

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

Article

Accepted Version

Mather, M., Clewett, D., Sakaki, M. ORCID: <https://orcid.org/0000-0003-1993-5765> and Harley, C. W. (2017) GANeIng traction: the broad applicability of NE hotspots to diverse cognitive and arousal phenomena. Behavioral and Brain Sciences, 39. e228. ISSN 0140-525X doi: 10.1017/S0140525X16000017 Available at <https://centaur.reading.ac.uk/52682/>

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To link to this article DOI: <http://dx.doi.org/10.1017/S0140525X16000017>

Publisher: Cambridge University Press

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GANeing Traction: The Broad Applicability of NE Hotspots to Diverse Cognitive and Arousal
Phenomena

Mara Mather

David Clewett

University of Southern California

Michiko Sakaki

University of Reading

Carolyn W. Harley

Memorial University of Newfoundland

Abstract (60 words)

GANE 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 ‘hotspot’ feedback mechanism and its implications in a variety of psychological domains, inspiring exciting avenues for future research.

GANeing Traction: The Broad Applicability of NE Hotspots to Diverse Cognitive and Arousal Phenomena

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, local level of glutamatergic neurotransmission signifies the priority of an activated representation. When glutamate spillover from activated synapses activates NMDA receptors on nearby segments of a LC neuron around the same time that the LC neuron is depolarized, this leads to more local release of NE, which further amplifies glutamate release and the activation of the information the highly excited neurons are representing. Elsewhere, lower glutamate levels fail to ignite hotspots and undergo greater suppression via NE-induced inhibition. We proposed that, in addition to enhancing activation of prioritized representations, the NE-glutamate hotspots 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 1). 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 hotspot 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 hotspot: 1) an arousing-inducing stimulus that can stimulate LC activity (NE), and 2) a stimulus that has high priority (glutamate). As outlined in Table 1, 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.

1. Arousal

A number of commentaries raise questions regarding arousal.

1.1. 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 for initiating sexual arousal (Pfaff, 2006; of relevance for **Mouras'** commentary), while noradrenergic input to the amygdala is critical for enhancing memory for emotionally arousing stimuli (see **Roozendaal et al.** commentary and the section below 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, being physically active 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, Gherezghiher, & Nomura, 1984; Wilhelm, 2008). During sleep, pupils are constricted compared to waking (Yoss, Moyer, & Hollenhorst, 1970). During wakefulness, aerobic exercise (Ishigaki, Miyao, & Ishihara, 1991) or muscular exertion (Nielsen & Mather, 2015; Nielsen, Barber, Chai, Clewett, & Mather, 2015) increase pupil dilation. Arousal induced by stimuli or tasks also increase pupil dilation. For instance, emotionally arousing scenes (Bradley, Costa, & Lang, 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, Miccoli, Escrig, & Lang, 2008). These consistencies across different

elicitors of arousal provides an important starting point to elucidate the underlying mechanisms by which encountering emotionally arousing stimuli modulates cognitive and brain processing. **Eldar, Cohen and 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.

1.2. How the heartbeat influences LC activity. The LC is influenced not only by external stimuli and one's own thoughts, but also by interoceptive signals. For instance, distension of the bladder or colon increases LC activity (Elam, Thorén, & Svensson, 1986), whereas an increase in blood pressure decreases LC activity (Elam, Yoa, Svensson, & Thoren, 1984). LC neurons also show a 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, Fornal, & Jacobs, 1986).

Critchley and 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 they were originally detected and at what heartbeat phase they 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. Thus, 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 and 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 shown in their figure, there was not a significant difference between fear and disgust or happy faces, and the disgust and happy faces showed trends towards enhancement where neutral faces showed a trend towards impairment at diastole. Fear faces are often more salient than happy or disgust faces (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Mather & Knight, 2006), thus, 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.

2.3. 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 hotspots due to 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 hormone 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, due to 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, Chai, & Mather, in preparation). Thus, evidence suggests that arousing negative pictures have similar bottom-up salience for older adults as they do for younger adults.

2.4. Relation to appraisal theory. Based on 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 shows phasic activity to goal-relevant stimuli (Aston-Jones & Cohen, 2005; Aston-Jones, Rajkowski, & Cohen, 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, Brosch, & Sander, 2013) and prioritize attention to those stimuli (Pool, Brosch, Delplanque, & Sander, 2015). In contrast, our GANE model can explain their findings of enhanced processing of goal-relevant stimuli: once the

amygdala and/or higher cortical regions detect goal-relevant stimuli and recruit the LC, NE hotspots will be generated in circuits transmitting goal-relevant information and, in turn, hotspots will enhance memory and perception for those stimuli. Thus GANE does not contradict the appraisal model but instead extends it.

2.5. 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) where 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. Based on 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, Kerridge, Dimsdale, & Hoyt, 2007).

2. Priority

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

2.1. Perspectives on physiological mechanisms of priority. Larkum and Phillips describe a novel physiological mechanism for contextual information to modulate 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 they show the interaction of 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 and Amadeo** make the interesting point that conscious (thus prioritized) oneiric processing occurs during 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.

2.2. Fluency may be related to priority. **Carbon & Albrecht** point out that fluency (i.e., processing information more easily) is an important factor which determines stimulus priority. Greater fluency can arise because of perceptual salience (e.g., reading a word printed in a clear and 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) showed 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 nicely with GANE.

3. Predictive utility of GANE

Commentaries by **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 vs. neutral stimuli. As discussed in our target article, emotional stimuli tend to have higher priority than neutral stimuli due to 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 be especially 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 having a long interval would not increase the priority of neutral stimuli as high as that of emotional stimuli; it is likely that emotional stimuli still have higher priority than neutral stimuli when they are presented randomly even with a long interval. In addition, since 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, Schaefer, Tsivilis, & Talmi, in

prep), 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 for a long duration (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, Sakaki, Cheng, Velasco, & Mather, 2014; Sakaki, Fryer, & Mather, 2014; Sutherland & Mather, 2012). One way to achieve this in the context of Barnacle et al. (in prep) 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 the experiment is set up properly.

4. 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.

A.



B.

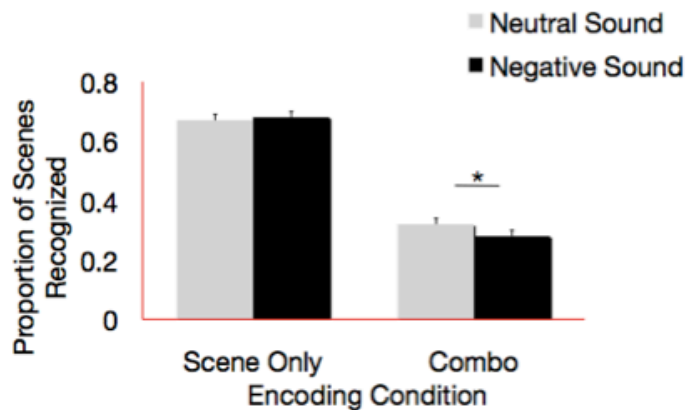


Figure 1. (A) Arousing negative sounds heard after seeing either a background scene alone or superimposed with a foreground object (B) impaired memory for the scene only when it was seen behind the object and therefore was somewhat suppressed by that competitor (Ponzio & Mather, 2014).

4.1. NE-only model. Strange and Galarza-Vallejo propose that the glutamate aspect of the model is not necessary -- that a simpler model is that 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, Fryer, et al., 2014). 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 set-up 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 either shown alone or with an object superimposed on it (Figure 1A), 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 (Figure 1B; 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 either conditioned to predict 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, Greening, & Mather, 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.

4.2. Amygdala-based model. Roozendaal et al. 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 that its role in mediating the effects of NE is only **necessary** when the amygdala is the primary site of the neural representation in question.

Data from individuals with amygdala lesions helps 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 showed 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 showed 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, Talmi, Hurlemann, Patin, & Dolan, 2011). Someone with complete bilateral amygdala lesions who could not recognize fear from faces still showed normal rapid detection of those faces (Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009). Thus, the amygdala is not necessary for the initial selective attention and encoding advantages seen for emotionally arousing stimuli, suggesting that NE-glutamate hotspots 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 instance, in studies of fear conditioning, individuals with amygdala lesions show normal skin conductance responses to aversive stimuli such as loud noises (Bechara et al., 1995; Klumpers, Morgan, Terburg, Stein, & van Honk, 2014). Likewise, three patients with bilateral amygdala lesions each had a panic attack when inhaling 35% CO₂ (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, Adolphs, Damasio, & Tranel, 2011).

This pattern of findings suggests 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; Klumpers 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 showed skin conductance responses to the CS+ (Bechara et al., 1995). Thus,

amygdala lesions impair physiological responding but not explicit learning about which cues predict threat. Amygdala lesions also impair physiological responding to simulated monetary rewards and losses in the context of a gambling game (Bechara, Damasio, Damasio, & Lee, 1999), indicating that the amygdala is necessary for an abstract stimulus predicting something positive or negative to yield a physiological affective response.

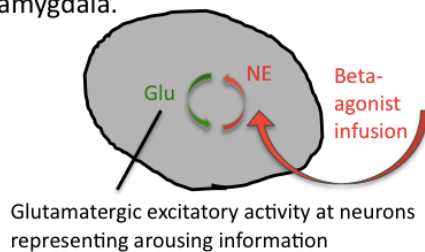
The findings that patients with amygdala lesions no longer have physiological responses to predictive cues despite as much explicit knowledge about the contingencies as normal controls suggests that: 1) there are amygdala-based neural representations of associations between neutral cues and potential 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 about fear conditioning contingencies despite showing a skin conductance response to the CS+ suggests that there also are amygdala-independent hippocampal-based neural representations of associations between CS and US. 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).

One domain in which the noradrenergic contributions to interactions between amygdala and hippocampus have been examined is in 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 minutes 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, Anderson, Donowho, & McIntyre, 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 (Figure 2A). This hotspot activity increases glutamatergic signaling to the hippocampus (Figure 2B) 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 (Figure 2C; see target article for more details on hotspot mechanisms). In summary, McReynolds’ data suggests 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 NE also modulates excitation and inhibition directly in these other brain regions via local release. The critical experiments to test this have not been done yet (see relevant proposed study in Table 2).

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.

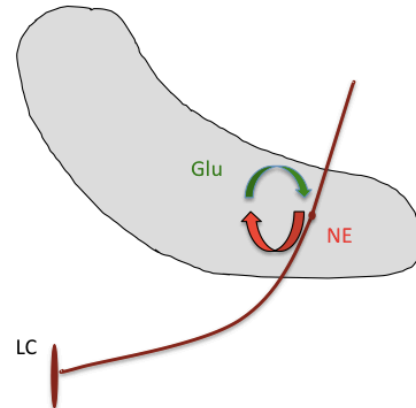
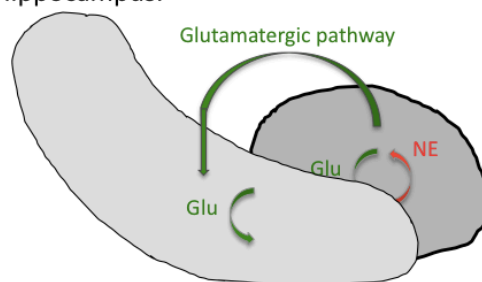


Figure 2. Glutamate-NE hotspots originating in the amygdala modulate hippocampal activity via glutamatergic pathways. However, local NE release within the hippocampus also has an impact.

Rooszendaal et al. 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-BLA infusion of a beta-adrenergic agonist (clenbutorol) decreases hippocampal excitability in non-IA trained control animals. However, their interpretation appears to be incorrect, as in that study, there was no significant difference between vehicle and clenbutorol in the untrained rats.

5. The role of NE hotspots in long-term memory formation

Some commentaries raise questions concerning the role of NE hotspots in memory. First,

Hurlemann, Nauerm & 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 and colleagues demonstrated that NE and glucocorticoids interact during processing of emotional stimuli (Hurlemann, 2008; Kukulja et al., 2008; Kukulja, Klingmüller, Maier, Fink, & Hurlemann, 2011). In particular, their work suggests that NE interacts with cortisol to enhance learning of emotional information within the amygdala-hippocampal network.

Acute stress and administration of glucocorticoids lead to enhanced glutamate release both in the amygdala (Reznikov et al., 2007) and hippocampus (Moghaddam, Bolinao, Stein-Behrens, & Sapolsky, 1994) via mechanisms mediated by glucocorticoid receptors (GR) and mineralocorticoid receptors (MR; for reviews see Popoli, Yan, McEwen, & Sanacora, 2012; Sandi, 2011). In the amygdala and hippocampus, interactions between glucocorticoids and NE have been observed as well (for reviews Joëls, Fernandez, & Roozendaal, 2011; Krugers, Karst, & Joels, 2012). These results suggest the interesting possibility that glucocorticoids help NE create hotspots in the amygdala-hippocampus circuit by enhancing glutamatergic activity. One question is whether the NE-cortisol interaction goes beyond the amygdala-hippocampus circuit. While most previous research focuses on the effects of glucocorticoids either in the amygdala-hippocampus pathway or the PFC, glucocorticoids might also amplify NE hotspots in other cortical regions, given that GRs are widely expressed in brain (Morimoto, Morita, Ozawa, Yokoyama, & Kawata, 1996). Furthermore, elevated cortisol and NE levels tend to impair goal-directed attentional processes in the PFC (Schwabe, Tegenthoff, Höffken, & Wolf, 2012), which should enhance the impact of the bottom-up, salience-driven hotspots predominant in sensory brain regions.

Second, **Ritchey, Murty & Dunsmoor** state that the tag-and-capture model is better able than GANE hotspot mechanisms to explain the effects of arousal on memories for events that happened minutes to hours before the arousing event. For example, initially weak memories can be strengthened by a subsequent salient signal, such as novelty or aversive events (Dunsmoor, Murty, Davachi, & Phelps, 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 proteins 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.

While in our target article we focused mainly on the immediate effects of NE hotspots, we believe that evidence indicates a role of these hotspots in tag-and-capture scenarios. β -adrenergic receptor activity stimulates protein synthesis and gene expression alterations associated with long-term potentiation maintenance (Maity, Jarome, Blair, Lubin, & Nguyen, 2015; O'Dell, Connor, Gelinas, & Nguyen, 2010). NE hotspots should play a role in tag-and-capture by elevating local NE levels to activate β -adrenergic receptors as well as by increasing glutamatergic activation of NMDA receptors. Both β -adrenergic and NMDA activity (in addition to dopamine D1/D5 receptor activity) are essential to “set the learning tag” for an initial weak memory and β -adrenergic receptor activation is required during exposure to the modulating novel event occurring an hour later (Moncada, Ballarini, Martinez, Frey, & Viola, 2011). A particularly intriguing finding is that the behavioral tagging phenomena 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, Moncada, Martinez, Alen, & Viola, 2009). Likewise, Dunsmoor et al. (2015) found that fear conditioning enhanced memory for previously learned images only when those images are 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 hotspots and raises the interesting question of just how widely the plasticity-related proteins stimulated via β -adrenergic receptor activation at NE hotspots 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. While 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 β -adrenergic activity induced by arousing modulatory events will be fruitful.

6. How GANE amplifies prioritized representations during a “network reset”

According to a prominent theory, NE release orchestrates a “network reset” that reorients 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 **Susan 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 reorienting 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, Wais, & Gabrieli, 2006; Knight & Mather, 2009; Sakaki, Fryer, et al., 2014), which appears to be the opposite of a network reset effect. Based on 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. **Sebastian 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.

One domain with evidence related to the “altered” representation view is the fear/evaluative conditioning paradigm; events repeatedly followed by emotional outcomes acquire emotional properties (for a review see Baeyens, Field, & Houwer, 2005). Our previous research also demonstrates 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, Ycaza-Herrera, &

Mather, 2014). These results are in line with Bouret's argument that arousal enhances memory for preceding information when the preceding information is integrated with the arousing events.

However, there is also evidence consistent with the idea that arousal strengthens original representations for high-priority information. Empirical evidence suggests that emotional arousal enhances the veracity of the original representation, or detail memory, rather than gist alone (Sakaki, Fryer, et al., 2014). 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).

7. Alternative ways to trigger LC activity

While 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.

7.1. Prediction errors activate LC. Prediction is a central feature of efficient cognitive processing. As described by **Fernando 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, Coenen, Bombeke, van Bochove, & Notebaert, 2015; Preuschoff, Marius't Hart, & Einhäuser, 2011). Furthermore, in monkeys, phasic LC activity ceases to signal the occurrence of reward once it follows a specific action predictably (Sara & Segal, 1991). Emotional arousal likely elicits the most robust biased competition effects, because it represents the "net sum" of several types of prediction error, including sensory, affective, and task-related mismatches (Barrett & Simmons, 2015; Vogel, Shen, & Neuhaus, 2015).

7.2. Uncertainty activates LC. As pointed out by **Nassar, Bruckner and Eppinger** (as well as by Bouret), it is important to consider the purpose of having different levels of arousal change cognitive processing. 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 just 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 hotspots. They suggest that older adults' deficits in learning under conditions of uncertainty may be linked with age-related declines in LC function.

7.3. Conflict activates LC and is related to gamma and theta oscillations. As highlighted by **Hans Phaf**, there is much evidence that competition and conflict between representations can induce arousal. These stimuli/events are likely to produce hotspots too, based on evidence that conflict - along with novelty, target detection, uncertainty, and performance errors - elicit LC activity (for reviews see Berridge & Waterhouse, 2003; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010; Yu & Dayan, 2005). Fundamentally, GANE predicts that *any* stimulus that activates the LC-NE system will produce hotspots 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) initiating a network reset via the LC.

One particularly useful contribution to GANE is **Phaf's** description of 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 inter-cortical communication. Subsequently, gamma

oscillations facilitate a resetting and stabilization of “winning” representations. We also agree with his assertion that competition begets arousal, as conflict can elicit LC responses.

His description is consistent with **Susan Sara’s** empirical data. In her commentary, Sara describes evidence that stimulating the LC briefly suppresses gamma oscillations for 200ms, which is followed by a near doubling of the gamma power immediately after, 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, McNaughton, James, & Kelly, 1975). It could be useful to re-examine this theta signature of LC activation (for more recent support see Walling, Brown, Milway, Earle, & Harley, 2011) and its role in synchronizing activity for prioritized representations. Another interesting question is whether (as suggested in the target article) NE hotspots enhance local gamma power via a beta-adrenergic pathway, thereby increasing selective attention.

8. 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 post-synaptic alpha2 receptors, the subthreshold input promoting role of alpha1 receptors, the synergistic role of alpha1 with beta-adrenergic receptors or recently described astrocytic functions of alpha1 receptors. The co-release of peptides from LC varicosities is not considered nor are 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 and the role of arousal in engaging self-regulatory mechanisms. Below we discuss some of the mechanistic issues raised in the commentaries.

8.1. 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 alpha2 receptors that play important roles in the PFC (see commentaries by **Abdallah et al.** and **Todd et al.**) and which also occur in other areas of neocortex (Venkatesan, Song, Go, Kurose, & Aoki, 1996). **Navarra and Waterhouse** and **Gaucher and Edeline** point out that alpha1-adrenoreceptors have more varied actions, including synergies with beta-adrenoreceptor effects, potentiating effects on their own, and astrocytic actions. In particular, they highlight that the role of alpha1-adrenoreceptor 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, Ding et al., (2013) have shown that global astrocytic calcium waves are initiated via LC-NE activation of astrocytic alpha1-adrenoreceptors (Ding et al., 2013), consistent with a model in which LC-NE global effects recruit both alpha1- and alpha2-adrenoreceptors.

8.2. NE has mainly suppressive effects in sensory regions. **Gaucher and 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.

8.3. Differential effects of adrenergic receptors in the prefrontal and posterior cortex.

Chadi Abdallah and colleagues 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 DLPFC. Based on animal and human research, they suggest hotspot effects are most likely to occur in sensory and limbic (e.g., amygdala, hippocampus) synapses where beta-adrenoreceptors promote glutamate responses and LTP. In the PFC, in contrast to “classic” sensory areas, beta-adrenoreceptor activation has been shown to impair rather than enhance postsynaptic function via increased cAMP signaling (Arnsten, Raskind, Taylor, & Connor, 2015;

Ramos & Arnsten, 2007). Like beta-adrenoreceptors, alpha1- and alpha2-adrenoreceptors also appear to have contrasting influences on neuronal activity in the PFC versus sensory cortices: whereas alpha1 receptors enhance sensory neuron firing, they tend to impair PFC function and working memory (Ramos & Arnsten, 2007); on the other hand, whereas alpha2 receptors enhance inhibitory signals and suppress noisy activity in the posterior cortex, their activation strengthens DLPFC functional network connectivity and promotes working memory (Arnsten, Wang, & Paspalas, 2012).

These inverted rules of adrenoreceptor function in the PFC have important implications for how GANE influences cognitive processing during sudden arousal. Whereas 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, Walling, Milway, & Harley, 2005). Thus DLPFC impairments may facilitate reorienting during arousal to information that has bottom-up salience and is associated with hotspots of high activity in sensory regions but not in PFC.

8.4. 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 in the PFC accords well with the timing hypotheses proposed by **Warren et al.** 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 amplify the effects of priority in perception and memory regardless of whether the priority occurred via top-down goals or bottom-up salience, since cognitive control goals have had sufficient time to strengthen goal-relevant representations elsewhere in cortex before any potential disruption of PFC due to moderate-to-high levels of NE occurs (Ramos & Arnsten, 2007). In contrast, the source of priority may matter more when experiencing arousal before a stimulus is perceived. While pre-stimulus arousal should amplify the effects of bottom-up salience, it might actually 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 pre-stimulus arousal enhances the impact of bottom-up salience (Lee, Itti and Mather, 2013; Sutherland and Mather, 2011; Sutherland and Mather, 2015), while post-stimulus arousal enhances the impact of top-down prioritization (Lee, Greening and Mather, 2015; Sakaki et al., 2014). 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 PFC ability to prioritize an otherwise non-salient stimulus, arousal should diminish the impact of top-down priority because the goal-relevant representation isn't 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, Lee, & Mather, in preparation). Based on the impairing effects of high NE on DLPFC, in order for a pre-stimulus arousal to enhance processing of a goal-relevant item, the goal prioritization process would need to be relatively independent of PFC, perhaps because it is automatic or habitual.

8.5. 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 non-alert, moderate LC activity promotes being focused, and high tonic LC activity promotes distractibility. In their commentary, **Navarra and Waterhouse** bring up the question of 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 post-synaptic 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 post-synaptic 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 post-synaptic 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 connect with the apical amplification ideas of Larkum and 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 2, more research is needed measuring *in vivo* interactions of glutamate and NE, as the GANE hotspot mechanism involves interactions between the LC and distant cortical representations.

8.6. Individual differences. **Geva** points out that tonic levels of arousal predict whether infants orient towards novel or familiar stimuli and suggests that infancy is an interesting test case for GANE as, unlike in later stages of development, infants lack “established neural network(s)” and aren’t, “set with implicit “know-how’s” that provide the glutamatergic priority signal necessary to ignite hotspots under arousal. Differences at the other end of life are also relevant, as **Nassar et**

al. point out. Genetic variation in adrenergic receptors also may matter, as **Todd et al.** make the case that ADRA2b deletion carriers have reduced inhibitory autoreceptor function.

9. Conclusion

As evinced by the diverse range of commentary, the NE hotspot 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 isn't 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.

Table 1. General topics raised in commentaries.

What elicits LC activity?	<p>Higher levels of arousal associated with uncertainty may help new salient information gain priority via hotspot mechanisms whereas lower levels of arousal may protect existing strong predictions from distracting information under conditions of high certainty (Nassar, Bruckner & Eppinger).</p> <p>Prediction errors may trigger a phasic NE response that facilitates the selective updating of predictions in the prioritized manner outlined by GANE (Ferreira-Santos).</p> <p>Competition elicits arousal, which leads to an increase in theta and gamma oscillations that select and stabilizing “winning” representations (Phaf).</p> <p>Negative stimuli might evoke more arousal than positive stimuli (Kaspar).</p>
Forms of priority	<p>Fluently processed stimuli yield a stronger signal (or are more salient) and so GANE can explain how arousal amplifies responses to these stimuli. (Carbon)</p>
How does GANE operate in relation to specific aspects of brain function?	<p>Commentators discussed dendritic integration (Larkum & Phillips), relative timing of oscillatory patterns (Phaf), the role of the dentate gyrus in memory selection (Houghton), and genetic variations in the ADRA2B gene (Todd, Ehlers & Anderson).</p>
The spatial extent of hotspots	<p>Eldar et al. recognize that in the GANE model hotspots would be co-extant with distributed cortical representations, while Gaucher and Edeline are expecting more spatially extensive loci. This difference in visualization highlights the need for tools to identify active hotspot 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 (Hull)</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 (Sara).</p> <p>Salient stimuli may predict threatening or significant stimuli (Bouret)</p>
Relevance of GANE in various domains	<p>Stress. Endocrine signals, in particular cortisol, work in tandem with NE to promote long-term adaptive changes and memories (Hurlemann, Maier, & Scheele).</p> <p>Sleep and memory. Acetylcholine is likely to have different hotspot properties than NE and so low NE and high acetylcholine during REM sleep may help explain lack of memory for dreams (Becchetti & Amadeo).</p> <p>Early development. The LC shows 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 (Geva).</p> <p>Responses to sexual stimuli. Contrary to expectations of posture showing approach/avoidance biases, people viewing either threatening or sexual stimuli show a freezing-like reaction in which they are more</p>

	<p>immobile (Mouras).</p> <p>Emotion regulation. Arousal levels should influence the ability to alter behavioral responses (Hull).</p> <p>Appraisal theory. Stimuli that are relevant for individuals' goals, needs and values induce strong arousal and amygdala activity (Montagrin & Sander)</p>
Factors that should be addressed	<p>Commentators pointed out that GANE needs further development to specify timing (Talmi & Barnacle; Navarra & Waterhouse; Warren, Murphy, & Nieuwenhuis), address different effects in prefrontal cortex (Abdallah et al.), role of context and individual differences in determining salience (Huntsinger & Storbeck), the role of alpha-1 receptors (Navarra & Waterhouse). and again the role of timing in beat-to-beat the functional effects LC firing modulation and cortical activity modulation (Critchley).</p>
Alternatives to GANE	<p>Priority is coded by phasic NE release and so there is no need for glutamate to signal priority (Strange & Galarza-Vallejo; see response in section 4.1)</p> <p>The amygdala is necessary for NE to enhance selective processing and memory consolidation of arousing stimuli (Roosendaal, Luyten, de Voogd, & Hermans; see response in section 4.2)</p> <p>The tag-and-capture model is better able than GANE hotspot mechanisms to explain the effects of arousal on memories for events that happened minutes to hours before the arousing event (Ritchey, Murty, & Dunsmoor; see response in section 5).</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, Bouret argued that such enhanced memories could be accounted for by network reset if the qualitative nature of the representation changed (see discussion in section 6).</p>

Table 2. 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, Joseph, Slesinger, & Kleinfeld, 2014).
Does NE interact with apical amplification priority signaling?	The Larkum and Phillips 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 a 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 while 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 in order 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 glutamate activation of NMDA receptors has slow decay that can last hundreds of milliseconds (Lester, Clements, Westbrook, & Jahr, 1990), but more work is needed to quantify the timing of glutamate and NE actions at hotspots (allowing for formal modeling, as highlighted by Warren et al. 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 <i>in vivo</i> , 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 hotspots in humans	During task-related fMRI involving an arousal x 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. Thus, this would provide an estimate of how LC responses selectively modulate local cortical activity.
Test Roozendaal et al.'s 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 (while NE release in the amygdala can lead to glutamatergic activation of hippocampus, it does not directly increase NE in the

	hippocampus; see Figure 2). 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, McGaugh, & Roozendaal, 2014)
The inverted U curve	A direct examination of inverted U curve effects with norepinephrine 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.

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