects of an emotional stimulus influence attention, neural mechanisms underlying prioritization of affective stimuli and how these may differ between individuals, and how affective biases are acquired through experience.

5. Potential neural pathways and mechanisms underlying affect-biased attention

5.1. Neuroanatomical pathways mediating ABA

Previous research has established that feedback connections between the amygdala and visual areas play an important role in mediating enhancement of visual cortex activity for affectively salient stimuli [32,80–82]. There are bidirectional connections between the amygdala and early visual areas in the striate and extrastriate cortices [83,84]. Moreover, patients with amygdala lesions and an intact visual cortex lack the typically found enhanced neural response to affectively salient stimuli [80]. fMRI research using sophisticated analysis approaches such as dynamic causal modelling have provided functional evidence for amygdala modulation of visual cortex when participants view affectively salient stimuli [85]. Yet although much research has focused on amygdala pathways, critics of an amygdalo-centric approach suggest that the amygdala is not the sole hub of affective salience detection but is one hub among several participating in parallel cascades of activations in networks mediating the influence of affectively salient stimuli on sensory processing [86,87]. Other regions that serve as hubs in an "anterior affective system", such as the orbitofrontal cortex (OFC) are also potential modulators [10,44].

Pessoa and Adolphs further argue that visual information is processed by multiple parallel channels, and that the cortex plays a large part in filtering visual information [87]. They propose that a key region for ABA is the pulvinar – especially its medial nucleus. The pulvinar receives visual input from the superior colliculus, retina and striate and extrastriate visual cortices, and its medial nucleus may be responsible for determining the behavioural relevance of a stimulus due to its connection with amygdala as well as multiple cortical regions such as the OFC, cingulate cortex, insula and parietal regions [87]. These authors suggest that the amygdala is a "convergence zone" for information relevant to object processing. The importance of the amygdala for ABA comes from its broad connectivity to other subcortical regions and to the cortex. The amygdala not only receives visual information from higher-order visual association cortices in the anterior temporal lobe [84], it also has many connections to the cortex including medial, orbital and lateral regions of the prefrontal cortex [88]. Thus, the amygdala impacts visual processing through both of these (direct and indirect) connections to the visual cortex. Another recent model emphasizes the role of NE in amygdala entrainment of widespread network co-activation in response to salient events [89]. In this paper we further emphasize the role of the LC/NE system in modulating specific neuronal mechanisms of selective attention in visual cortex in interaction with the anterior affective system.

5.2. Biased competition as a mechanism of ABA

Neural mechanisms underlying modulation of the visual cortex by regions tagging affective salience are as yet underspecified; however, a potential mechanism is biased-competition, since this is a well-mapped mechanism underlying executive influences on visual attention. In biased-competition models of visual attention, top-down 'attentional control settings' bias attention to features of the environment that are relevant to one's goals. Biased competition has been characterized in terms of three principles: competition, i.e. the brain systems that represent visual information are competitive and a gain in processing for one stimulus comes at the cost of inhibition of activation tuned to other stimuli; control, i.e. there are mechanisms to allocate increased weight to a certain stimulus, and integration, i.e. when competition is resolved in favour of a certain stimulus in one system this stimulus will gain dominance in other systems as well [90].

Beck and Kastner have reviewed evidence that stimuli compete for representation throughout the visual cortex and that competition can be biased for spatial location as well as object features [91]. For executive attentional biasing, frontoparietal networks modulate visual cortex activation so that activity is enhanced in regions responsible for task-relevant stimuli and activation is suppressed in regions responsible for competing stimuli. For instance single cell recordings of monkey visual cortex have shown that when a monkey attends to one of two competing stimuli within a neuron's receptive field (RF), responses to the pair of stimuli in areas V2, V4 and MT are weighted to the attended stimuli, i.e. they are similar to response given to the attended stimulus presented alone [92–94]. Such findings are supported by fMRI studies on humans, which show increased activation in V4 and TEO in situations of competition [95]. Thus in directing their attention, subjects were able to enhance processing of one stimulus and suppress processing of competing stimuli. Beck and Kastner [90] review evidence of executive modulation via the frontoparietal cortex based on spatial location and stimulus features, though they note that top-down modulation is also possible based on memory or emotional mechanisms.

We posit that activity in hubs of the anterior affective system (amygdala, orbitofrontal/ventromedial cortices) as well as the locus coeruleus similarly modulates visual cortex activity based on the affective salience of the stimulus. This hypothesis is supported

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by recent findings in non-human primates that visual cortex activation is modulated by stimulus reward value in the same way that it is modulated by executive attention [96,97]. The BANE model suggests that findings related to reward value may extend to overall stimulus salience, and further propose that connections with key salience hubs modulate visual cortex activation for emotionally relevant stimuli while suppressing activation for competing stimuli.

The notion of affect-biased competition is still somewhat speculative, but recent work provides preliminary evidence of biased competition in visual cortex based on the affective salience of stimuli. EEG evidence of rapid primary visual cortex modulation by facial expressions is consistent with findings of biased competition modulated by executive attention [47]. A study taking advantage of high temporal and spatial resolution of magnetic encephalography (MEG) [10] further employed dynamic causal modelling to predict MEG differentiation of affectively salient from neutral stimuli and found evidence for a top-down model that included both cortical and subcortical pathways allowing for rapid top-down modulation of visual processing by the anterior affective system. The orbitofrontal/ventromedial prefrontal cortices play a key role in this model. Convergent research further suggest that the anterior affective system plays a key role in maintaining affective control settings by maintaining templates for salient items based on past experience that function as a 'predictive set' that enhances context-dependent visual processing of salient stimuli [98]. Moreover, OFC/VMPFc activations based on implicitly learned stimulus associations between facial features and personality traits have been found to predict subsequent inferotemporal activations [99], again suggesting a key role for ventral prefrontal cortex in maintaining pre-existing templates linked to stimulus salience – or what we have called affective control settings – that modulate visual cortex activity.

In an innovative study specifically examining patterns of affect-biased competition in visual cortex, Wieser et al. [100] employed steady state visually evoked potentials (ssVEPs) to examine patterns of ABA related to trait anxiety. The ssVEP is an oscillatory EEG response to flickering stimuli whose oscillatory frequency matches that of the driving stimulus. ssVEPs are useful indices of attentional allocation, as ssVEP amplitude is linked to allocation of attention resources to the driving stimulus, and it can be modulated by both 'bottom-up' sensory processing and 'top-down' modulation of sensory activity. In this study participants viewed Gabor patches (gratings) which were superimposed over pictures of angry, neutral and happy faces [100]. Gabor patches and faces each oscillated at a different frequency so that ssVEPs for each could be distinguished. Participants were asked to detect changes in the direction of the grating of the Gabor patches, a task which required directing attention away from the underlying face stimuli. Participants were selected for either high or low social anxiety (HSA and LSA) based on a preliminary questionnaire. The study found that ssVEP amplitudes for Gabor patches were attenuated by angry faces relative to neutral and happy faces for HSA individuals and by happy faces relative to angry and neutral faces for LSA individuals. Furthermore, the highest cost for processing of Gabor patches occurred when the underlying face was angry for HSA individuals and happy for LSA individuals. This evidence suggests that affective salience can operate according to mechanisms of biased competition similar to those that have been well mapped for visual attention, since competition from the face stimuli resulted in diminished resource allocation to the Gabor patch. Moreover, this study is an elegant demonstration that individuals may differ in patterns of ABA to differently valenced stimuli. Thus, preliminary research suggests that, at the level of neuronal populations, processes of biased competition, potentially tuned via Hebbian learning, may subserve ABA.

5.3. Acquisition of affective biases

The question of the learning processes by which such biases are acquired and sensory systems are tuned is essentially a developmental question, as many things become salient over repeated experience in infancy, childhood, and beyond [8]. On a shorter time scale, such questions can be tractably addressed in the laboratory in sessions where salience is learned through conditioning. We can think about the process of conditioning in terms of the creation and tuning of affective control settings which track the stimuli that have proved a significant source of punishment and reward. Human conditioning studies have revealed that associative learning mechanisms play a key role in acquisition of ABA. Convergent research suggests that learning history continuously retunes neuronal sensitivity to the features of salient stimuli, and that this effect can be observed in early stages of visual processing. This may occur both through re-entrant activation of visual cortex from other regions in affective salience networks, including the amygdala, OFC and LC, as well as increased local neuronal sensitivity in early visual cortex – processes that may operate at different time scales (for thorough review see [86]). Again, ssVEPs have been used effectively to index enhancement of neuronal population of responses in specific learning contexts. Recent evidence suggests that sensory tuning to the salience of conditioned stimuli is mediated by implicitly acquired Hebbian mechanisms of temporally coordinated neuronal activity, rather than explicit expectations, again suggesting some independence from executive modulation of attention [101]. Along similar lines, future research can examine the role of other learning processes, such as vicarious learning, in the acquisition of ABA. Developmental research can address the question of whether there are sensitive time windows in early life during which affective associations may be more easily acquired or changed.

6. The role of norepinephrine in affect-biased attention and memory

6.1. The role of norepinephrine in ABA and memory

A further question concerns neuromodulatory influences on neuronal activity linked to ABA. A comprehensive body of research on LC–NE activity indicates a potentially key role for this neurochemical system in driving aspects of ABA. Non-human animal studies have found that motivationally relevant stimuli elicit LC response [for review see [14,13], and LC–NE activity has been shown to directly modulate visual cortex activation [102]. Moreover, NE activity in the amygdala is important for recruiting and coordinating the brain regions that direct attention to emotionally salient events [103,104]. Let us elaborate further on this evidence.

The LC is structurally well positioned to facilitate ABA. It receives inputs from the central nucleus of the amygdala [12] as well as ventral prefrontal regions important for stimulus evaluation and decision-making (for review see [105]) facilitating tuning of LC activity to what is motivationally relevant. The LC also projects to regions of the thalamus and visual cortex [106], allowing for rapid tuning of sensory responses.

A wide body of evidence suggests that LC neurons facilitate responses to the behavioural and biological relevance of a stimulus [13], regardless of stimulus valence [12], while suppressing those to less relevant stimuli. Arousing stimuli elicit phasic LC activation resulting in release of NE [107–110]. Released NE may tune target neurons by improving their signal-to-noise ratio, inhibiting responses to neighbouring frequencies while sparing response to the best frequency [111]. It is also important for sensory gating, allowing silent neurons to become responsive to relevant stimuli [13]. In non-human animal studies, increased extracellular NE has

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been shown to decrease spontaneous firing while leaving intact evoked response to sensory stimulation in somatosensory, olfactory and auditory pathways [112–114]. For example, NE applied to auditory neurons in awake monkeys, who were presented with a series of conspecific vocalizations, resulted in a decrease in spontaneous activity but a spared response to the auditory stimulus [115]. NE also improves spike timing and rhythmicity in somatosensory and olfactory neurons, suggesting that it provides a basis for encoding and perceptual accuracy [116–120]. All of these studies reinforce the view that the LC–NE system is sensitive to the behavioural relevance of stimuli and influences perceptual responses.

LC activity is also important in associative learning of *what* is salient. LC neurons fire in response to direct reward and punishment, and subsequently to any stimuli associated with the salient event [13]. NE modulation of long-term changes in synaptic strength and gene transcription allow this system to guide behaviour based on stimulus salience within a given context [12].

Thus, the LC–NE system has the functional and anatomical connections needed to facilitate ABA. LC activity is driven by affectively salient stimuli and is capable of modulating visual cortex activation. Based on this evidence, BANE posits LC–NE activity as an important driving force behind ABA. One hypothesis that emerges from this model is that, in humans, LC–NE activity modulates biased competition in the visual cortex, biasing processing of affectively salient stimuli (Fig. 5).

According to the modulation hypothesis [121] the influence of NE linked to arousal at encoding interacts with the influence of NE on more sustained consolidation processes, resulting in more vivid memories for emotionally salient stimuli. In this regard, non-human animal studies have implicated NE in memory consolidation and the formation of long-term memories [122]. The amygdaloid complex influences memory consolidation processes in the hippocampus, caudate nucleus and other regions. It is also a key target site for the LC–NE system, possessing many NE receptors [106]. Cahill and McGaugh [16] provide evidence that NE, stress hormones, and the amygdala are part of an endogenous memory modulating system, which influences recall based on the emotional meaning of a stimulus. Noradrenergic activity is implicated in memory modulation, since infusion of adrenergic antagonists into the amygdala eliminates memory modulation effects [123]. Non-human animal studies provide further evidence that modulation of stress hormones influencing consolidation are mediated by beta-adrenergic activity in the amygdala [16]. For instance, lesions of the amygdala and stria terminalis (a major amygdala output path) block the memory-enhancing effects of adrenaline, glucocorticoids, and drugs that affect the opiate and gabaergic systems [124,125].

The basolateral amygdala (BLA) plays a key role modulating the effects of other neurotransmitters and stress-released hormones on memory consolidation [104,16]. Selective post-training inactivation of the BLA induces retrograde amnesia [126] and lesions of the BLA block stress-hormone induced memory enhancement [125]. BLA activation can also modulate synaptic plasticity in other brain regions key for memory consolidation [15]. Moreover, the role of BLA in modulation of emotional memory consolidation has been found to be in part mediated by alpha(2)-adrenoreceptors [127]. In humans, NE activity has been found to play a role in reconfiguring brain network activity both during and subsequent to exposure to a stressor, suggesting that noradrenergic modulation of encoding and memory occurs via reorganization of large-scale co-activation between regions sensitive to affective salience [85,89]. Thus, not only is NE activity key for ABA for salient stimuli within any given context, but noradrenergic activity in the amygdala at encoding may interact with NE activity implicated in memory consolidation processes, ensuring that events tagged as most salient are not only more vividly perceived but better remembered. The BANE model further hypothesizes that noradrenergic activity modulates behavioural and neural correlates of emotionally enhanced perceptual and mnemonic vividness found in our previous studies (Fig. 5).

7. Individual differences in NE influence on affect-biased attention and memory

7.1. Individual differences in ABA

Individuals differ both in the capacity for ABA and memory and in the relative salience of different categories of stimulus – in particular stimulus valence. In the study of individual differences, attentional biases are typically not measured by indices of ABA as we have defined it in terms of affectively biased attentional sets that pre-tune visual attention prior to encountering stimuli. Rather, biases are measured primarily by indices of difficulty in disengaging spatial attention from the location of affectively salient stimuli after they have been presented [128] – as a kind of attentional "stickiness," or failure of executive control processes.

Behavioural and ERP studies of attentional biases indicate that individuals with temperamental anxiety show greater attentional stickiness to threatening stimuli than non-anxious individuals [129–131]. Attentional bias for threatening stimuli is also associated with lower threshold for amygdala activation to threat [130,132]. Recent reviews have summarized current research on the relation between threat-bias and anxiety [133], including an examination of the time course of responses to threat-related stimuli in attentional bias [134], as well as biases associated with personality measures [135]. In the other direction, biases towards positive stimuli have been linked to extraversion [136]. In addition to being linked with traits, attentional biases can be learned through conditioning and are associated with trauma [137–139]. For instance, individuals with PTSD showed increased perceptual and amygdala sensitivity to stimuli associated with the trauma [140,141].

Individual differences in attentional biases have been observed early in development, and can influence behavioural outcomes. Attentional stickiness to the location of threatening stimuli in children with temperamental inhibition has been found to predict whether they would show social withdrawal behaviour at age five [142]. Such biases can be reinforced by experience over the course of development. For instance, children with a short version of the *5HTTLPR* (serotonin-transporter-linked polymorphic region) in *SLC6A4*, the serotonin transporter gene, which is associated with temperamental fearfulness and amygdala sensitivity to threat [143,144], are more likely to have a family environment that emphasizes threat stimuli, thus exacerbating the underlying trait [145,146]. On the other hand, sensitivity to negative stimuli can be attenuated by the ability to shift attention. Children high in negative affect and effortful control – a trait which includes the ability to volitionally focus and shift attention – do not show the attentional bias to threat displayed by children with negative affect and low effortful control [147]. Clinical research has explored the possibility of improving anxiety symptoms by training attention. Attentional Bias Modification (ABM) uses a cueing task to train participants' attentional biases by placing targets more frequently at the location of neutral than negative stimuli. ABM has diminished attentional bias towards negatively valenced stimuli and reduced anxiety scores in clinical and non-clinical populations [148] as well as children [149]. That training attentional biasing has an effect on anxiety scores suggests that attentional biases may be partially responsible for producing anxiety symptoms. However, it should be noted that ABM research is in its preliminary stages, effect sizes

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are small, and replication studies are needed to confirm the effect of ABM on subsequent outcomes and emotional responses [150].

7.2. Genetic influences on ABA

Now that we have reviewed the role of NE in ABA and memory, we turn to genetic variations linked to NE availability that may partly underlie these individual differences. A deletion variant of the *ADRA2b* gene coding the inhibitory noradrenergic α_{2B} receptor is missing 9 base pairs, which impairs receptor regulation by G protein-coupled receptor kinase leading to a loss of receptor desensitization [151]. As inhibitory activity is itself inhibited, carrying the deletion variant results in higher levels of extracellular NE availability.

A recent seminal study linked the *ADRA2b* deletion variant, which was previously associated with vasoconstriction, to emotional memory [152]. In this study, participants viewed neutral and affectively salient images and performed a free recall task shortly afterward. Whereas all participants showed greater recall for the arousing images, *ADRA2b* deletion carriers showed a significantly greater emotional memory enhancement in the laboratory. The same study found that survivors of Rwandan genocide who carried the deletion variant were more vulnerable to intrusive memories characteristic of post-traumatic stress disorder (PTSD).

A further question concerns whether the *ADRA2b* influences emotional memory by enhancing encoding, consolidation, or both. The hypothesis that *ADRA2b* plays a role in perception is supported by evidence that deletion carriers show increased amygdala activation to negative arousing images relative to non-carriers [153]. Furthermore, in a study using the emotional attentional blink, participants given reboxetine (a selective NE reuptake inhibitor which increases the amount of available NE) showed a smaller blink for emotional stimuli – a greater emotional sparing – than participants given a placebo [154]. In a recent study, we used an emotional attentional blink paradigm to directly examine the influence of *ADRA2b* on affective biases in perception in a large sample of healthy young adults [155]. The study employed the AB task to investigate differences in ABA for positive, negative, and neutral words between deletion variant carriers and non-carriers while controlling for sex as well as individual differences in trait neuroticism, working memory, and other genes potentially implicated in attentional biases. Whereas all participants showed the classic emotional sparing for positive and negative over neutral words, deletion carriers showed a further sparing for negative over positive words (Fig. 4). Thus, this study showed that *ADRA2b* affects visual encoding, suggesting that NE has an important role in ABA.

LC activity has two phases, ongoing oscillatory tonic activity and stimulus-locked phasic activity [156]. The *ADRA2b* deletion variant influences activity at NE α-receptors, leading to their desensitization and putative greater NE availability [151]. Whereas NE β-receptor activity is linked with the influence of phasic release of NE on the attention blink task [157], the emotional sparing effect in the attentional blink task is associated with a tonic increase in synaptic NE [154]. Our finding that deletion carriers showed a greater emotional sparing in the AB task suggests that α-receptor activity may be the mechanism behind emotional sparing, and thus ABA, via increased tonic levels of NE. This interpretation is consistent with a study by Cousijn et al. [158]. In this study, participants viewed either a violent movie (stress condition) or a neutral movie (non-stress condition) and then saw sets of dynamic fearful and happy faces. Amygdala activation was measured during the movie and face stimuli. Non-carriers showed an increased amygdala response to emotional faces only in the non-stress condition, whereas deletion carriers had such a response in both the stress and non-stress conditions. As the authors suggest, while non-deletion carriers seemed to be hitting a ceiling in their amygdala response

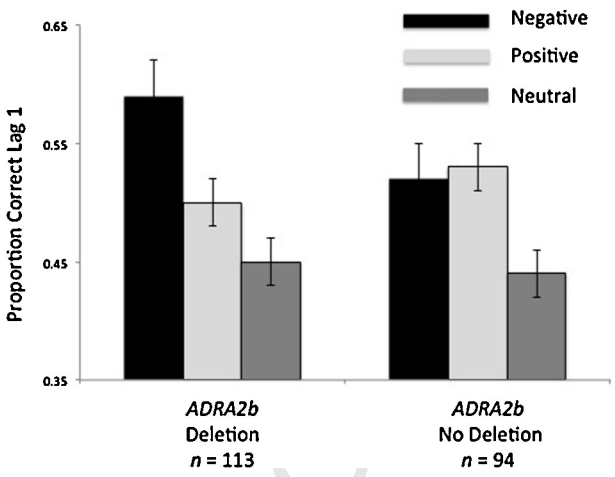

Fig. 4. ADRA2b influence on the attentional blink as measured by accuracy at Lag 1, when the second target word directly follows the first and the attentional blink effect is greatest. Whereas both ADRA2b deletion carriers and non-carriers showed the typical 'emotional sparing,' or greater accuracy for affectively salient words, only deletion carriers showed an additional sparing over non-carriers, suggesting biased perceptual encoding of negative stimuli is associated with higher levels of extracellular NE.

to emotional stimuli, deletion carriers possess a further range of activation. We may speculate that, as deletion carriers have less activity at inhibitory alpha2b receptors, a sustained mood induction may increase tonic NE levels in carriers only, whereas it may inhibit them in non-carriers. The greater tonic NE in deletion carriers would then interact with phasic activity to increase amygdala activation in non-carriers.

In our study, *ADRA2b* deletion carriers showed greater ABA towards negative stimuli, consistent with previous findings that carriers show enhanced amygdala activation during perception of negative stimuli [153]. An outstanding question concerns whether deletion carriers show enhanced ABA for negative stimuli because they find negative stimuli to be more salient than non-carriers, or whether they show enhanced NE-driven activity for stimuli that are generally salient to carriers and non-carriers alike (after controlling for key trait differences), since young adults in this age group show an overall bias for negative stimuli (e.g. [159]).

The enhanced perceptual processing of emotional events displayed by deletion carriers may result in enhanced emotional memory via NE α-receptors in the amygdala. A further study examined whether subjective ratings of affective experience at encoding predicted the accuracy and confidence of subsequent memory [160]. The same group of healthy young adults rated positive, negative, and neutral scenes for level of emotional arousal and subsequently performed a surprise recognition memory task one week later. Results showed that, for negative images, subjective ratings of arousal at encoding predicted better memory accuracy one week later in deletion carriers. In contrast, non-carriers showed poorer memory when they rated images as higher in arousal. *ADRA2b* deletion carriers also demonstrated a stronger overall relationship between the subjective arousal level of each image at encoding and memory confidence for the same image one week later [160]. According to the modulation hypothesis, phasic arousal related to perceptual vividness interacts with more tonic arousal extending beyond initial encoding to further enhance memory consolidation [121]. Our finding that carriers of the deletion variant showed a greater association between arousal at encoding and memory for emotionally salient images suggests that, for these individuals, it is precisely this NE-mediated relationship between encoding and post-encoding processes that is enhanced – at least for moderately arousing events [see also [122]]. Of course, noradrenergic

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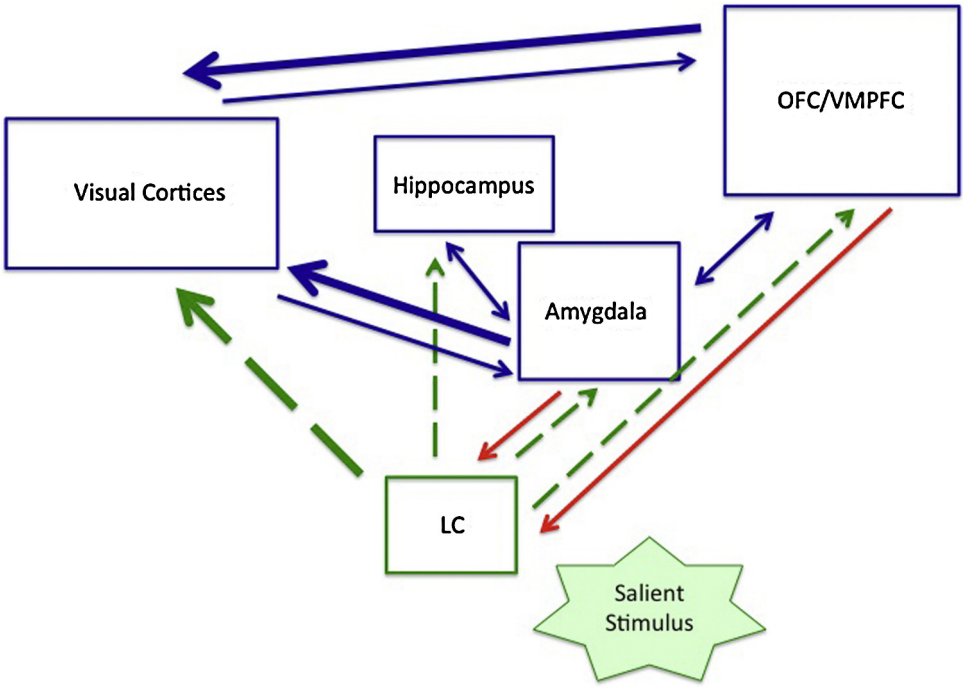

Fig. 5. Key pathways emphasized by BANE model: Green dashed lines indicate NE pathways. Red lines indicate projections to the LC. Thicker lines indicate direct modulation of visual cortex activity in affect-biased attention. NE activity is implicated in both stimulus encoding and selective attention [13]. A salient stimulus activates LC neurons, which project widely to cortical and subcortical regions. LC neurons are highly sensitive to previously acquired associations between a stimulus and punishment or reward. Q10 Descending influences from amygdala (central nucleus) and ventral prefrontal cortices Aston-Jones et al., 2007) provide information about contextually determine relevance, which can then modulate the pattern of LC firing accordingly. Activity from LC can modulate activity in visual cortex directly, facilitating gating and tuning of neuronal activity Q11 and enhancing perceptual acuity directly as well as via the amygdala and prefrontal cortices. The amygdala receives contextual information from the hippocampus as well as prefrontal regions and in turn modulates hippocampus activity related to memory encoding and consolidation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

influences on perception, encoding, and memory do not work in isolation, but interact with the influence of other neuromodulators [13,14]. Although we did not find any interactions with genes modulating serotonin or dopamine, the influence of NE at adrenoceptors found in terminals of serotonergic and dopaminergic neurons [14] may also play a role in the influence of *ADRA2b* on encoding and memory. Moreover, other neurochemicals may play a role in different aspects of attentional biases. For example, whereas NE may modulate activity in brain regions associated with object-based aspects of affective salience, serotonin may influence activity in region sensitive to spatial attention/contextual aspects of affective salience linked to attentional stickiness.

Future fMRI research can use *ADRA2b* groupings to examine the role of NE in neural and behavioural markers of emotionally enhanced perceptual vividness and its relation to memory vividness, on post-encoding processes in humans as well as potential gene-gene interactions (epistasis) and interactions with life experience.

8. Summary

The BANE model's core claim is that ABA is partly driven by LC–NE processes, which interact with activity in hubs of anterior affective system key for tagging affective salience and modulating activity in visual cortices. BANE provides a unified explanation for multiple streams of data related to ABA. Building on a large body of evidence indicating that emotional stimuli elicit enhanced visual processing compared to neutral stimuli, convergent evidence points to the amygdala and OFC as among the regions that are important for modulation of visual cortex in ABA. Pharmacological and non-human animal studies have revealed that affective salience related activity of this network is partly driven by LC–NE activity. A body of evidence indicates LC activation is implicated in tuning and gating of perceptual responses to salient stimuli, allowing for enhanced responses to what is already salient as well as learning of new associations. Thus, NE activity in the amygdala may play an important role for recruiting visual cortex activation associated with ABA (Fig. 5).

The importance of NE in ABA and memory is supported by genetics studies on *ADRA2b*, a polymorphism that affects levels of extracellular NE. *ADRA2b* deletion carriers are more sensitive to emotionally salient stimuli. They show greater ABA for negative stimuli, show a stronger relation between subjective arousal and memory, experience greater emotional enhancement of memory, and are more likely to suffer from intrusive traumatic memories. However, it should be noted that is possible that higher levels of tonic NE availability associated with the deletion variant increase responsiveness to salient stimuli in general, and not just those that are affectively significant. It will be important to investigate whether deletion carriers are more sensitive to low-level visual features than non-carriers and control for any such differences when investigating the influence of *ADRA2b* in ABA. It is also important to note that genetics studies reveal only a correlational relationship between NE activity and ABA. Further pharmacological studies of NE demonstrating a causal role for NE systems in human ABA would substantially strengthen the model.

The BANE model is similar to – and substantially overlaps with – another recent model of ABA, the MAGiC model [18]. According to the MAGiC model, emotional stimuli gain enhanced perceptual processing via multiple amplification mechanisms operating in parallel (and not via a single top-down modulatory source). The MAGiC model emphasizes the key causal role the amygdala plays in adaptive gain processes subserving ABA, and the relative independence of the amygdala-centred affective attention system. Thus, it focuses

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on the degree to which amygdala-centred systems can process affectively salient stimuli even when they are task-irrelevant [161] or when emotional information is presented outside the focus of frontoparietal attention [80,162,163]. Like MAGiC, the BANE model proposes that affectively salient stimuli bias perception through a ventral attentional system – although according to BANE these do not necessarily operate independently from frontoparietal attention (for a similar perspective see [164]). The BANE model further emphasizes the additional role of the LC–NE system.

9. Future directions

The BANE model makes a number of predictions that can be tested by future research. First, we predict that NE availability modulates individual differences in EEV, and that *ADRA2b* deletion carriers will show enhanced EEV supported by enhanced amygdala/ventromedial activation, which will in turn predict subsequent memory vividness. Second, we predict that NE availability influences electrophysiological correlates of biased competition underlying ABA, and that *ADRA2b* deletion carriers will show greater evidence of biased competition for arousing stimuli than non-carriers. Third, future research can use the *ADRA2b* genotype to investigate noradrenergic contributions to post-encoding processes associated with affectively enhanced memory. Fourth, the BANE model can be integrated with computational models of influence of affective salience on perceptual expectations that guide attention according to context [98,165,166]. Finally, pharmacological interventions can further probe causal effects of NE availability on ABA.

A longer term research programme can involve investigation of the role of NE in learning processes by which ABA develops over the lifespan, and the influence of both genotype and life experience in both normal and pathological patterns of ABA, extending salience-based models of predictive coding to address ABA in a developmental context. Understanding the interaction between genotype and epigenetic changes due to specific types of experience will be an important part of such a research programme.

Finally, an important area for future research is to understand the role of ABA in post-traumatic stress-disorder (PTSD) in conjunction with research on the influences of genotype, life experience, and traumatic event on neurophysiological processes associated with generation and perpetuation of PTSD symptoms. For example are pre-existing patterns of ABA a risk factor for PTSD? Do *ADRA2b* deletion carriers show evidence of greater ABA for trauma-related stimuli than non-carriers and do these patterns of ABA predict intrusive memory? Ultimately understanding mechanisms underlying individual differences in ABA and memory can help us understand mechanisms underlying how they are shaped by life experience over development and in trauma.

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