Learning, the P3, and the locus coeruleus-norepinephrine system

Sander Nieuwenhuis

Institute of Psychology, Leiden University, the Netherlands

Leiden Institute for Brain and Cognition, Leiden University, the Netherlands

This chapter can be cited as:

Nieuwenhuis, S. (2011). Learning, the P3, and the locus coeruleus-norepinephrine system. In: R. Mars, J. Sallet, M. Rushworth, and N. Yeung (Eds.) *Neural Basis of Motivational and Cognitive Control*. Oxford University Press, p. 209-222.

Address correspondence to: Sander Nieuwenhuis, Leiden University, Institute of Psychology, Cognitive Psychology Unit, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands. Phone: +31-6-28070875. Fax: +31-71-5273783. E-mail: snieuwenhuis@fsw.leidenuniv.nl.

1) Introduction

Recent research has suggested that the neuromodulatory brainstem nucleus locus coeruleus (LC) is critical for the regulation of cognitive performance (Aston-Jones & Cohen, 2005; Kehagia, Murray, & Robbins, 2010; Nieuwenhuis & Jepma, 2010; Sara, 2009; Yu & Dayan, 2005). The LC exhibits a strong phasic increase in activity during the processing of motivationally relevant stimuli, leading to the release of the neuromodulatory neurotransmitter norepinephrine (NE) in the hippocampus, neocortex, and many other projection areas. This LC-mediated noradrenergic innervation increases the responsivity (or gain) of efferent target neurons (Berridge &Waterhouse, 2003). It has been shown that, when applied in a temporally strategic manner (e.g., when driven by the identification and evaluation of motivationally relevant stimuli), increases in gain produce an increase in the signal-to-noise ratio of subsequent processing and a concomitant improvement in the efficiency and reliability of behavioral responses (Servan-Schreiber, Printz, & Cohen, 1990). Accordingly, it has been found that LC phasic activation reliably precedes and is temporally linked to behavioral responses to attended stimuli (Bouret & Sara, 2004; Clayton, Rajkowski, Cohen, & Aston-Jones, 2004). The idea that the LC may serve as a temporal filter—facilitating responses to task-relevant information at the moment that such information is being actively represented—is a key component of the adaptive gain theory (Aston-Jones & Cohen, 2005), which posits an important role for the LC-NE system in optimizing task performance.

In recent work, I and others have proposed that the neuromodulatory effect of phasic NE release in the neocortex can be measured non-invasively in human subjects by recording the the P3(00) component of the scalp-recorded event related potential (ERP; Nieuwenhuis, Aston-Jones, & Cohen, 2005). The P3 is a prominent positive large-amplitude ERP component with a broad, midline scalp distribution, and a typical peak latency between 300 and 400 ms following presentation of stimuli in any sensory modality (for a review see Polich, 2007). First reported in 1965 (Sutton, Braren, Zubin, & John, 1965), the P3 has undoubtedly been the single most studied ERP component. Yet, until recently, psychologists and neuroscientists had failed to come up with a precise, mechanistic account that elucidates the functional role in information processing of the process underlying the P3, as well as its neural basis. The LC-P3 theory was the first account of the P3 that was both mechanistically explicit and based on firm neuroscientific knowledge. The theory claims that the P3 reflects the response of the LC-NE system to the outcome of internal decision-making processes and the consequent effects of noradrenergic potentiation of information processing.

The goal of this chapter is two-fold: The first goal is to review similarities between the P3 and phasic LC-NE responses in terms of their relationship with learning. The original discussion of the LC-P3 theory focused on the relationship between the P3, LC activity and performance in two-choice reaction time tasks, and emphasized the importance of the LC/P3 response in facilitating rapid action—a key tenet of adaptive gain theory. In contrast, there was little discussion of the empirical evidence suggesting a close relationship between the LC/P3 response and learning. One goal of this chapter is to fill this hiatus. The second goal is to briefly review recent accounts of the role of the LC –NE system in learning, and to show that one of these accounts (Dayan & Yu, 2006) is strikingly similar to the context-updating hypothesis (Donchin, 1981), the most influential account of the functional significance of the P3. This analysis is meant to elucidate the relationship between the LC-P3 theory and the context-updating hypothesis, showing that the two are more closely related than previously thought.

2) The LC-P3 theory

The hypothesis that the P3 reflects the LC-mediated phasic enhancement of neural responsivity in the cortex is supported by a wealth of data from intracranial recordings, lesion studies, psychopharmacology, functional imaging, and other methods, as summarized below (for an extensive review see Nieuwenhuis, Aston-Jones et al., 2005). First, the antecedent conditions for the P3 are similar to those reported for the LC phasic response. In general, P3 amplitude is more closely related to the overall motivational significance and/or arousing nature of a given stimulus than to the affective valence of the stimulus. Important factors affecting the amplitude of the P3 are the subjective probability of the eliciting stimulus, its task-relevance,

and its salience (e.g., intensity, novelty). Like the LC phasic response, the P3 is also enlarged for stimuli with intrinsic significance such as emotionally valent stimuli, whether experienced as positive or negative.

Second, the distribution and timing of intracranial and scalp-recorded P3 activity are consistent with the anatomical and physiological properties of the noradrenergic system. For example, functional imaging studies, inctracranial recordings, and lesion studies have indicated that brain areas showing or contributing to P3 activity are scattered across the brain (Soltani & Knight, 2000), consistent with the widespread projections from the LC to cortical and subcortical areas. In addition, the pattern of P3 generators shows a spatial specificity that mirrors the projection density of the LC. Furthermore, P3 onset latency in simple two-alternative forced-choice tasks is consistent with the latency of LC phasic activity (~150-200 ms), if one takes into account the relatively slow conduction velocity of LC fibers. Additionally, the relatively early timing of P3 activity in frontal and subcortical areas (e.g., thalamus) is consistent with the trajectory of LC fibers, which first reach these areas and only then veer backwards to innervate posterior cortical areas.

Third, several studies have reported direct evidence for an LC generator of the P3. These include psychopharmacological studies, which have shown that P3 amplitude is modulated in a systematic fashion by noradrenergic agents such as clonidine, and entirely abolished following drug-induced NE depletion (e.g., Swick, Pineda, & Foote, 1994). Also, a recent study has found that individual differences in the noradrenergic gene that affects the activity of the alpha-2a receptor are a key determinant of P3 amplitude (Liu et al., 2009). In addition, lesion studies have demonstrated a selective effect on P3 amplitude of LC lesions (Pineda, Foote, & Neville, 1989).

Finally, larger and faster P3s are associated with more accurate and faster behavioral responses and stronger stimulus-related sympathetic nervous system responses (Nieuwenhuis, de Geus, & Aston-Jones, 2010). This pattern mirrors the relation between LC phasic activity, task performance and sympathetic nervous system activity, and is consistent with the functional role ascribed to the noradrenergic system by the adaptive gain theory: to afford rapid action in response to motivationally significant stimuli. The LC-P3 theory does not claim that the P3 process is necessary for responding; of course, subjects can decide to respond before their perceptual system has fully analyzed the stimulus. The theory claims that *if* the P3 occurs before the response, then the response will be facilitated and more efficient.

3) The role of the LC –NE system in learning: neurophysiological data

Because it built on the framework of adaptive gain theory, the LC-P3 theory focused primarily on the role of the LC-NE system in optimizing the speed and accuracy of responding in choice reaction-time tasks. However, neurophysiological data also suggest an important role for the LC-NE system in learning.

Kety (1970) was the first to propose that phasic NE release might serve as a learning signal, by producing persistent facilitation of synaptic inputs occurring in conjunction with the NE release: “The aroused state induced by novel stimuli, or by stimuli genetically recognized as significant, is pervasive and affects synapses throughout the central nervous system, suppressing most, but permitting or even accentuating activity in those that are transmitting the novel or significant stimuli.” Thus, the phasic NE release associated with motivationally significant stimuli selectively acts on synapses that are actively involved at the time of learning, thus strengthening the corresponding memory trace. Such strengthening of synaptic connections is the predominant neuroscientific model of learning in the nervous system.

Various basic properties of the LC-NE system support its role in learning. Phasic LC responses occur following both positive and negative reinforcers, and following novel, unexpected and other stimuli requiring animals to update their representation of the environment. The LC’s widespread projection system is consistent with the fact that representations of the elements that constitute a memory are distributed across multiple sensory processing areas according to their content. The timing of LC activity at several time scales is also consistent with a role in learning. LC neurons increase their activity during learning of new stimulus associations, habituate rapidly, and respond again when the stimulus changes its predictive value, well before learning is visible at the behavioral level. The timing of LC-NE phasic activity within a trial is also sufficiently rapid to afford modulation of the neural trace of the stimulus that triggered the phasic response.

NE also has several post-synaptic effects that support Kety's original hypothesis (Harley, 2004; Sara, Vankov, & Hervé, 1994). First, NE can enhance or even permit cellular responses to synaptic input, and thus promote the impact of stimuli in LC projection areas. For example, iontophoretically applied NE can reduce spontaneous neuronal activity in various brain areas while at the same time preserving or enhancing neuronal responses to potent and specific synaptic input. Second, considerable evidence indicates that NE is able to modulate long-term potentiation (LTP) in the hippocampus, the prevalent cellular model of memory (Berridge &Waterhouse, 2003). LTP is a long-lasting enhancement in synaptic strength between two neurons that results when the synapse is rapidly stimulated for a brief period. NE promotes LTP through actions at beta-adrenergic receptors (Gibbs & Summers, 2002). A critical precondition is the close temporal proximity of the NE release and evoked synaptic activity (Reid & Harley, 2010). Finally, there is evidence that NE suppresses intracortical and feedback synaptic transmission, while sparing, or even boosting, thalamocortical processing (e.g., Kobayashi, 2000). For example, NE can change the mode of activity of thalamic neurons from burst to spike mode, necessary for the accurate transfer of incoming information to the neocortex (McCormick, 1992); and LC activation enhances the processing of concomitant sensory input by reducing feedforward inhibitory interneuron activity, and reduces"binding" oscillations hypothesized to stabilize existing memories (Brown, Walling, Milway, & Harley, 2005). These actions promote learning by favoring bottom-up, sensory signals at the expense of top-down, expectation-driven signals (cf. Yu & Dayan, 2005).

4) The relationship between the P3 and learning

The neurophysiological evidence for an important effect of phasic LC-NE responses on learning is mirrored by similar evidence for a close relationship between the P3 and learning.

Numerous ERP studies have reported a 'Dm effect', a broad positive ERP deflection during encoding of stimuli that are later remembered compared to stimuli that are later forgotten (reviewed in Wagner, Koutstaal, & Schacter, 1999). Although some studies have reported Dm effects that do not appear to be restricted to the P3, a P3 amplitude difference generally makes up an important part of the effect (Fabiani & Donchin, 1995). The Dm effect has been found when trials are sorted on the basis of both recall performance and recognition performance (Paller, Kutas, Mayes, 1987), and is larger for stimuli that are both recalled and recognized than for stimuli that are neither recalled nor recognized; stimuli that are recognized but not recalled elicit an intermediate positive deflection (Fabiani & Donchin, 1995). Fabiani and Donchin have also replicated the Dm effect using the reverse procedure: sorting and binning trials on the basis of single-trial P3 amplitudes, and then comparing recall and recognition performance between these bins.

In incidental encoding tasks (i.e. when subjects do not know their memory for the stimuli will be tested), the Dm effect is larger for stimuli that are processed more deeply (e.g., semantically) during encoding, but it is also observed in shallow encoding tasks (Friedman, Ritter, & Snodgrass, 1996). Additionally, the Dm effect has been examined using tasks in which a small proportion of the stimuli are physically or semantically different from the majority of the stimuli (Fabiani, Karis, & Donchin, 1986; Karis, Fabiani, & Donchin, 1984). These 'isolated' stimuli are remembered significantly more often than 'non-isolated' stimuli and elicit a larger P3 during encoding. However, the correlation between P3 amplitude and later memory is also found within stimulus categories; for example, non-isolated stimuli are associated with a larger P3 amplitude if they are later remembered. Interestingly, there is some evidence that the Dm effect is absent during the encoding of abstract visual stimuli (e.g., Van Petten & Senkfor, 1996). This suggests that the presence of a Dm effect may, at least in some situations, depend on whether stimuli can access or be integrated with pre-existing semantic or other knowledge (cf. Wagner et al., 1999).

In intentional encoding tasks (i.e. subjects know their memory for the stimuli will be tested), researchers have also found typical Dm effects on P3 amplitude, but only in subjects who engaged in 'rote' rehearsal (e.g., silent repetition of the to-be-encoded stimuli), either by choice or by instruction (Karis et al., 1984; Fabiani, Karis, & Donchin, 1985, 1990). Subjects who used elaborate encoding strategies (e.g., forming images or sentences based on the to-be-encoded stimuli) performed better in the test phase and showed a normal centro-parietal P3 during the study phase, but this P3 did not correlate with subsequent

memory performance. Instead, these subjects showed another neural correlate of subsequent learning: a later positive component that was largest at frontal scalp electrodes. These findings suggest that the P3 process is most strongly related to later memory when subjects engage in relatively simple rehearsal strategies. If subjects engage in further processing of the stimuli, then other processes (perhaps supported by the prefrontal cortex) influence the accuracy of memory and the relative contribution of the P3 process is reduced.

These P3 findings are consistent with the notion that phasic NE signals influence learning in a bottom-up way. That is, subsequent memory effects on P3 amplitude may reflect sources of variability in the strength of the LC-NE responses associated with the to-be-encoded stimuli: systematic variability due to experimental manipulations (e.g., manipulations that make an item "stand out" in a physical or semantic sense) and uncontrolled variability due to (subject-specific) differences in the motivational significance of the encoded stimuli (e.g., some words are more meaningful to a subject than other words). The contribution of these NE signals to learning may be reduced to the extent that subjects engage in top-down strategies for learning. The effect of these (e.g., prefrontal) strategies tends to de-correlate the relationship between P3 amplitude and learning.

5) The role of the LC-NE system in learning: recent theories

Since the publication of the LC-P3 theory (Nieuwenhuis et al., 2005), researchers have advanced several new accounts that build on the role of phasic LC responses in learning (Bouret & Sara, 2005; Dayan & Yu, 2006; Verguts & Notebaert, 2009). These accounts may enhance our understanding of the P3 literature.

The work of Verguts and Notebaert builds on the effect of LC activity on strengthening synaptic connections (see section 3), and was inspired by recent findings of item-specific conflict adaptation effects. A hallmark finding in cognitive control experiments is that congruency effects (e.g., in the Stroop task) are smaller on trials immediately following an incongruent trial. Botvinick and colleagues have explained such conflict-adaptation effects by assuming that high conflict signals in anterior cingulate cortex (ACC) on trial *n*-1 are used to strengthen task representations (e.g., a colour-naming representation) in prefrontal cortex on trial *n*, thus increasing cognitive control and reducing congruency effects. This conflict-control loop model has successfully accounted for a wide range of phenomena in the cognitive control literature (Botvinick, Cohen, & Carter, 2004). However, the task-level representations in this model cannot account for recent findings that conflict-adaptation effects are stronger for some stimulus-stimulus and stimulus-response associations within a given task than for others. For example, if in a Stroop task some color words are presented mostly congruently, and other colorwords mostly incongruently, the congruency effect is larger for the former type of stimuli. These item-specific conflict-adaptation effects have led Verguts and Notebaert (2008, 2009) to propose a new model of conflict adaptation.

According to this model, ACC conflict signals are not (directly) relayed to the prefrontal cortex, but instead trigger a phasic response of the LC. The consequent phasic release of the NE enhances ongoing (LTP-mediated) Hebbian learning as discussed above, and thus strengthens associations between active (i.e. usually task-relevant) representations. Item-specific conflict-adaptation effects occur because the NE-dependent modification of synaptic weights is proportional to the degree of conflict associated with particular stimulus-stimulus or stimulus-response associations. For example, conflict is larger for incongruent red colour words if the colour red is usually paired with the congruent word "red". More formally, in the Hebbian learning rule, weight changes between two connected cells are proportional to the product of presynaptic and postsynaptic activity:

$$\Delta w_{ij} = \lambda \times x_i \times x_j \qquad \text{(Equation 1)}$$

where x_i and x_j are the activation of the sending cell *i* and receiving cell *j*, respectively. According to Verguts and Notebaert, the learning-rate parameter λ is modulated by trial-to-trial changes in conflict-dependent phasic NE release. This model is consistent with the hypothesized ACC-LC interactions in adaptive gain theory (Aston-Jones & Cohen, 2005) and with recent findings that ACC activity and pupil diameter (a correlate of LC activity; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010) correlate with trial-to-trial changes

in learning rate in volatile environments (Behrens, Woolrich, Walton, & Rushworth, 2007; Nassar, Wilson, Kalwani, Heasly, & Gold, 2010). In recent work Notebaert and colleagues have started investigating the relationship between the P3 and conflict-related adaptations in cognitive control parameters (Núñez Castellar, Kühn, Fias, & Notebaert, 2010).

Dayan and Yu's (2006) account of phasic LC-NE function and learning builds on the role of NE in promoting bottom-up as opposed to top-down processing, and hence learning about the external environment (see section 3; see also Yu & Dayan, 2005). According to this account, phasic NE signals encode unexpected uncertainty about the current state within a task, and serve to interrupt the ongoing processing associated with the default task state. Dayan and Yu implemented their ideas in a Bayesian model of the oddball task, the most commonly used task for studying the P3: "For the [oddball] task modeled here, the specific effect of the NE-mediated interrupt is to arouse the animal from default inaction to release a continuously pressed bar in response to an unexpected target stimulus. More general roles for such an interrupt include organizing more general aspects of behavioral responding as well as ensuring that top-down influences on sensory processing associated with the default, current state are immediately nullified once their statistical foundations have been undermined. (…) NE's fast responses and diffuse projections make it particularly suitable for signaling the detection of such unexpected state changes. The actual maintenance of the contextual model, and the computation of the posterior probabilities, are likely to be subserved by the prefrontal cortex … and also the anterior cingulate cortex …. Both these neural structures exert a powerful influence over the locus coeruleus, as indeed do subcortical structures, which could occasion interrupts based on more primitively assessed unexpected events" (p. 342-343). Dayan and Yu showed that their model captures some key aspects of monkey LC activity observed in the oddball task.

This account is consonant with Bouret and Sara's (2005) view of NE as a neural interrupt signal that promotes learning (see also Bouret & Sara, 2004; David Johnson, 2003): "… these [LC] neurons are activated within behavioral contexts that require a cognitive shift – that is, interruption of ongoing behavior and adaptation. This LC activation occurs whenever there is a change in environmental imperative, such as the appearance of a novel, unexpected event, or a change in stimulus-reinforcement contingencies within a formal learning situation."

The ideas reviewed above are also broadly consistent with the adaptive gain theory (Aston-Jones & Cohen, 2005). Although primarily a theory of the role of the LC-NE system in the regulation of attention and performance, the adaptive gain theory implicitly suggests a role for this system in modulating learning rate and long-term memory. Specifically, higher levels of NE and, through an increased gain, greater neural activity at the time of the stimulus (i.e. increased x_i and x_j in Equation 1; cf. Verguts & Notebaert, 2009) may promote larger adjustments in current probabilistic beliefs, speeding learning and enhancing memory.

6) The context-updating hypothesis of the P3

Dayan and Yu's (2006) account of phasic LC function shows a striking correspondence with the prevalent account of the functional significance of the P3, the context-updating hypothesis (Donchin, 1981; Donchin & Coles, 1988; Donchin, Karis, Bashore, Coles, & Gratton, 1986).

Donchin and colleagues hypothesized that the function of the P3 process is to update the mental model (or schema) that we maintain of the environment. For example, Donchin (1981, p. 507-508) proposed that "… the process manifested by the P300 is not elicited for the purpose of tactically responding to a given stimulus in a given trial, but rather to what I call strategic information processing. This is the information processing that will affect the manner in which we respond to *future* stimuli… (…) *These are activities that affect our schema rather than our actions.* (…) The schema may be conceptualized as a large and complex map representing all available data about the environment. (…) When there is a need, the model is revised by building novel representations through the incorporation of incoming data into schema[ta] based on long-term memory data. It is likely that it is this updating process that we see manifested by the P300. (…) It is the degree to which the event requires a revision of the model, not its inherent attributes, that is the crucial determinant of P300 [amplitude]." In later work, Donchin and Coles (1988) described the mental model as representing the probabilistic structure of the environment.

Furthermore, to explain why task-relevant stimuli elicit larger P3s, they assumed that "Only those segments of the context that are central to the tasks performed by the subject are likely to bring about the changes in the model of the environment" (p. 369).

The context-updating hypothesis led Donchin and colleagues to investigate the possible effect of the P3 process on subsequent performance through the restructuring of the subject's model of the environment. In this context they asked to what extent P3 amplitude predicts the probability that items will be remembered. As discussed in section 4, Donchin's group and, subsequently, other researchers found strong evidence for a close relationship between these variables. The finding that the target probability effect on P3 amplitude in the oddball task diminishes with increasing interstimulus intervals (with changes on the order of seconds; Donchin et al., 1986) provides further evidence that the P3 reflects a decaying memory representation of the task structure. The context-updating hypothesis also offers a possible account of why the Dm effect is not observed during encoding of abstract visual stimuli (Van Petten & Senkfor, 1996): subjects do not have an existing mental model of these stimuli, and therefore stimuli differ little in terms of the evoked mismatch with already present knowledge.

The similarities between the context-updating hypothesis and Dayan and Yu's (2006) account are clear: Both hold that the subject has an (implicit or explicit) internal model of the external environment, for example a model that reflects the current task's statistical structure. If the corresponding expectations are violated by sensory observations (e.g., an infrequent target in the oddball task), the system produces an LC phasic response (Dayan and Yu) or P3 (Donchin). A result of that process is that the internal model is updated and the subject is learning.

7) Unexpected uncertainty, surprise, the LC-NE system, and the P3

According to Dayan and Yu (2006), phasic NE encodes a decision variable that is important for learning: unexpected uncertainty, or surprise, about the current state within a task. More specifically, they proposed that in tasks like the oddball task phasic NE reports on the ratio between the posterior probability of a target being present (given the sensory data) and its prior probability. Thus, infrequent targets elicit a phasic LC response because of their low prior probability. Furthermore, increasing the prior probability of a target (i.e. the denominator of the equation) should reduce the magnitude of the phasic NE signal associated with a target. This prediction is consistent with the finding that increasing target frequency reduces the magnitude of phasic LC responses (Alexinsky, Aston-Jones, Rajkowski & Revay, 1990). As noted above, Dayan and Yu believe that prior probability is represented and posterior probability is computed by brain structures projecting to the LC, not by the LC itself. Indeed, if Dayan and Yu's hypothesis is right, this does not imply that surprise is the only variable encoded by the LC: the LC may receive and encode various other signals, for example about the task relevance or intrinsic motivational significance of a stimulus.

The hypothesis that phasic NE reports on the ratio between posterior probability and prior probability of a task state is consistent with the well-known sensitivity of the P3 to (subjective) prior probability (e.g., Daffner et al., 2000; Squires, Wickens, Squires, & Donchin, 1976; see also Barceló, Periáñez,& Knight, 2002). For example, P3 amplitude is highly sensitive to expectations elicited by the recent stimulus-sequence history in an oddball task: the P3 to an oddball target stimulus is larger when the target stimulus is preceded by a series of nontarget stimuli than when it is preceded by a series of other targets (Squires et al., 1976; but see Holm, Ranta-aho, Sallinen, Karjalainen, & Müller, 2006). Presumably, increasing the number of preceding non-target stimuli decreases the subjective prior probability of a target. Other evidence suggests that the P3 also closely tracks unexpected uncertainty in the oddball task when there are frequent reversals of the probabilities of the target and non-target stimuli (i.e. a volatile environment; Johnson & Donchin, 1982). Donchin (1981) argued that "on the basis of data like these we can assert that *surprising* events elicit a large P300 component" (p. 498, italics added).

Other evidence indicates that in addition to prior probability, P3 amplitude is sensitive to posterior probability, the numerator in Dayan and Yu's (2006) surprise equation (Ruchkin & Sutton, 1978a, b). This variable reflects the subject's uncertainty about having correctly perceived the stimulus: the smaller the posterior probability associated with a task state (e.g., "a target is presented on the screen"), the lower the

amplitude of the corresponding P3. For example, P3 amplitudes become smaller if stimuli are degraded and cannot be easily classified, and when there is uncertainty about the anticipated time of stimulus onset.

Some researchers have related the P3 to alternative but similar definitions of surprise. Kopp (2006) has proposed that P3 amplitude varies as a function of the difference (not ratio) between prior probability and posterior probability, that is, as a function of the magnitude of the evidence-based probability revision. Mars and colleagues have shown that single-trial amplitudes of the P3 can be well explained by an information-theoretic definition of surprise—a monotonically decreasing function of the subjective prior probability of a given stimulus on a particular trial (Mars et al., 2008). They showed that this model could account for the data better than a model based on blockwise (objective) stimulus probabilities and some alternative models based on information theory. Regardless of which specific definition of surprise does best describe P3 amplitudes, the sensitivity to violations of expectations provides yet another similarity between the P3 and LC-NE activity.

8) Conclusions

In 1981, Emanuel Donchin already noticed the similarities between the P3 and the LC-NE system in terms of their relationship with learning: "The model I propose assumes that the P300 is intimately involved with the process of memory modification or, if you will, learning. (…) Things appear to be learned if, and only if, they are surprising. In the neurophysiological literature, we find increasing emphasis on the role of the norepinephrine system in the incorporation of memories ... Things are apparently learned if, and only if, they activate this system" (Donchin, 1981, p. 508).

In this chapter I discussed the intimate relationship between phasic LC activity, the P3, and learning, and suggested how these phenomena may be related: Phasic NE release, for example following a surprising stimulus, promotes learning about the eliciting stimulus. Stimuli that elicit a larger LC-NE response are more likely to be remembered. Assuming that phasic NE release is reflected in the P3, this explains why stimuli that elicit a larger P3 are more likely to be remembered. I also tried to highlight the marked similarities between recent theories of phasic LC-NE function (Bouret & Sara, 2005; Dayan & Yu, 2006) and the context-updating hypothesis of the P3 (Donchin, 1981; Donchin & Coles, 1988). These accounts suggest that phasic NE and the P3 reflect unexpected uncertainty or surprise, and that these signals promote updating of the internal model of the environment. Altogether, this analysis provides strong additional support for the LC-P3 theory. It also suggests that the LC-P3 theory and context-updating hypothesis are not competing accounts of the P3: Context updating in response to surprising and motivationally significant stimuli, and facilitating behavioral responses to such stimuli, are each consistent with the broad temporal filtering function of phasic LC-NE activity (Aston-Jones & Cohen, 2005). Therefore, the LC-P3 theory explains both the close relationship between the P3 and learning (as proposed by Donchin and reviewed here) and the link between the P3 and the speed and accuracy of responding in reaction-time tasks (as reviewed in Nieuwenhuis et al., 2005).

Of course the LC-P3 theory remains a theory. The relationship between LC activity and the P3 may be much more indirect than proposed. Also, there is some evidence that subcomponents of the P3 are influenced by other neuromodulators, such as dopamine (e.g., Polich, 2007). But critical tests of the LC-P3 theory are underway: various labs are currently using newly developed optogenetic imaging methods (Berdyyeva & Reynolds, 2009) to test the LC-P3 theory in monkeys. In these monkeys, LC neurons will be genetically modified so that they become highly sensitive to a particular light frequency. Careful light stimulation at this frequency then allows the experimenters to selectively activate or suppress these LC neurons with extremely high temporal precision (in the millisecond range) while the monkeys are performing a task. The critical questions that can then be addressed are: What happens if a target stimulus is presented while the LC is suppressed? Is the LC response necessary for observing a P3 at the scalp? And what happens if we present no stimulus but briefly activate the LC under optical control? Is such an LC response sufficient for observing a P3 at the scalp? Or is it necessary that the monkey is doing a task, so that there is sufficient cortical activity that can be modulated by NE? Eventually, these methods will also be an extremely powerful means for directly testing the role of LC-NE activity in learning.

References

Alexinsky, T., Aston-Jones, G., Rajkowski, J., & Revay, R. S. (1990). Physiological correlates of adaptive behavior in a visual discrimination task in monkeys. *Society for Neuroscience Abstracts, 16,* 164.

Aston-Jones, G. & Cohen, J.D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience, 28*, 403-450.

Barceló, F., Periáñez, J.A., & Knight, R.T. (2002). Think differently: a brain orienting response to task novelty. *Neuroreport, 13,* 1887-1892.

Berdyyeva, T.K., & Reynolds, J.H. (2009). The dawning of primate optogenetics. *Neuron, 62,* 159-160.

Behrens, T.E., Woolrich, M.W., Walton, M.E., & Rushworth, M.F. (2007). Learning the value of information in an uncertain world. *Nature Neuroscience, 10,* 1214-1221.

Berridge C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews, 42,* 33-84.

Botvinick, M.M., Cohen, J.D., & Carter, C.S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciencese, 8,* 539-546.

Bouret, S., & Sara, S. J. (2004). Reward expectation, orientation of attention and locus coeruleus–medial frontal cortex interplay during learning. *European Journal of Neuroscience, 20*, 791–802.

Bouret, S., & Sara, S.J. (2005). Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci ence, 28,* 574-582.

Brown, R.A., Walling, S.G., Milway, J.S., & Harley, C.W. (2005). Locus ceruleus activation suppresses feedforward interneurons and reduces beta-gamma electroencephalogram frequencies while it enhances theta frequencies in rat dentate gyrus. *Journal of Neuroscience, 25,* 1985-1991.

Clayton, E. C., Rajkowski, J., Cohen, J. D., & Aston-Jones, G. (2004). Phasic activation of monkey locus coeruleus neurons by simple decisions in a forced choice task. *Journal of Neuroscience, 24*, 9914-9920.

Daffner, K.R., Scinto, L.F., Calvo, V., Faust, R., Mesulam, M.M., West, W.C., & Holcomb, P.J. (2000). The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. *Journal of Cognitive Neuroscience, 12,* 393-406.

David Johnson, J. (2003). Noradrenergic control of cognition: global attenuation and an interrupt function. *Medical Hypotheses, 60,* 689–692.

Dayan, P., & Yu, A.J. (2006). Phasic norepinephrine: a neural interrupt signal for unexpected events. *Network, 17,* 335-350.

Donchin, E. (1981). Surprise! . . . Surprise? *Psychophysiology, 18,* 493–513.

Donchin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11,* 357–374.

Donchin, E., Karis, D., Bashore, T. R, Coles, M.G.H., & Gratton, G. (1986). Cognitive psychophysiology: systems, processes, and applications. In: Coles MGH, Donchin E, Porges S, editors. *Psychophysiology: systems, processes, and applications.* New York: The Guilford Press, p. 244–267.

Fabiani, M., & Donchin, E. (1995). Encoding processes and memory organization: a model of the von Restorff effect. *Journal of Experimental Psychology: Learning Memory and Cognition, 21,* 224-240.

Fabiani, M., Karis, D. & Donchin, E. (1985). Effects of strategy manipulation on P300 amplitude in a Von Restorff paradigm. *Psychophysiology, 22,* 588-589.

Fabiani, M., Karis, D., & Donchin, E. (1986). P300 and recall in an incidental memory paradigm. *Psychophysiology, 23,* 298–308.

Fabiani, M., Karis, D., & Donchin, E. (1990). Effects of mnemonic strategy manipulation in a Von Restorff paradigm. *Electroencephalography & Clinical Neurophysiology, 75,* 2–35.

Friedman, D., Ritter, W., & Snodgrass, J.G. (1996). ERPs during study as a function of subsequent direct and indirect memory testing in young and old adults. *Cognitive Brain Research, 4,* 1-13.

Gibbs, M.E., & Summers, R.J. (2002). Role of adrenoceptor subtypes in memory consolidation. *Progress in Neurobiology, 67,* 345-391.

Gilzenrat, M.S., Nieuwenhuis S., Jepma, M., & Cohen, J.D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience, 10,* 252-269.

Harley, C.W. (2004). Norepinephrine and dopamine as learning signals. *Neural Plasticity, 11,* 191-204.

Holm, A., Ranta-aho, P.O., Sallinen, M., Karjalainen, P.A., & Müller, K. (2006). Relationship of P300 single-trial responses with reaction time and preceding stimulus sequence. *International Journal of Psychophysiology, 61,* 244-252.

Johnson. R., & Donchin, E. (1982). Sequential expectancies and decision making in a changing environment: an electrophysiological approach. *Psychophysiology, 19,* 183-200.

Karis, D., Fabiani, M., & Donchin, E. (1984). ‘‘P300’’ and memory: Individual differences in the von Restorff effect. *Cognitive Psychology,16,* 117–216.

Kehagia, A.A,. Murray, G.K., & Robbins, T.W. (2010). Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Current Opinion in Neurobiology, 20,* 199-204.

Kety, S. (1970). The biogenic amines in the central nervous system: their possible roles in arousal,emotion and learning. In: Schmitt FO, ed, *The Neurosciences: Second Study Program.* New York, NY, USA: Rockefeller Press; pp. 324-335.

Kobayashi, M. (2000). Selective suppression of horizontal propagation in rat visual cortex by norepinephrine. *European Journal of Neuroscience, 12,* 264–272.

Kopp, B. (2006). The P300 component of the event-related brain potential and Bayes’ theorem. *Cognitive Sciences, 2,* 113–125.

Liu, J., Kiehl, K.A., Pearlson, G., Perrone-Bizzozero, N.I., Eichele, T., & Calhoun, V.D. (2009). Genetic determinants of target and novelty-related event-related potentials in the auditory oddball response. *Neuroimage, 46,* 809-816.

Mars, R.B., Debener, S., Gladwin, T. E., Harrison, L.M., Haggard, P., Rothwell, J.C., & Bestmann S. (2008). Trial-by-trial fluctuations in the event-related electroencephalogram reflect dynamic changes in the degree of surprise. *Journal of Neuroscience, 28,* 12539-12545.

McCormick, D.A. (1992). Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Progress in Neurobiology, 39,* 337-388.

Nassar, M., Wilson, R.C., Kalwani, R., Heasly, B.,& Gold, J.I. (2010) Pupillometric evidence for a role of locus coeruleus in dynamic belief updating. In: *Proceedings of Computational and Systems Neuroscience 2010* (COSYNE-2010, Salt Lake City, Utah).

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J.D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychological *Bulletin, 131,* 510-532.

Nieuwenhuis, S., de Geus, E.J., & Aston-Jones, G. (2010). The anatomical and functional relationship between the P3 and autonomic components of the orienting response. *Psychophysiology, 47,* **-**.

Nieuwenhuis, S., & Jepma, M. (2010). Investigating the role of the noradrenergic system in human cognition. In T. Robbins, M. Delgado, & E. Phelps (Eds.), *Decision making. Attention & Performance, Vol. XXIII.* Oxford: Oxford University Press.

Núñez Castellar, E., Kühn, S., Fias, W., & Notebaert, W. (2010). Outcome expectancy and not accuracy determines posterror slowing: ERP support. *Cognitive Affective & Behavioral Neuroscience, 10,* 270-278.

Paller, K.A., Kutas, M., & Mayes, A.R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroencephalography & Clinical Neurophysiology, 67,* 360-371.

Pineda, J. A., Foote, S. L., & Neville, H. J. (1989). Effects of locus coeruleus lesions on auditory, long-latency, event-related potentials in monkey. *Journal of Neuroscience, 9*, 81-93.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*, 2128-2148.

Reid, A.T., & Harley, C.W. (2010). An associativity requirement for locus coeruleus-induced long-term potentiation in the dentate gyrus of the urethane-anesthetized rat. *Experimental Brain Research, 200,* 151-159.

Ruchkin, D.S., & Sutton, S. (1978a). Equivocation and P300 amplitude. In: *Multidisciplinary perspectives in event-related brain potential research* (Otto D, ed), pp. 175–177. Washington, DC: U.S. Government Printing Office.

Ruchkin, D.S., & Sutton, S. (1978b). Emmitted P300 potentials and temporal uncertainty. *Electroencephalography & Clinical Neurophysiology, 45,* 268-277.

Sara, S.J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience, 10*, 211-223.

Sara, S.J., Vankov, A., & Hervé, A. (1994). Locus coeruleus-evoked responses in behaving rats: a clue to the role of noradrenaline in memory. *Brain Research Bulletin, 35,* 457-465.

Servan-Schreiber, D., Printz, H., & Cohen, J. D. (1990). A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. *Science, 249*, 892-895.

Soltani, M., & Knight, R.T. (2000). Neural origins of the P300. *Critical Reviews in Neurobiology, 14,* 199-224.

Squires, K. C., Wickens, C., Squires, N. K., & Donchin, E. (1976). The effect of stimulus sequence on the waveform of the cortical event-related potential. *Science, 193,* 1142–1146.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*, 1187–1188.

Swick, D., Pineda, J. A., & Foote, S. L. (1994). Effects of systemic clonidine on auditory event-related potentials in squirrel monkeys. *Brain Research Bulletin, 33*, 79-86.

Verguts, T., & Notebaert, W. (2008). Hebbian learning of cognitive control: dealing with specific and nonspecific adaptation. *Psychological Review, 115,* 518-525.

Verguts, T., & Notebaert, W. (2009). Adaptation by binding: a learning account of cognitive control. *Trends in Cognitive Sciences, 13,* 252-257.

Wagner, A.D., Koutstaal, W., & Schacter, D.L. (1999). When encoding yields remembering: insights from event-related neuroimaging. *Philosophical Transactions of the Royal Society B: Biological Sciences, 354,* 1307-1324.

Van Petten, C., & Senkfor, A.J. (1996). Memory for words and novel visual patterns: repetition, recognition, and encoding effects in the event-related brain potential. *Psychophysiology, 33,* 491-506.

Yu, A.J., & Dayan, P. (2005). Uncertainty, neuromodulation, and attention. *Neuron, 46,* 681-692.

Acknowledgements

The author thanks Christopher Warren and Jonathan Cohen for fruitful discussions about LC function and learning. This research was supported by a VIDI-grant from the Netherlands Organization for Scientific Research.