The role of the locus coeruleus-noradrenaline system in temporal attention and uncertainty processing

Brown, S.B.R.E.

7. General discussion and future directions

7.1 Introduction

The chapters of the current dissertation are of a relatively heterogeneous nature. Therefore, it seems difficult to draw very detailed conclusions about specific details of the theories that form the foundation of this dissertation (i.e. the adaptive gain and uncertainty-processing theories). Instead, I have attempted to provide a number of general conclusions about the two themes that are central to this dissertation: the role of the locus coeruleus-noradrenergic (LC-NE) system in temporal attention and in learning. To aid the legibility of this closing chapter, and given its reflective and interpretative nature, no literature references are presented: the reader is kindly referred to the General Introduction of the dissertation for relevant literature suggestions.

7.2 The role of the LC-NE system in temporal attention

Although this dissertation contains some unexpected and null findings, the first three empirical chapters clearly suggest a role for the LC-NE system in temporal attention. Regarding the late positive potential (LPP), our findings suggest that this ERP may reflect the inhibition of irrelevant stimulus representations in the visual cortex, allowing for more selective processing of the emotional stimulus that evoked it. Given the proposed relationship between the LPP and the noradrenergic system, we have tentatively demonstrated the LC-NE system to be involved in temporal fluctuations in attention.

Although we found no reliable effect of the noradrenergic drug clonidine on the attentional blink, we found clear effects of this drug on T1 identification accuracy and related ERP components. While this finding may have implications for the theory that related the attentional blink to phasic noradrenergic activity, these findings do suggest a general role for the LC-NE system in temporal

attention, as reflected in behavioral (reduction of noradrenergic baseline activity reduces target identification accuracy) and electrophysiological results (reduction of noradrenergic baseline activity reduces the amplitude of two information-processing related ERPs).

The final chapter devoted to temporal attention suggests that phasic noradrenergic bursts do not mediate the accessory stimulus effect, contrary to our expectations. However, administration of clonidine did *increase* the size of the accessory stimulus effect. We provide an explanation in terms of compensatory mechanisms (drug-related decreases in cognitive performance can be compensated for by arousing stimuli). Again, even though we did not provide evidence for the theory that phasic noradrenergic bursts subserve the accessory stimulus effect, we did show that reducing noradrenergic baseline activity influenced temporal attention.

In sum, although we have found some counterintuitive effects that do not necessarily provide evidence for popular theories that propose a role for noradrenaline in temporal attention, our work does show that the LC-NE system influences temporal attention.

7.3 The role of the LC-NE system in learning

The two dissertation chapters that are devoted to the role of the LC-NE system in learning present a more complicated conclusion than the results on temporal attention. Regarding our P3 study, we did not confirm the hypothesis that the P3b to rare target stimuli is subserved by the noradrenergic system while the P3a to novel stimuli is subserved by the cholinergic system. Clonidine attenuated baseline noradrenergic activity, but it actually increased the amplitude of the target-related P3b (while it decreased the amplitude of the P3a). Scopolamine decreased the amplitude of the novel-related P3a, but, like clonidine, it increased the

amplitude of the target-related P3b. These effects are difficult to interpret: although scopolamine antagonizes muscarinic receptors, it does so both pre- and postsynaptically, which can actually lead to increased extracellular levels of acetylcholine. Given our relatively high dose of scopolamine, presynaptic stimulation is to be expected, but contrary to the hypothesis that we tested, the purportedly increased levels of acetylcholine were not accompanied by an increased P3a amplitude.

The question that arises, is what these results imply functionally. Our findings seem in line with a theory on uncertainty processing that relates noradrenergic activity to the signaling of unexpected uncertainty and cholinergic activity to the signaling of expected uncertainty (cf. Chapter 1 of this dissertation). Indeed, administration of a drug that reduces noradrenergic baseline activity reduces the P3 amplitude to (unexpected) novel-related targets, while a drug that increases extracellular levels acetylcholine levels increases the P3 amplitude to (expected) target stimuli. Another theory may functionally account for these observations: P3 amplitude is related to context updating, so our findings may imply that a drug that reduces noradrenergic activity leads to less updating of an agent's current context (reflected by a smaller P3 amplitude), while a drug that increases availability of acetylcholine leads to increased context updating (reflected by a larger P3 amplitude). The behavioral effects of modulated context updating are unclear: in this and other work we have shown that ingestion of clonidine and scopolamine is associated with increased reaction times, and decreased accuracy and perceptual sensitivity.

The final chapter of the dissertation reveals a complicated image of the role of the LC-NE system in learning as well. We find mainly counter-evidence for the conflict-modulated Hebbian learning hypothesis that suggests that registration of conflict is associated with arousal and leads to LC activation, phasic noradrenergic release, and concomitant increased Hebbian learning. Although behavioral results

from a Stroop task are in accordance with this hypothesis and therefore suggest a role of the LC-NE system in this type of learning, a purported physiological marker of noradrenergic activity (i.e. pupil dilation) suggests no such relationship. Furthermore, we found no correlation between arousal and learning rate, which again provides no support for this hypothesis.

In sum, we find mixed evidence for a role of the LC-NE system in learning. It is possible that the LC is involved in other types of learning that we have not studied here. Our only manipulation of unexpected uncertainty was the inclusion of novel stimuli in one oddball block – but participants did not have to respond to these stimuli, which does not allow us to study whether presentation of these stimuli led to altered behavioral performance.

7.4 On the possible interactions between the noradrenergic and cholinergic neuromodulator systems

One remarkable finding in this dissertation is that clonidine and scopolamine had very similar effects on two measures of temporal attention (the attentional blink and accessory stimulus effect) and one electrophysiological reflection of learning (the P3). These results were unexpected but highly consistent, supporting their reliability. We offer a number of explanations for these results in the relevant dissertation chapters: one important option is that the noradrenergic and cholinergic neuromodulators interact during the execution of specific cognitive processes. For example, scopolamine has been shown to antagonize muscarinic receptors in the rat LC, while clonidine has been demonstrated to inhibit acetylcholine release in the forebrain.

In sum, three studies presented in this dissertation present a powerful demonstration of the importance of studying the *interactions between neuromodulator systems* as opposed to isolated neuromodulator systems.

Studying isolated neuromodu-lator systems is associated with the risk of creating chemical homunculi.

7.5 Future directions

The human brain is an extremely complicated organ, with about half as many cells as there are stars in the Milky Way galaxy (give or take a few billion neurons – estimates vary quite a bit). This observation complicates studying the brain considerably. Even with modern technology—a host of neuroimaging methods with increasingly fine-grained spatial and temporal resolution—studying the brain remains complex, all the more so given the impressive amount of interactions between various brain areas and neuromodulator systems. As a result, this dissertation has not proven, once and for all, the functional significance of the LC-NE system. Then again, attempting to provide such evidence in the span of five years would be exceedingly ambitious.

Instead, the work in this dissertation has provided a few more pieces of the puzzle: we have provided evidence that the LC-NE system seems to be involved in temporal attention, albeit not necessarily in the way popular theories predict, and we have studied the involvement of the LC-NE system in learning; although those findings are relatively complicated, they do suggest that the LC-NE system is involved in specific forms of learning.

Much more work is needed to fully understand the functions of the LC-NE system. A few suggestions are listed below, following the chronological order of the dissertation chapters.

1. Our work on the LPP provides tentative evidence for what we termed the *global inhibition hypothesis*. It would be interesting to further test predictions made by this hypothesis. Because other work from our lab suggests that attenuation of noradrenergic baseline activity reduces LPP

amplitude, it would be interesting to test whether pharmacological attenuation of baseline noradrenergic activity would be associated with reduced global inhibition in the visual cortex, as reflected by a reduced-amplitude LPPs to arousing stimuli and attenuated P1/N1 components.

2. Based on our work, the role of the LC-NE system in the attentional blink remains elusive. It is crucial to shed more light on this problem, especially given the intuitive appeal of the phasic noradrenaline-attentional blink theory. As we describe in Chapter 3 of this dissertation, clonidine attenuates noradrenergic baseline activity, but it may leave phasic noradrenergic bursts intact. If a pharmacological agent can be found that reduces phasic noradrenergic responses in addition to tonic LC responses, it would be interesting to administer this drug and then have participants perform an attentional blink task. If the theory on the role of the LC-NE system in the attentional blink is correct, the blink should be strongly modulated after ingestion of this drug.
3. We found that clonidine increases the size of the accessory stimulus effect. It would be interesting to see if other pharmacological agents that attenuate noradrenergic baseline activity (e.g. propranolol) evoke similar effects, and whether agents that increase noradrenergic baseline activity (e.g. yohimbine, atomoxetine) reduce the size of the accessory stimulus effect. Such findings would corroborate our finding that phasic noradrenergic responses do not mediate the accessory stimulus effect in the manner that is often proposed.
4. We did not provide evidence that suggests that the posterior target-related P3b is subserved by the noradrenergic system and that the anterior novel-related P3a is subserved by the cholinergic system. Given the body of evidence that suggests that this is the case, our pharmacological agents may not have been chosen optimally. Another possibility is that in other empirical work, the distinction between P3a and P3b was not made by a

quantitative method as was implemented in our work (i.e. principal components analysis), but by other methods (e.g. “eyeballing” the data). The latter observation might have far-fetched implications for our conceptualization of the subcomponents of the P3. It would be interesting to replicate our findings with other pharmacological manipulations, to gain more insight in the robustness of our findings and the role of the noradrenergic and cholinergic neuromodulator systems in the generation of the different subcomponents of the P3.

5. Our results regarding the conflict-modulated Hebbian learning hypothesis appear relatively clear-cut: we find little empirical evidence for this hypothesis in two experiments. Therefore, the model that generated this hypothesis requires more empirical evidence to remain tenable, or be revised. In this context, the tenet discussed in section 8.4 might be particularly relevant: perhaps the model is correctly specified, but the noradrenergic system might not be the only neuromodulator system involved in conflict processing and learning rate; perhaps other neuromodulators like dopamine and/or acetylcholine are involved in these processes. It would therefore be interesting to conduct a study in which activity of these systems is attenuated systematically (through pharmacological manipulations or perhaps, in the case of dopamine, transcranial magnetic stimulation or transcranial direct current stimulation) and in which specific predictions generated by the conflict-modulated Hebbian learning model are tested.

7.6 Concluding remarks

“If you wish to make an apple pie from scratch, you must first invent the universe.” These words of cosmologist Carl Sagan apply to cognitive neuroscience as well as to patisserie. We are trying to understand the LC-NE system, but given

the many projection areas of the LC, the various noradrenergic receptor types, the LC's different modes of firing, the many functions of the neuromodulator noradrenaline, not to mention its interactions with other neuromodulators, there are many challenges to be overcome. This leads to a paradoxical situation: to study the functions of the LC-NE system, we must completely comprehend (rather than invent, as Sagan proposes) all of these constituents of the LC-NE system, but to adequately comprehend the functions of the LC-NE system, we must study them. We clearly cannot take all variables (receptor types, interactions with other brain areas and neuromodulator systems) into account in isolated experiments, and much work remains to be done in this field. However, we have provided some pieces of the grand LC-NE puzzle with the work that is presented in this dissertation.