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Title: Locus coeruleus, noradrenaline and behavior: network effect, network effects?

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Abstract:

How does the noradrenergic nucleus locus coeruleus acts on target networks to regulate behavior? Zerbi et al combine functional neuroimaging and pharmacogenetics in mice to tackle that issue, uncovering a network action underlying stress. And providing insight for cognition?

Body

Noradrenaline (NA) is one of the major neuromodulatory systems, with a key role in vigilance, stress attention and decision-making (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Sara and Bouret, 2012). As in all major neuromodulatory systems, few neurons located in a small brainstem nucleus affect behavior through a complex influence on a vast number of target structures. But how does it work? Since the discovery of NA as a neurotransmitter in the brain, one of the major challenges has been to understand the influence of NA containing neurons of the locus coeruleus (LC) on the activity of their forebrain target networks, and the corresponding effect on behavior and cognition. Over the years, researchers have recorded the activity of LC neurons in various behavioral conditions and, usually in separate experiments, examined the consequence of LC activation or NA release in a subset of brain regions. Several theories have been proposed to articulate these results together and extrapolate a scenario relating the network action of LC activation and its influence on behavior (Arnsten, 2000; Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Sara and Bouret, 2012). But until the work of Zerbi et al, in this issue of *Neuron*, it had been very speculative (Zerbi et al., 2019).

To address directly the relation between the behavioral effect of LC activation and its underlying neurobiological action at a network level, Zerbi et al undertook a very ambitious approach: they combined functional neuroimaging with chemogenetic activation of LC neurons in mice, together with a quantification of local NA turnover and local expression of noradrenergic receptors in target areas. In awake mice, chemogenetic activation of the LC induced an increase in behavioral markers of stress. In anesthetized animals, the same LC activation induced a reliable change in functional connectivity among brain structures. Typically, LC activation induced an increase in connectivity among regions of the 'salience network' (eg anterior cingulate and insular cortex, ventral striatum, central thalamus and hippocampus) and regions of the amygdala network. Critically, the authors could demonstrate that these network changes were not only related to the activation of LC neurons but also dependent upon local processes. Indeed, the pattern of functional connectivity evoked by LC stimulation was directly related to the local noradrenergic activity (assessed through local turnover ratio) and to the local expression level of noradrenergic receptors (especially alpha 1 and alpha 2, less so for beta 1 and beta 2). Of course, there are limitations: the relation with behavior is indirect, the specific implication of distinct receptor subtype varies across regions and levels of NA, the relation between behavior, NA levels and its network effects are complex and dynamic and the LC is probably not as homogenous as it was thought to be. And how does that study on stress articulate with the known role of NA in cognitive functions such as attention

and memory? But rather than limitation, these issues can be seen as new frontiers for the field, and this study provides exciting directions to push these frontiers even further.

Functional neuroimaging had already provided a critical insight into the network action of the LC/NA system, by providing a global image of network changes in conditions known to activate the LC, including high levels of arousal. For example, Hermans et al (2011) had shown that stress-induced mobilization of the salience network was dependent upon beta noradrenergic receptors in humans, in line with seminal work demonstrating the key action of NA in arousal (Arnsten, 2000; Berridge and Waterhouse, 2003; Sara and Bouret, 2012). The work of Zerbi et al confirms and extends these finding by showing that LC activation is necessary and sufficient for this reconfiguration. Indeed, even if Zerbi et al conducted their imaging study in anesthetized mice, whereas Hermans et al imaged the brain of human participants during the stressful experience, the network changes revealed by these two studies are extremely similar. In other words, the network modulation of LC stimulation seems to be a very reliable neurobiological substrate of stress, rather than a side effect. But the role of the LC/NA system is not limited to stress. To what extent can this work provide further insight into other functions of the NA system such as memory, attention or decision making?

In the case of emotional memory, there might be a direct continuity, since several imaging studies in humans confirm the long established action of NA on emotional memory through its action on amygdala network (see Sara and Bouret, 2012 for review), which is coherent with the mobilization of the salience and amygdala network mobilized in Zerbi et al. But things could be a bit more complicated for attention and decision making which, in contrast to stress, are not related to arousal and NA level in a simple, monotonic fashion (Aston-Jones and Cohen, 2005; Sara and Bouret, 2012). Indeed, the relation between arousal and cognitive performance follows an inverted U relation, such that performance initially increases with arousal, but deteriorates for highest levels of arousal. Several pieces of evidence indicate that this inverted U relation between cognitive performance and arousal is at least in part mediated by the noradrenergic system (Berridge and Waterhouse, 2003; Arnsten, 2000). At intermediate levels of LC activation, NA would mostly stimulate high affinity receptors located in the prefrontal cortex and improve executive function. At higher levels of LC activation/ NA release, the recruitment of other receptors subtypes, displaying a lower affinity but more ubiquitous in the brain, would cause the disengagement of the prefrontal cortex at the benefit of more posterior regions, involved in more basic sensory-motor responses (Arnsten, 2000). In that theoretical frame, the level of LC activation associated with stressful conditions would far exceed the levels enabling efficient cognition. Lower LC/NA levels would be associated with a distinct pattern of functional connectivity in the forebrain, more compatible with executive functions. Recent experiments in primates indicate that it is could be the case. Hadj-Bouziane & collaborators used atomoxetine (an inhibitor of NA recapture) to examine the consequence of NA stimulation on network reconfiguration using resting state fMRI in rhesus monkeys (Guedj et al., 2016). Interestingly, they could show that atomoxetine reliably enhanced a fronto-parietal network in anesthetized animals, at doses that improved attention performance in behaving monkeys, with virtually no effect on stress. Interestingly, as in Zerbi et al, the network reconfiguration effects of NA stimulation in anesthetized animals is very coherent with the observed behavioral effects in awake animals. So even if the effect of NA stimulation differs markedly between these studies, they converge to show that when described in terms of network reconfiguration, the biological influence of NA activation is so reliable that it can predict the behavioral effect in awake animals. There are many reasons for which the network effects of NA stimulation differ between these studies (to begin with, species and method of NA activation), but it seems more interesting to consider an interpretation in terms of magnitude of NA activation, in the light of the complex relation between NA, arousal, and executive functions. Indeed, the work of T. Donner & collaborators indicates that, in humans, transient and moderate increases in arousal (measured with pupilometry) were associated with a improvement in decision making (bias reduction) and a reinforcement of corresponding activity in fronto-parietal networks, together with an increase in LC activity (de Gee et al., 2017). Thus, assuming that at least some of what de Gee et al (2017) observed in humans was related to the network reconfiguration described by Guedj et al (2016) in monkeys, it is tempting to assume that they were both related to a moderate LC activation, which might be different from what Hermans et al (2011) or Zerbi et al (2019) observed in more stressful conditions. All these studies could

all fit in the framework proposed by A. Arnsten decades ago, by assuming that the difference among those studies is related to the level of LC/ NA activation: moderate levels of LC/NA activation set the forebrain into a mode compatible with executive function, by reinforcing a fronto-parietal networks (as in the studies of Hadj-Bouziane et col. in monkeys and Donner et col. in humans). But higher levels LC/NA activation would induce a distinct configuration (saliency and amygdala network), more compatible with stress responses (as in the work of Bohacek et col. in mice and Fernandez et col. in humans). That remains an open question, to be tested directly, and characterized at a mechanical level, without all the potential confounds. But clearly, these studies combining large scale imaging and LC/NA manipulations should continue to provide a critical insight into neuromodulation functions.

As pointed out by the authors in the discussion, describing the network changes in behaving animals will be essential for understanding how network changes evoked by LC stimulation vary as a function of the behavioral and cognitive context, and the corresponding brain activity. As discussed just above, however, the network effects in anesthesia seem to be reliable enough to predict behavior in awake animals, when described as relatively stationary processes (once established by the treatment, the state of the system is stable in time), both at a neurobiological and at a behavioral level. In other words, these studies can reliably capture the difference across stable behavioral states associated with stable network configurations determined by distinct global levels of NA/ LC activity. But neurophysiological studies have described a very dynamic relation between LC activation and specific task events, as well as between transient LC activation and information processing in target regions. And this has led to several theories of LC function, which try to understand on the dynamic relation among cognitive processes, salient events, LC activation and network changes (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Sara and Bouret, 2012). Even if these theories remain very speculative, and the boundary between transient vs sustained effects of NA activation remain debated, they emphasize the importance of including the dynamic relation between brain activity and behavior to understand complex cognitive processes. Future studies aimed at relating network changes evoked by LC activation and behavior will probably need to use tools such as optogenetics or electrophysiologically triggered fMRI and match the dynamic of cognitive and behavioral processes in animals performing standard laboratory tasks to address these questions.

Another critical issue to address in future studies is the anatomical organization of the LC. Noradrenergic LC neurons have long been regarded as a functionally homogenous population, such that an increase in saliency or arousal would be associated with a global increase in the activity of all LC neurons. But a series of recent studies suggest that the organization of LC neurons is not that simple. Chandler and colleagues showed that LC neurons projecting to the frontal cortex had a higher excitability compared to those projecting to the motor cortex (Chandler et al., 2014). In and of itself, this could have a strong influence on how global LC activation influences target networks: all other things being equal, PFC regions would receive more NA than more posterior regions for a given level of LC activation. But things seem to be even more complicated: in addition to this functional heterogeneity of LC neurons based on their projection pattern, this heterogeneity of LC projections could also be related to their input pattern. By combining anatomical tracing with behavioral studies, Uematsu and colleagues identified a modular organization of the LC, such that LC neurons could be separated not only based on which regions they project to, but also which regions they receive inputs from. In other words, LC neurons would be organized into relatively independent modules, interacting with a given set of forebrain structures involved in a specific functional network (here, consolidation vs extinction of fear) (Uematsu et al., 2017). Given this modular organization, the pattern of LC activation across behavioral and cognitive functions would vary not only in terms of number of neurons involved, but also in the identity of neurons involved. The exact nature of these modules, and their relative weight on the function of the LC (compared to more homogenous inputs from the medulla, (Aston-Jones and Cohen, 2005; Sara and Bouret, 2012) is just beginning to be investigated, but it should definitely be taken into account to understand the network action of the locus coeruleus.

In conclusion, this work is a technical 'tour de force', providing not only a rich and rare set of data but also inspiration for future studies. Given the complexity of these processes, computational modeling

will be required at some point, but in any case, this work should definitely boost the field of noradrenaline and other neuromodulatory systems.

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