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## GANeIng traction: The broad applicability of NE hotspots to diverse cognitive and arousal phenomena

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### Abstract

The GANE (glutamate amplifies noradrenergic effects) model proposes that local glutamate–norepinephrine interactions enable “winner-take-more” effects in perception and memory under arousal. A diverse range of commentaries addressed both the nature of this “hot spot” feedback mechanism and its implications in a variety of psychological domains, inspiring exciting avenues for future research.

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We proposed the glutamate amplifies noradrenergic effects (GANE) model to fill a gap in our understanding: What are the brain mechanisms that allow arousal to simultaneously enhance processing of salient or high-priority stimuli and impair processing of inconspicuous or low-priority stimuli? In our model, the local level of glutamatergic neurotransmission signifies the priority of an activated representation. In the cortex, when glutamate spillover from activated synapses activates *N*-methyl-*D*-aspartate (NMDA) receptors on nearby varicosities of locus coeruleus (LC) neurons that are being depolarized by LC action potentials, this leads to more local release of norepinephrine (NE), which further amplifies glutamate release and enhancement of the information the highly excited neurons are representing. Elsewhere, lower glutamate levels fail to ignite hot spots and undergo greater suppression via NE-induced inhibition. We proposed that, in addition to enhancing activation of prioritized representations, the NE–glutamate hot spot effects selectively recruit metabolic resources, enhance neuronal oscillations, and trigger synaptic plasticity processes that enhance long-term memory of prioritized information.

Across the commentaries discussing GANE’s relevance to cognitive and neural processes, several important themes emerged (see Table R1). Generally, the responses can be grouped as having one of two foci (with some exceptions): behavioral and cognitive aspects of the arousal by priority interaction relevant to GANE or the NE hot spot mechanism itself.

To predict which information will be selectively enhanced or impaired by arousal, it is important to focus on the two key factors necessary to ignite a hot spot: (1) an arousing–inducing stimulus that can stimulate LC activity (NE), and (2) a stimulus that has high

priority (glutamate). As outlined in Table R1, several of the commentaries elaborated on these two factors, as well as on other issues and themes. We discuss the issues raised in the commentaries here in our response, starting with the topic of arousal.

## R1. Arousal

A number of the commentaries raise questions regarding arousal.

### R1.1. Nature of arousal

In our view, the LC–NE system is not the only brain system involved in a generalized arousal response (see Pfaff 2006 for a review of arousal pathways in the brain), but its activation is a common theme that runs through all different modes of arousal. For instance, NE inputs to cells in the ventromedial hypothalamus are critical in initiating sexual arousal (Pfaff 2006; of relevance for **Mouras**' commentary), whereas noradrenergic input to the amygdala is critical in enhancing memory for emotionally arousing stimuli (see **Roosendaal, Luyten, Voogd, & Hermans**' commentary and Section R4.2 on the role of the amygdala).

What is arousal? At the most basic level, we have the contrast between sleep and wakefulness. NE is low during most sleep states (see **Becchetti & Amadeo**). Then, during wakefulness, physically activity increases NE (Carter et al. 2010). But in addition to these broad-scale changes, the arousal system is also exquisitely sensitive and can adapt rapidly to small changes in the environment or internal goals.

These arousal responses can be detected by measuring pupil dilation. NE system activity increases pupil dilation, as NE released by the LC inhibits pupil constriction (Koss et al. 1984; Wilhelm 2008). Pupils are constricted during sleep, compared with wakefulness (Yoss et al. 1970). During wakefulness, aerobic exercise (Ishigaki et al. 1991) or muscular exertion (Nielsen & Mather 2015; Nielsen et al. 2015) increases pupil dilation. Arousal induced by stimuli or tasks also increases pupil dilation. For example, emotionally arousing scenes (Bradley et al. 2015), sexually arousing stimuli (Bradley et al. 2015), surprise, uncertainty, loud noises, and cognitive effort all increase pupil dilation. Subjective arousal ratings given for emotional images correlate with pupil diameter during viewing (Bradley et al. 2008). These consistencies across different elicitors of arousal provide an important starting point at which to elucidate the underlying mechanisms by which encountering emotionally arousing stimuli modulates cognitive and brain processing. **Eldar, Cohen, & Niv** review a recent line of work in which they used pupil dilation as a marker of NE activity and found that indices of high NE function are associated with increased selectivity in learning, perception, and memory, consistent with their neural network models in which NE was modeled as global increase in gain. GANE complements and extends this approach by providing hypotheses about how NE implements neural gain.

We agree with **Mouras** and **Kaspar** regarding the relevance of sexual arousal and internal sources of arousal (such as from one's thoughts). Our point of view is that these different types and sources of arousal can be accommodated by the GANE model, as evidence suggests that LC activation is a common theme for all of them.

## R1.2. How the heartbeat influences LC activity

The LC is influenced not only by external stimuli and an individual's own thoughts, but also by interoceptive signals. For instance, distension of the bladder or colon increases LC activity (Elam et al. 1986), whereas an increase in blood pressure decreases LC activity (Elam et al. 1984). LC neurons also exhibit cardiac periodicity. For instance, in cats, LC neurons are most likely to fire 80–180 ms after the peak of the cardiac R-wave (during diastole) and least likely to fire 40 ms before to 60 ms after the R-wave (during systole) (Morilak et al. 1986).

**Critchley & Garfinkel** have shown that stimuli detection and memory encoding differ during the systole (contraction) and diastole phases of the heartbeat. During systole, participants are better able to detect fear (but not neutral) faces in an attentional blink paradigm and rate them as more intense (Garfinkel et al. 2014). When words are the T2 stimuli in an attentional blink paradigm, later memory for the words depends on both the confidence with which the words were originally detected and at what heartbeat phase the words were detected (Garfinkel et al. 2013). Words detected with high confidence during systole have a memory advantage, whereas words detected with low confidence during systole have a memory disadvantage. Therefore, during systole, highly salient stimuli such as fear faces and clearly detected target words get a boost in processing or later consolidation. But why would this GANE-like pattern occur during systole when the LC neurons are *less* likely to fire? This surprising aspect of the findings suggests the possibility that LC activity and salient glutamatergic representations may interact best when they are offset slightly in time.

**Critchley & Garfinkel** argue that the GANE notion that LC–NE activity amplifies salience is not sufficient to account for their findings because their cardiac cycle effects sometimes appear to be driven by fear rather than arousal more generally. However, as illustrated in their figure, there was not a significant difference between fear and disgust or happy faces, and the disgust and happy faces showed trends toward enhancement where neutral faces showed a trend toward impairment at diastole. Fear faces are often more salient than happy or disgust faces (Anderson et al. 2003; Mather & Knight 2006); therefore, we think more work is needed before a specific-emotion account must be invoked in place of a salience mechanism such as that provided by GANE.

## R1.3. How arousal may amplify the salience of negative stimuli

**Kaspar** makes the case that negative stimuli may be more likely than positive stimuli to ignite neuronal hot spots because of the evolutionary pressure not to miss potential threats. One challenge is how to test this hypothesis, as negative stimuli, on average, induce more arousal than positive stimuli (Grühn & Scheibe 2008), and so any differences in processing or memory between negative and positive stimuli could be due to different levels of arousal when processing them, rather than to different levels of priority. To try to address this question, we recently ran a study in which we induced arousal independently by having participants squeeze a ball in their hand as hard as they could before they viewed emotional pictures and examined how the resulting increases in arousal influenced memory for the pictures (Nielsen et al. 2015). We were interested in hormonal effects, and all participants

were younger female women. Consistent with **Kaspar**'s predictions, we found that handgrip-induced arousal enhanced memory for the negative, but not the positive pictures. This effect was most pronounced for women with low estrogen and progesterone levels at the time of testing.

**Kaspar** also suggested that because of declines in the LC–NE system, negative stimuli lose their arousing potential as people age. However, the evidence suggests that the older adults' positivity effect is not due to a lack of bottom-up salience for negative stimuli. Like younger adults, older adults look first at arousing stimuli regardless of their valence (Knight et al. 2007) and notice arousing or threatening stimuli more quickly than other types of stimuli (Leclerc & Kensinger 2008; Mather & Knight 2006). Bottom-up affective salience should play less of a role in influencing processing for low-arousal pictures, and indeed, the positivity effect appears to be stronger among valenced stimuli low rather than high in arousal (Kensinger 2008). In addition, we found that arousal induced by handgrip selectively benefited memory encoding of negative pictures (compared with positive or neutral pictures) in older women not taking hormone supplements, as well as in younger women with low estrogen and progesterone levels (Nielsen et al., in preparation). The evidence thus suggests that arousing negative pictures have similar bottom-up salience for older and younger adults.

#### **R1.4. Relation between arousal and appraisal theory**

On the basis of appraisal theory, **Montagrin & Sander** raise a question about how arousal and priority interact. They argue that arousal and goal relevance are not independent and stimuli that are relevant for individuals' goals, needs, and values induce strong arousal and amygdala activity. We agree with them: Given that the LC exhibits phasic activity in response to goal-relevant stimuli (Aston-Jones & Cohen 2005; Aston-Jones et al. 1999), it seems possible that goal-relevant stimuli become arousing. However, the appraisal theory approach they discuss does not detail the neural mechanisms by which arousal induced by goal-relevant stimuli helps people memorize (Montagrin et al. 2013) and prioritize attention to those stimuli (Pool et al. 2015). In contrast, our GANE model can explain their findings of enhanced processing of goal-relevant stimuli: once the amygdala and/or prefrontal regions detect goal-relevant stimuli and recruit the LC (see Sara & Bouret 2012 for discussion of amygdala and prefrontal inputs to LC), NE hot spots will be generated in circuits transmitting goal-relevant information and, in turn, hot spots will enhance memory and perception for those stimuli. Therefore, GANE does not contradict the appraisal model, but instead extends it.

#### **R1.5. Arousal and emotion regulation**

**Hull** argues that the role of arousal in GANE is relevant for understanding impairments in emotion regulation. In particular, when stuck on a particular representation associated with negative emotions, decreases in arousal may be necessary to allow for less emotionally disturbing representations to be prioritized. Although not addressed in Hull's commentary, a related point is the relevance of GANE for disorders such as post-traumatic stress disorder (PTSD), in which intrusive thoughts are a problem. A particular disturbing thought or memory may induce arousal, which, in turn, enhances attention to and memory reconsolidation of that particular representation. On the basis of GANE, beta blockers

during initial encoding or retrieval of the memory should attenuate the immediate strength of its activation and its long-term synaptic strength. Consistent with this are some observational findings suggesting that beta blockers may help prevent intrusive thoughts or PTSD (Krauseneck et al. 2010; Lindgren et al. 2013), although random assignment has yielded some null effects (Stein et al. 2007).

## R2. Priority

Other commentaries focused on physiological and psychological aspects of priority, a key factor in GANE.

### R2.1. Perspectives on physiological mechanisms of priority

**Larkum & Phillips** describe a novel physiological mechanism by which contextual information modulates pyramidal cell activity. Neocortical pyramidal cell bodies have an apical trunk that ascends to a dendritic branching pattern called an *apical tuft*, which resides in a different cortical layer than the cell body and the basal dendrites around it. The long distance of the apical tuft from the cell body sets it up to serve a modulatory role in driving cell activity (Phillips 2015). Apical amplification could, for example, provide top-down priority selection of a quiet bottom-up auditory input to cortical output circuits. In their figure, Larkum & Phillips illustrate the interaction between GANE and apical amplification priority, providing an experimentally testable physiological model. **Houghton** argues that, computationally, the mossy cell hilar circuit in hippocampus would set priority for hippocampal processing and suggests heavy hilar NE innervation is consistent with GANE amplification of that mechanism. **Becchetti & Amadeo** make the interesting point that conscious (and, thus, prioritized) oneiric processing occurs during rapid eye movement (REM) sleep, likely supported by high acetylcholine modulation. But with active suppression of LC–NE during REM, there is little or no memory of those priority events, also consistent with GANE.

### R2.2. Possible relation between fluency and priority

**Carbon & Albrecht** point out that fluency (i.e., processing information more easily) is an important factor determining stimulus priority. Greater fluency can arise because of perceptual salience (e.g., reading a word printed in a clear, high-contrast font more quickly than a blurry word) or because of prior knowledge or experience (e.g., reading a familiar word more easily than an unfamiliar word). Previous findings had suggested that people feel more positively about stimuli that they process more fluently (e.g., Winkielman & Cacioppo 2001). In a recent study, Albrecht and Carbon (2014) presented affective pictures that were either preceded (507 ms earlier) by that same image or by a different image shown for only 7 ms and asked participants to rate the valence of the pictures. There was no main effect of valence, but, instead, an amplification effect, with highly positive pictures rated more positively when they had been primed and highly negative pictures rated more negatively when they had been primed. Insofar as fluently processed stimuli yield higher glutamatergic activity than less fluently processed stimuli (something that seems plausible but remains to be tested) and that the emotional stimuli elicited arousal, their findings that valence judgments of emotional stimuli are amplified by fluency fit with GANE.

### R3. Predictive utility of GANE

**Huntsinger & Storbeck** and **Talmi & Barnacle** argued that GANE does not provide clear predictions concerning whether the presentation of emotionally arousing stimuli would enhance or impair cognitive processing of stimuli that appear nearby in time or space. Huntsinger & Storbeck state that GANE can provide *post hoc* explanations about the effects of emotional stimuli in a range of situations, but question GANE's predictive utility. Talmi & Barnacle also argue that because we don't know exactly how long emotional stimuli dominate competition for representation, we can explain either the enhanced or impaired effects of emotional stimuli on nearby neutral stimuli by GANE.

We agree with them that it is hard to determine priority when comparing emotional with neutral stimuli. As discussed in our target article, emotional stimuli tend to have higher priority than neutral stimuli because of their goal relevance, bottom-up salience, and emotional salience. Thus, in the hypothetical experiment **Huntsinger & Storbeck** mention, where emotional stimuli are presented as distractors with task-relevant neutral stimuli, emotional distractors can have higher priority than neutral goal-relevant stimuli. This could especially be the case when the top-down control mechanisms are not strong enough to establish the goal relevance of neutral stimuli (see **Warren, Murphy, & Nieuwenhuis**).

**Talmi & Barnacle** suggest that one can get around the issue of the different salience between emotional and neutral stimuli by having a long interval between emotional and subsequent neutral stimuli. But it is not clear that having a long interval would increase the priority of neutral stimuli as high as that of emotional stimuli. In addition, because high arousal can impair top-down prioritization (Arnsten 2011; Kuhbandner & Zehetleitner 2011), top-down control mechanisms might fail to increase the priority of neutral stimuli presented after emotional stimuli. These considerations suggest that in their EEG study (Barnacle et al., in preparation), neutral stimuli intermixed with emotional stimuli still had lower priority than neutral stimuli presented in a neutral list, which led to the impaired processing of neutral stimuli in the intermixed condition as predicted by GANE. Furthermore, having a long interval has the disadvantage that the effects of phasic arousal and NE release might not last long enough to yield modulatory effects (see Section 9 in our target article).

In summary, it is difficult to test GANE in experimental settings where researchers simply include emotionally arousing stimuli and neutral stimuli without a clear manipulation of priority. In our view, to test GANE, it is important to manipulate the priority of neutral stimuli, independently from arousal (Lee et al. 2014; Sakaki et al. 2014a; Sutherland & Mather 2012). One way to achieve this in the context of Barnacle et al. (in preparation) would be to have high-priority neutral images and low-priority neutral images in the mixed list condition. Similar changes can be made in the bridge study mentioned by **Huntsinger and Storbeck** (Dutton & Aron 1974); GANE predicts that arousal induced by the scary bridge will enhance memory for nearby high-priority stimuli (e.g., a woman seen on the bridge if the participant were asked to approach a woman and ask her something) while impairing memory for nearby low-priority stimuli (e.g., a man on the bridge who has no task



relevance or particular interest). In summary, GANE can provide clear predictions as long as priority levels can be manipulated or assessed in the experiment.

## R4. Alternatives to GANE proposed in commentaries

Several of the commentaries propose alternatives to GANE to explain the mechanisms by which arousing stimuli affect cognitive processing.

### R4.1. NE-only model

**Strange & Galarza-Vallejo** propose that the glutamate aspect of the model is not necessary; they describe a simpler model in which priority is coded by phasic NE release in the brain. They work through an example from research on the emotional oddball – 1 (E-1) effect, in which emotional oddballs (words or pictures) impair memory for the immediately preceding item on the list if that item was low priority for the participant, but enhance it if that item was high priority (e.g., Sakaki et al. 2014a). A problem with their NE-only model is that it is not clear how phasic NE release can selectively “tag” the E-1 item and not other items. Perhaps in the simple setup they describe, in which one word or object appears at a time in the list, phasic NE release could mark activated neural networks via a temporal tagging process. However, they do not consider findings that when multiple items are shown simultaneously, whether and how much memory for them is enhanced or impaired by a subsequent emotional item depends on their priority. For example, in an experiment in which a scene was shown either alone or with an object superimposed (Fig. R1A), if the image was followed by an emotional sound, there was impaired memory for the scene later, but only if it had been made lower priority by being in the background (Fig. R1B) (Ponzio & Mather 2014). Likewise, in another study in which participants saw four items at the same time that were then followed by a tone that was conditioned to predict either a shock (CS+) or no shock (CS–), having a subsequent arousing tone affected later memory for the simultaneously shown items differently depending on the relative priority of the items (Lee et al. 2015). The model Strange and Galarza-Vallejo propose does not explain how phasic LC activation could have different effects on items shown at the same time. In our view, this is the main contribution of GANE: by positing a mechanism for local cortical modulation of NE, it provides the only explanation to date of how arousal can have simultaneous differential effects on items based on their priority.

### R4.2. Amygdala-based model

**Roozendaal, Luyten, Voogd, & Hermans** argue that the amygdala is necessary for NE to enhance selective processing and memory consolidation of arousing stimuli. We agree that the amygdala plays a critical role, but argue that its role in mediating the effects of NE is **necessary** only when the amygdala is the primary site of the neural representation in question.

Data from individuals with amygdala lesions help reveal which types of representations depend on the amygdala and which types can be supported by other brain regions. Compared with controls, unilateral amygdala patients exhibited as much enhanced visual cortex activity when viewing emotionally salient images (Edmiston et al. 2013), as much of

an advantage for detecting emotional targets (Piech et al. 2010), and as much emotional capture by emotional stimuli during an attentional blink task (Piech et al. 2011). Two individuals with selective bilateral amygdala lesions exhibited a significant advantage in recalling aversive (compared with neutral) words during an attentional blink task, and this advantage was as large as that seen for matched control participants (Bach et al. 2011). Someone with complete bilateral amygdala lesions who could not recognize fear from faces still showed normal rapid detection of those faces (Tsuchiya et al. 2009). Thus, the amygdala is not necessary for the initial selective attention and encoding advantages seen for emotionally arousing stimuli, suggesting that NE–glutamate hot spots in sensory brain regions can occur even in the absence of the amygdala.

In addition, highly salient sensory stimuli yield normal physiological responses in people missing amygdalae (e.g., Tranel & Damasio 1989). For example, in studies of fear conditioning, individuals with amygdala lesions have normal skin conductance responses to aversive stimuli such as loud noises (Bechara et al. 1995; Klumbers et al. 2014). Likewise, three patients with bilateral amygdala lesions each had a panic attack when inhaling 35% CO<sub>2</sub> (Feinstein et al. 2013), indicating that amygdala lesion patients still experience fear in response to interoceptive alarming cues. These intact responses to interoceptive or external sensory stimuli contrast with the lack of fear shown by amygdala patients in response to experiences or visual stimuli (e.g., a haunted house or a live snake) that typically elicit fear because of their association with danger (Feinstein et al. 2011).

This pattern of findings suggests that the amygdala is essential for anticipatory physiological responses to stimuli that predict something aversive. This possibility is supported by fear conditioning studies with individuals with amygdala lesions (Bechara et al. 1995; Klumbers et al. 2014). These individuals lacked skin conductance responses to CS+ cues that predicted loud noises, even though they acquired explicit knowledge about the CS+ contingency. In contrast, an individual with bilateral hippocampal lesions failed to acquire explicit knowledge about the contingency, but had skin conductance responses to the CS+ (Bechara et al. 1995). Therefore, amygdala lesions impair physiological responding to cues that predict threat, but do not impair explicit learning about these cues. Amygdala lesions also impair physiological responding to simulated monetary rewards and losses in the context of a gambling game (Bechara et al. 1999), indicating that the amygdala is necessary for an abstract stimulus predicting something positive or negative to yield a physiological affective response.

The findings that patients with amygdala lesions no longer have physiological responses to predictive cues despite having as much explicit knowledge of the contingencies as normal controls suggests that: (1) there are amygdala-based neural representations of associations between neutral cues and potential affectively relevant outcomes; and (2) these amygdala-based representations are necessary to trigger signals to sympathetic pathways to mount a physiological response, possibly in part via amygdala projections to the LC (Cedarbaum & Aghajanian 1978).

Likewise, the finding that an individual with a hippocampal lesion lacked explicit knowledge of fear conditioning contingencies despite exhibiting a skin conductance response to the CS



+ suggests that there also are amygdala-independent, hippocampus-based neural representations of associations between CSs and USs. However, in people with intact amygdalae and hippocampi, these separate representations in the two regions are likely to have close interactions, in part supported by a direct glutamatergic pathway from the basolateral amygdala to the CA1 region of the hippocampus (Rei et al. 2015).

Noradrenergic contributions to interactions between amygdala and hippocampus have been examined using one-trial learning to avoid a shock (McIntyre et al. 2005). In this paradigm, the  $\beta$ -adrenergic receptor agonist clenbuterol is infused into the basolateral complex of the amygdala shortly after a rat learns that moving from a brightly lit compartment of an alley through a door to a dark compartment is associated with a shock. The  $\beta$ -adrenergic stimulation of the amygdala increases Arc expression (indicating more synaptic changes occurred) in the hippocampus in the 45 min after the shock. Of particular relevance in this context, however, are findings that the increased Arc expression depends not only on greater NE activity in the amygdala itself, but also on arousal levels more generally (McReynolds et al. 2014). Specifically, whereas basolateral amygdala infusions of a  $\beta$ -agonist increased Arc protein levels for the inhibitory avoidance shock task, as seen in previous studies and also for a “high-arousal” version of an object recognition task, NE activity in the amygdala was not sufficient to increase Arc in the hippocampus when the object recognition task was not arousing. These findings suggest that glutamate–NE feedback loops in the amygdala can be intensified by within-amygdala local  $\beta$ -adrenergic activation (Fig. R2A). This hot spot activity increases glutamatergic signaling to the hippocampus (Fig. R2B), but does not directly increase NE levels in the hippocampus. However, the increased glutamatergic activity in the hippocampus can stimulate local release of NE via NMDA receptor activity at LC neuron varicosities if the LC is depolarized (Fig. R2C; see target article for more details on hot spot mechanisms). In summary, McReynolds and colleagues’ data suggest that NE can influence hippocampal activity either indirectly via glutamatergic pathways from the amygdala or directly via local release from LC varicosities. More generally, we posit that NE action within the amygdala has important glutamatergic modulatory effects elsewhere in the brain (in particular in the hippocampus), but that the LC also modulates excitation and inhibition directly in these other brain regions via local release of NE. The critical experiments necessary to test this hypothesis have not been performed yet (see relevant proposed study in Table R2).

**Rooszendaal, Luyten, Voogd, & Hermans** also argue that “the impairing effects of amygdala–NE interactions on memory of non-salient/non-arousing information involve an *active* process that is dependent on the amygdala.” They make this case based on Lovitz and Thompson (2015), whom they interpret as showing that intra-basolateral amygdala infusion of a  $\beta$ -adrenergic agonist (clenbuterol) decreases hippocampal excitability in non-inhibitory avoidance-trained control animals. However, their interpretation appears to be incorrect, as in that study, there was no significant difference between vehicle and clenbuterol conditions in the untrained rats.

## R5. Role of NE hot spots in long-term memory formation

Some commentaries raise questions concerning the role of NE hot spots in memory. First, **Hurlemann, Maier, & Scheele** point out the importance of cortisol, in addition to NE and glutamate, in explaining the effects of arousal on memory. Combining neuroimaging with a psychopharmacological approach, Hurlemann et al. demonstrated that NE and glucocorticoids interact during processing of emotional stimuli (Hurlemann 2008; Kukulja et al. 2008; 2011). In particular, their work suggests that NE interacts with cortisol to enhance learning of emotional information within the amygdala–hippocampus network.

Acute stress and administration of glucocorticoids lead to enhanced glutamate release both in the amygdala (Reznikov et al. 2007) and in the hippocampus (Moghaddam et al. 1994) via mechanisms mediated by glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) (for reviews, see Popoli et al. 2012; Sandi 2011). In the amygdala and hippocampus, interactions between glucocorticoids and NE have been observed, as well (for reviews Joëls et al. 2011; Krugers et al. 2012). These results suggest the interesting possibility that glucocorticoids help NE create hot spots in the amygdala–hippocampus circuit by enhancing glutamatergic activity. One question is whether the NE–cortisol interaction goes beyond the amygdala–hippocampus circuit. Although most previous research focuses on the effects of glucocorticoids either in the amygdala–hippocampus pathway or in the prefrontal cortex (PFC), glucocorticoids might also amplify NE hot spots in other cortical regions, given that GRs are widely expressed in brain (Morimoto et al. 1996). Furthermore, elevated cortisol and NE levels tend to impair goal-directed attentional processes in the PFC (Schwabe et al. 2012), which should enhance the impact of the bottom-up, salience-driven hot spots predominant in sensory brain regions.

Second, **Ritchey, Murty, & Dunsmoor** state that the tag-and-capture model is better able than GANE hot spot mechanisms to explain the effects of arousal on memories for events that occurred minutes to hours before the arousing event. For example, initially weak memories can be strengthened by a subsequent salient signal, such as a novelty or aversive event (Dunsmoor et al. 2015; Redondo & Morris 2011). The tag-and-capture model explains these results by asserting that memory traces are tagged during initial learning, which allows for subsequent plasticity-related protein-mediated mechanisms to capture those tagged traces to create long-term memories. Ritchey et al. also argue that the effects of arousal on protein synthesis processes are mediated by dopaminergic neuromodulation.

Although in our target article we focused mainly on the immediate effects of NE hot spots, we believe that evidence indicates a role for these hot spots in tag-and-capture scenarios.  $\beta$ -Adrenergic receptor activity stimulates protein synthesis and gene expression alterations associated with long-term potentiation maintenance (Maity et al. 2015; O'Dell et al. 2010). NE hot spots should play a role in tag-and-capture by elevating local NE levels to activate  $\beta$ -adrenergic receptors, as well as by increasing glutamatergic activation of NMDA receptors. Both  $\beta$ -adrenergic activity and NMDA activity (in addition to dopamine D1/D5 receptor activity) are essential to “set the learning tag” for an initial weak memory, and  $\beta$ -adrenergic receptor activation is required during exposure to the modulating novel event occurring an hour later (Moncada et al. 2011). A particularly intriguing finding is that the behavioral

tagging phenomenon requires the initial weak event and the subsequent novel event to occur in the same sensory modality, thereby activating the same general population of neurons (Ballarini et al. 2009). Likewise, Dunsmoor et al. (2015) found that fear conditioning enhanced memory for previously learned images only when those images were semantically related to a fear-conditioned category; when images of animals were fear-conditioned, memories for previously learned animals were enhanced, whereas when images of tools were fear-conditioned, memories for previously learned tools were enhanced. This is consistent with the local nature of NE hot spots and raises the interesting question of just how widely the plasticity-related proteins stimulated via  $\beta$ -adrenergic receptor activation at NE hot spots modulate interconnected memory circuitries. The behavioral findings (Ballarini et al. 2009; Dunsmoor et al. 2015) suggest that they do not have an influence much beyond a local region that represents the same category or sensory modality of item. Although much still needs to be worked out about the potentially complementary roles of dopamine and norepinephrine on tag-and-capture phenomena, we believe that thinking about the local nature of the  $\beta$ -adrenergic activity induced by arousing modulatory events will be fruitful.

## R6. GANE amplification of prioritized representations during a “network reset”

According to a prominent theory, NE release orchestrates a “network reset” that re-orientates attention and, consequently, re-organizes underlying representational networks during a sudden and unexpected change in environmental imperatives (Bouret & Sara 2005; Sara & Bouret 2012). We agree with **Sara**’s perspective that GANE is complementary to the “reset” hypothesis. From the perspective of GANE, whether this type of reorienting occurs will depend on whether there are currently representations with high glutamatergic activity or not. If there are no current strongly active representations, both GANE and the network reset theory predict that the predominant effect of an increase in LC activity would be to enhance re-orientation to new salient stimuli. However, when there is already a highly active representation, GANE predicts that an increase in LC activity will further enhance processing of that representation (e.g., Anderson et al. 2006; Knight & Mather 2009; Sakaki et al. 2014a), rather than having a network reset effect. On the basis of these findings, in our target article we argued that the network reset perspective fails to account for the ability of arousal to enhance memory of preceding high-priority information. **Bouret** responded by suggesting that enhanced memory for a preceding event could be consistent with a network reset if, when an arousing event occurred, the preceding salient event was now represented in a qualitatively different way that was integrated with the arousing event.

Consistent with **Bouret**’s argument that arousal enhances memory for preceding information when the preceding information is integrated with the arousing events, in fear/evaluative conditioning paradigms events repeatedly followed by emotional outcomes acquire emotional properties (for a review, see Baeyens et al. 2005). Our previous research also demonstrated that when individuals are presented with neutral cues followed by emotional or neutral outcomes, emotional outcomes facilitate memory for neutral cues only when they are aware of the cue–outcome contingency (Mather & Knight 2008; Sakaki et al. 2014b).

To address the important question raised by **Bouret** about whether arousal changes the nature of representations, future research should probe the effects of arousal on the specificity of mental and neuronal representations. At least one recent study suggests active sensory representations are strengthened, rather than altered, by noradrenergic system activation (Shakhawat et al. 2015). In addition, our findings suggest that emotional arousal enhances the veracity of the original representation, or detail memory, rather than gist alone (Sakaki et al. 2014a).

## R7. Alternative ways to trigger LC activity

Although most of the target article focused on how emotionally arousing stimuli shape cognitive processing, non-emotional stimuli can also activate the LC and thereby influence cognition. In this section, we discuss how prediction errors, uncertainty, and competition each influence LC activity.

### R7.1. Prediction errors

Prediction is a central feature of efficient cognitive processing. As described by **Ferreira-Santos**, GANE fits well with “predictive coding” frameworks of cognition: sudden mismatches between predicted and actual sensory and affective inputs represent an important form of conflict and competition that can elicit arousal and LC activity. Supporting this view, pupil dilation has been linked to the occurrence of prediction errors (Braem et al. 2015; Preuschoff et al. 2011). Furthermore, in monkeys, phasic LC activity ceases to signal the occurrence of reward once the reward follows a specific action predictably (Sara & Segal 1991). Other research also indicates that affect enhances prediction error responses (Vogel et al. 2015) and that prediction errors are a fundamental component of generating interceptive feelings (Barrett & Simmons 2015).

### R7.2. Uncertainty

As pointed out by **Nassar, Bruckner, & Eppinger**, as well as by **Bouret**, it is important to consider the purpose of having one level of arousal modulate cognitive processing differently than another level. When is it useful for cognitive processing to remain focused on previously salient information? And when will it be advantageous to be open to new prioritized information? Nassar and colleagues argue that during times of uncertainty, it is especially important not simply to focus on current prioritized cues, but to amplify incoming prioritized sensory information (Yu & Dayan 2005). They review findings that pupil diameter is larger during periods of uncertainty than when expectations are reliable. Thus, tonically higher levels of NE should decrease the threshold for new salient stimuli to ignite hot spots. They suggest that older adults’ deficits in learning under conditions of uncertainty may be linked to age-related declines in LC function.

### R7.3. Competition and conflict

As highlighted by **Phaf**, there is much evidence that competition and conflict between representations induce arousal. These stimuli/events are also likely to produce hot spots, based on evidence that conflict, along with novelty, target detection, uncertainty, and performance errors, elicit LC activity (for reviews, see Berridge & Waterhouse 2003;

Nieuwenhuis et al. 2005; Ullsperger et al. 2010; Yu & Dayan 2005). Fundamentally, GANE predicts that *any* stimulus that activates the LC–NE system will produce hot spots in an activity-dependent manner, regardless of whether NE release is triggered by something emotional or not. If competition elicits arousal, it could very well be an effect driven by prediction errors (i.e., significant discrepancies between feedforward and feedback inputs; see Section R7.1), initiating a network reset via the LC.

**Phaf**'s also discusses the distinct but complementary roles of theta and gamma oscillations in signaling and resolving stimulus conflict, respectively. According to Phaf, theta arises from conflict, is a substrate of arousal, and helps select dominant representations via intercortical communication. Subsequently, gamma oscillations facilitate a resetting and stabilization of “winning” representations. His description is consistent with **Sara**'s empirical data. In her commentary, Sara describes evidence that stimulating the LC briefly suppresses gamma oscillations for 200 ms, which is followed by a near doubling of the gamma power immediately afterward, as well as an increase in theta power (Sara 2015). Interestingly, in an early report of conflict activating LC, the absence of expected reward elicited a specific theta band increase (~7.7 Hz) in hippocampus (Gray & Ball 1970). This effect was later demonstrated to require forebrain norepinephrine (Gray et al. 1975). It could be useful to re-examine this theta signature of LC activation (for more recent support, see Walling et al. 2011) and its role in synchronizing activity for prioritized representations. Another interesting question is whether (as suggested in the target article) NE hot spots enhance local gamma power via a  $\beta$ -adrenergic pathway, thereby increasing selective attention.

## R8. Additional mechanistic considerations/complications for GANE

As noted by several commentators, GANE is necessarily a simplification of a complex reality. It does not, for example, incorporate the function of postsynaptic  $\alpha_2$ -receptors, the subthreshold input promoting role of  $\alpha_1$ -receptors, the synergistic role of  $\alpha_1$ - with  $\beta$ -adrenergic receptors or recently described astrocytic functions of  $\alpha_1$ -receptors. The co-release of peptides from LC varicosities is not considered; neither is the probable role of other neuromodulators known to be elevated in various forms of arousal discussed. This is a beginning that will, ideally, lead to a more veridical model of cortical self-regulation that addresses how neurotransmitters released during arousal interact with local cortical conditions to modulate activity in flexible yet highly targeted ways.

### R8.1. Varied effects of adrenoceptors

As highlighted in several commentaries, the GANE model does not incorporate all known adrenoceptor functions. These omissions include the role of postsynaptic  $\alpha_2$ -receptors that play important roles in the PFC (see commentaries by **Abdallah, Averill, Krystal, Southwick, & Arnsten** and **Todd, Ehlers, & Anderson**) and that also occur in other areas of neocortex (Venkatesan et al. 1996). **Navarra & Waterhouse** and **Gaucher & Edeline** point out that  $\alpha_1$ -adrenoceptors have more varied actions, including synergism with  $\beta$ -adrenoceptor effects, potentiation of effects on their own, and astrocytic action. In particular, they highlight that the role of  $\alpha_1$ -adrenoceptor in sensory cortex may be

facilitatory: when activated, these receptors appear to potentiate postsynaptic excitatory responses and can boost subthreshold inputs (for a review, see Berridge & Waterhouse 2003). Furthermore, global astrocytic calcium waves are initiated via LC–NE activation of astrocytic  $\alpha_1$ -adrenoreceptors (Ding et al. 2013), consistent with a model in which LC–NE global effects recruit both  $\alpha_1$ - and  $\alpha_2$ -adrenoreceptors.

### R8.2. Suppressive effects of NE in sensory regions

**Gaucher & Edeline** emphasize the suppressive actions of exogenous NE on processing in auditory cortex as being inconsistent with GANE. But their finding that a small population of auditory neurons encoding natural stimuli are enhanced by NE (Gaucher & Edeline 2015) and contribute to discrimination is similar to newer findings in olfactory cortex that LC–NE modulation is essential for difficult natural odor discrimination and increases the stability of small distributed odor representations (Shakhawat et al. 2015), as predicted by GANE.

### R8.3. Differential effects of adrenergic receptors in prefrontal and posterior cortex

**Abdallah, Averill, Krystal, Southwick, & Arnsten** highlight the differences between the actions of NE on classic sensory synapses in subcortical and posterior sensory regions and newly evolved circuits in layer 3 of the dorsolateral PFC (DLPFC). On the basis of animal and human research, they suggest hot spot effects are most likely to occur in sensory and limbic (e.g., amygdala, hippocampus) synapses where  $\beta$ -adrenoreceptors promote glutamate responses and long-term potentiation. In the PFC, in contrast to “classic” sensory areas,  $\beta$ -adrenoreceptor activation has been found to impair rather than enhance postsynaptic function via increased cAMP signaling (Arnsten et al. 2015; Ramos & Arnsten 2007). Like  $\beta$ -adrenoreceptors,  $\alpha_1$ - and  $\alpha_2$ -adrenoreceptors also appear to have contrasting influence on neuronal activity in the PFC versus sensory cortices. Although  $\alpha_1$ -receptors enhance sensory neuron firing, they tend to impair PFC function and working memory (Ramos & Arnsten 2007). On the other hand, whereas  $\alpha_2$ -receptors enhance inhibitory signals and suppress noisy activity in the posterior cortex, their activation strengthens dorsolateral PFC functional network connectivity and promotes working memory (Arnsten et al. 2012).

These inverted rules of adrenoreceptor function in the PFC have important implications for how GANE influences cognitive processing during sudden arousal. Although an arousal-induced surge of NE may disrupt working memory representations in the DLPFC (e.g., current event models), it should also transiently enhance the throughput of strong glutamatergic signals in the hippocampus (Brown et al. 2005). Therefore, DLPFC impairments may facilitate reorientation during arousal to information that has bottom-up salience and is associated with hot spots of high activity in sensory regions but not in PFC.

### R8.4. Relative timing of arousal and prioritization process

The key distinction outlined in the previous section between the effects of NE in sensory cortices and limbic regions versus the PFC agrees well with the timing hypotheses proposed by **Warren, Murphy, & Nieuwenhuis**. In their commentary, Warren and colleagues present evidence that the relative strength of bottom-up and top-down (cognitive control) priority inputs changes rapidly within a single trial. Whereas bottom-up salience dominates the competition for mental resources early on, cognitive control processes take longer to develop



and overcome the initial dominance of perceptual salience. Warren et al. suggest that this time-variant model of salience determines whether phasic arousal enhances or impairs task-relevant (but not perceptually salient) information.

Indeed, the GANE model predicts that arousal-induced NE release will bias competition in favor of whatever information has the highest priority *at that moment*. Experiencing arousal while a representation is highly active should strengthen that representation regardless of whether top-down goals or bottom-up salience prioritized the representation, because the representation was activated before moderate to high levels of NE could disrupt goal-directed processing in the PFC (Ramos & Arnsten 2007). In contrast, the source of priority may matter more when experiencing arousal before a stimulus is perceived. Although prestimulus arousal should amplify the effects of bottom-up salience, it may diminish the effects of top-down priority if, as outlined in the previous section, working memory processes that help maintain and implement processing goals are impaired by the arousal (Ramos & Arnsten 2007).

Data from our lab provide clear evidence that prestimulus arousal enhances the impact of bottom-up salience (Lee et al. 2013; Sutherland & Mather 2011; 2015), whereas poststimulus arousal enhances the impact of top-down prioritization (Lee et al. 2015; Sakaki et al. 2014a; 2014b). Whether arousal enhances priority for the other two combinations remains to be seen. We have not yet tested scenarios in which something perceptually salient is followed by something arousing, but GANE would predict that as long as the representation associated with that perceptually salient item were still strongly active when arousal increased, it would benefit further from the arousal. In contrast, as outlined above, the situation in which arousal occurs before top-down prioritization occurs could show the reverse effect; insofar as arousal disrupts the ability of the PFC to prioritize an otherwise nonsalient stimulus, arousal should diminish the impact of top-down priority because the goal-relevant representation is not highly activated. Consistent with this, we have found that playing an emotional sound before a brief display of letters makes it harder for participants to selectively report the letters in the high point value color (Sutherland et al., under review). Given the impairing effects of high NE on DLPFC, for a prestimulus arousal to enhance processing of a goal-relevant item, the goal prioritization process would need to be relatively independent of the PFC, perhaps because it is automatic or habitual.

### **R8.5. Inverted-U relationship between LC firing and cognitive selectivity**

Aston-Jones and Cohen (2005) proposed an inverted-U model of tonic NE function, in which low tonic LC activity promotes being inattentive and nonalert, moderate LC activity promotes being focused, and high tonic LC activity promotes distractibility. In their commentary, **Navarra & Waterhouse** ask where along the inverted-U function the glutamate-NE interactions proposed in GANE would operate. Their question is in part inspired by data from Devilbiss and Waterhouse (2000), who simultaneously administered glutamate and NE into in vitro rat barrel field cortex slices. They found that some cells showed a monotonic suppression of the excitatory postsynaptic response to glutamate, as NE increased. Other cells showed an inverse U shape, in which there were increasing glutamate-evoked discharges as NE increased to 5 nA, but then decreasing glutamate-evoked

discharges as NE tonic levels were further increased (10–30 nA). These findings suggest that tonic levels of NE modulate postsynaptic responses to glutamatergic input, which is quite interesting. In particular, it seems that high tonic levels of NE would quiet activity in neurons exhibiting this postsynaptic NE suppression, which could contribute to the general decrease in neural noise seen under arousal (one interesting side note is that they found that, unlike in layers II/III, NE-induced facilitation of glutamate-evoked responses was the predominant response in layer V, which may be connected to the apical amplification ideas of **Larkum & Phillips**). However, the in vitro preparation of the study eliminated the LC from the equation and so did not provide the opportunity to observe the glutamate-evoked local release of NE proposed in GANE. As outlined in Table R2, more research is needed measuring in vivo interactions of glutamate and NE, as the GANE hot spot mechanism involves interactions between the LC and distant cortical representations.

### R8.6. Individual differences

**Geva** points out that tonic levels of arousal predict whether infants orient toward novel or familiar stimuli, and suggests that infancy is an interesting test case for GANE, as, unlike in later stages of development, infants lack an “established neural network set with implicit know-hows” that provide the glutamatergic priority signal necessary to ignite hot spots under arousal. Differences at the other end of life are also relevant, as **Nassar, Bruckner, & Eppinger** point out. Genetic variation in adrenergic receptors also may matter, as **Todd, Ehlers, and Anderson** make the case that ADRA2b deletion carriers have reduced inhibitory autoreceptor function.

### R9. Conclusions

As evinced by the diverse range of commentary, the NE hot spot mechanism goes beyond just the emotion–cognition literature to explain how arousal influences different forms of cognitive selectivity. One of GANE’s most vital contributions is that it showcases the ability of the cortex to regulate its own processing efficiency. Such local control of cognition represents a fundamental mechanism of adaptive brain function that has the potential to explain a variety of cognitive phenomena. As GANE exemplifies, synaptic activity is not just passively modified by neuromodulators. Instead, under situations of arousal that demand our attention, such as threat or excitement, salient brain signals recruit the ingredients necessary to form lasting memories.

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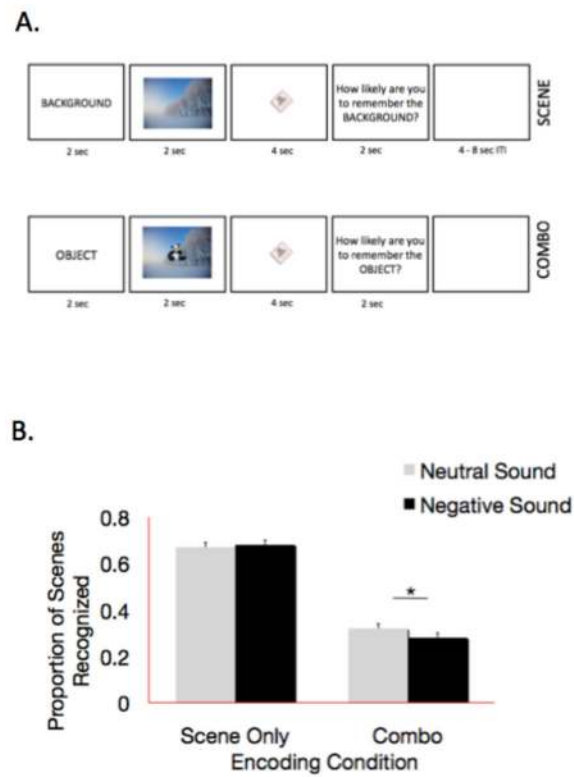
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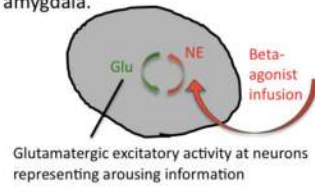
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**Fig. R1.**

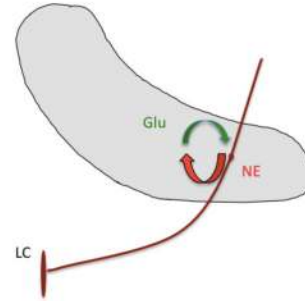
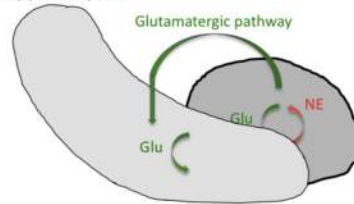
(A) Arousing negative sounds were heard after seeing a background scene either alone or superimposed with a foreground object. (B) The arousing sounds impaired memory for the scene only when it was seen behind the object and, therefore, was somewhat suppressed by that competitor (Ponzio & Mather 2014).

A. Beta-agonists increase hot spot activity in the amygdala.



C. If the locus coeruleus is depolarized, the amygdala-induced glutamatergic activation in the hippocampus stimulates local NE release and further amplifies glutamatergic activation via glutamate-NE hot spot mechanisms.

B. Amygdala glutamate-NE hot spots increase glutamatergic excitatory signals to the hippocampus.



**Fig. R2.**

Glutamate-NE hot spots originating in the amygdala modulate hippocampal activity via glutamatergic pathways. However, local NE release within the hippocampus also has an impact.

Table R1

General topics raised in commentaries.

What elicits LC activity?	<p>Higher levels of arousal associated with <b>uncertainty</b> may help new salient information gain priority via hot spot mechanisms, whereas lower levels of arousal may protect existing strong predictions from distracting information under conditions of high certainty (<b>Nassar, Bruckner &amp; Eppinger</b>).</p> <p><b>Prediction errors</b> may trigger a phasic NE response that facilitates the selective updating of predictions in the prioritized manner outlined by GANE (<b>Ferreira-Santos</b>).</p> <p><b>Competition</b> elicits arousal, which leads to an increase in theta and gamma oscillations that select and stabilize “winning” representations (<b>Phaf</b>).</p> <p><b>Negative</b> stimuli might evoke more arousal than positive stimuli (<b>Kaspar</b>).</p>
Forms of priority	Fluently processed stimuli yield a stronger signal (or are more salient), and so GANE can explain how arousal amplifies responses to these stimuli ( <b>Carbon &amp; Albrecht</b> ).
How does GANE operate in relation to specific aspects of brain function?	Commentators discussed <b>dendritic integration</b> ( <b>Larkum &amp; Phillips</b> ), relative timing of <b>oscillatory patterns</b> ( <b>Phaf</b> ), the role of the <b>dentate gyrus</b> in memory selection ( <b>Houghton</b> ), and <b>genetic variations</b> in the ADRA2B gene ( <b>Todd, Ehlers, &amp; Anderson</b> ).
Spatial extent of hot spots	<p><b>Eldar, Cohen, &amp; Liv</b> recognize that in the GANE model, hot spots would be co-extant with distributed cortical representations, whereas <b>Gaucher and Edeline</b> are expecting more spatially extensive loci. This difference in visualization highlights the need for tools to identify active hot spot elements. Immediate early genes may be useful in this regard.</p>
What are the adaptive functions of the neural effects of NE?	<p>GANE may be a general-purpose function that cuts across a variety of cognitive and behavioral effects (<b>Hull</b>).</p> <p>Salient events trigger the LC to release NE cortically, which facilitates a “network reset” that promotes quick changes in cortical states and adaptive behavioral responses (<b>Sara</b>).</p> <p>Salient stimuli may predict threatening or significant stimuli (<b>Bouret</b>).</p>
Relevance of GANE in various domains	<p><b>Stress.</b> Endocrine signals, in particular cortisol, work in tandem with NE to promote long-term adaptive changes and memories (<b>Hurlemann, Maier, &amp; Scheele</b>).</p> <p><b>Sleep and memory.</b> Acetylcholine is likely to have hot spot properties different from those of NE, and so low NE and high acetylcholine during REM sleep may help explain lack of memory for dreams (<b>Becchetti &amp; Amadeo</b>).</p> <p><b>Early development.</b> The LC exhibits developmental changes during infancy and early development, and early life stress shapes glutamate and GABA responses in ways that should be considered in the GANE model (<b>Geva</b>).</p> <p><b>Responses to sexual stimuli.</b> Contrary to expectations of posture showing approach/avoidance biases, people viewing either threatening or sexual stimuli exhibit a freezing-like reaction in which they are more immobile (<b>Mouras</b>).</p> <p><b>Emotion regulation.</b> Arousal levels should influence the ability to alter behavioral responses (<b>Hull</b>).</p> <p><b>Appraisal theory.</b> Stimuli that are relevant for individuals’ goals, needs, and values induce strong arousal and amygdala activity (<b>Montagrin &amp; Sander</b>).</p>
Factors that should be addressed	<p>Commentators pointed out that GANE requires further development to specify <b>timing</b> (<b>Talmi &amp; Barnacle; Navarra &amp; Waterhouse; Warren, Murphy, &amp; Nieuwenhuis</b>), address different effects in <b>prefrontal cortex</b> (<b>Abdallah et al.</b>), examine <b>context and individual differences</b> in determining salience (<b>Huntsinger &amp; Storbeck</b>), address role of <b><math>\alpha_1</math>-receptors</b> (<b>Navarra &amp; Waterhouse</b>), and address how <b>cardiac afferents</b> influence how LC modulates cortical activity (<b>Critchley &amp; Garfinkel</b>).</p>
Alternatives to GANE	<p>Priority is coded by phasic NE release and so there is no need for glutamate to signal priority (<b>Strange &amp; Galarza-Vallejo</b>; see response in Section R4.1)</p> <p>The amygdala is necessary for NE to enhance selective processing and memory consolidation of arousing stimuli (<b>Roosendaal, Luyten, de Voogd, &amp; Hermans</b>; see response in Section R4.2)</p> <p>The tag-and-capture model is better able than GANE hot spot mechanisms to explain the effects of arousal on memories for events that occurred minutes to hours before the arousing event (<b>Ritchey, Murty, &amp; Dunsmoor</b>; see response in Section R5).</p> <p>Countering the target article’s argument that a “network reset” model could not account for enhanced memory for well-attended items seen before an arousing event, <b>Bouret</b> argued that such enhanced memories could be accounted for by network reset if the qualitative nature of the representation changed (see response in Section R6).</p>

Table R2

Data needed to test hypotheses and better understand arousal–priority or NE–glutamate interactions.

Can we measure GANE-proposed neurotransmitter mechanisms in laboratory animals?	Direct measurements of local glutamate levels and NE or $\beta$ -adrenergic receptor activation levels in awake cortex with arousal/cue manipulations would make it possible to test our physiological GANE model. New techniques make it possible to track extra-synaptic glutamate activity (Okubo et al. 2010), and researchers are getting closer to being able to monitor levels of NE and G-couple protein receptor activation at spatial resolutions corresponding to a representational network (Muller et al. 2014).
Does NE interact with apical amplification priority signaling?	The <b>Larkum &amp; Phillips</b> hypothesis that NE modulates apical amplification in the output neurons of cortex as the mediator of top-down or cortico-cortical priority signals can be examined both in vitro and in vivo. Evidence for such gating would significantly expand the GANE model.
Is “network reset” a general motor–sensory or structure-specific effect?	Immediate early genes with the ability to reveal two brain activation sequences separated by a temporal interval could test the reset (reorganizing)-versus-amplification effects of phasic LC activation. We predict evoked sensory representations would be enhanced and stabilized by phasic glutamatergic activation of LC, whereas hippocampal and possible prefrontal representations would be reconfigured. Tonic effects of NE would not evoke reset.
How close in time does phasic arousal need to be to modulate the priority of another event?	Initial behavioral data suggest that arousal induced by one event can modulate processing of other events occurring within a few seconds (see target article for review). Previous work indicates that glutamate activation of NMDA receptors decays slowly and can last hundreds of milliseconds (Lester et al. 1990), but more work is needed to quantify the timing of glutamate and NE actions at hot spots (allowing for formal modeling, as highlighted by <b>Warren et al.</b> in their commentary).
Can we measure GANE-proposed neurotransmitter mechanisms in humans?	Advances in human magnetic resonance spectroscopy (MRS) enable the measurement of glutamate metabolites in vivo, but with poor spatial and temporal resolution. One straightforward test of GANE would be to examine whether an arousing stimulus can elicit a local, activity-dependent increase in glutamate levels for a prioritized stimulus.
Test of NE hot spots in humans	During task-related fMRI involving an arousal $\times$ priority manipulation, trial-by-trial estimates of pupil dilation to the arousing stimulus could be used to scale BOLD responses in cortical representational regions underlying the high-priority stimulus. This would provide an estimate of how LC responses selectively modulate local cortical activity.
Test Roozendaal et al. argument that NE effects on memory rely on the amygdala.	The fact that the hippocampus has many NE receptors suggests that NE can modulate memory consolidation in the hippocampus directly, without amygdala modulation (although NE release in the amygdala can lead to glutamatergic activation of the hippocampus, it does not directly increase NE in the hippocampus; see Fig. R2). A simple experiment would be to attempt to modulate consolidation of a hippocampally represented memory such as learning the context of a novel object by infusing NE into the hippocampus (as has been done with NE infused into the amygdala [Barsegyan et al. 2014])
Inverted-U curve	A direct examination of inverted-U curve effects with NE would be of interest. It is not clear if the functional shift seen at high levels of arousal is uniquely, or even critically, due to high NE levels or is a multifactorial effect depending on co-activation of other systems.