Contextual uncertainty in the primate locus coeruleus: Reconciling theory, behavior and physiology through a combined approach

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Summary

Mounting theoretical and experimental evidence suggests that major ascending modulatory systems including dopamine, norepinephrine, serotonin and acetylcholine play specific computational roles in neural processing beyond their classically attributed roles in mediating non-specific arousal. Indeed, recent computational work has linked activity in the locus coeruleus-norepinephrine (LC-NE) system to statistical properties of the environment in the form of unexpected uncertainty at two distinct timescales (Yu and Dayan, 2005 Dayan and Yu, 2006).

A key feature—and challenge—of modeling the LC-NE system with Bayesian theory is to take into account the observer's (subjective) beliefs about behavioral context and task demands. Thus, our approach is to construct generative models of behavioral strategy from choice-behavior, reaction time data and pupil diameter measurements that allow us to quantitatively test model-driven hypothesis about task-related LC neuronal activity. We believe that this approach will enable an unprecedented degree of interpretive power and specificity in studying the LC-NE system and its role in cognitive-behavioral control. Moreover, this work is likely to clarify the relationship between LC-NE activity and non-luminance-mediated pupil diameter modulations, which provide a valuable link to human studies and may to be useful as a non-invasive measurement of otherwise hidden internal states related to arousal and cognitive control.

Here we present data from preliminary experimental and modeling efforts. A promising candidate model of behavioral strategy qualitatively captures the biasing effects of contextual priors on choice-behavior and reaction times. In addition, preliminary pupillometric and putative LC recording data reveal complex effects of both within- and between-trial contextual uncertainty.

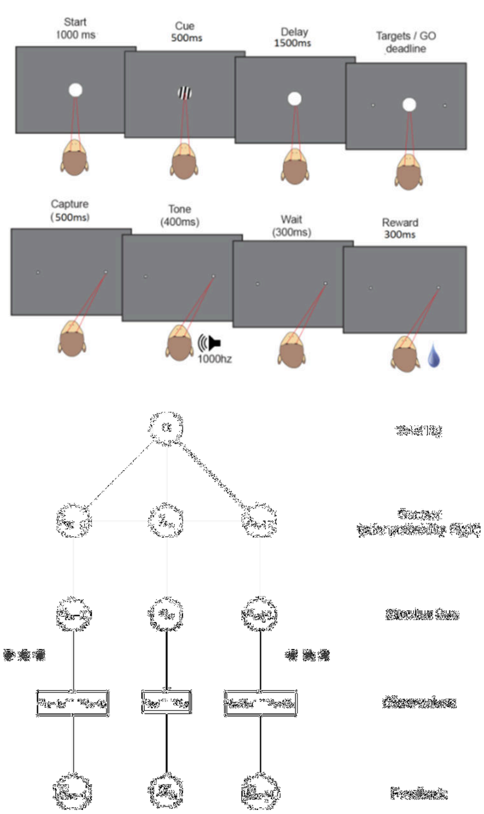


Figure 1. Behavioral task and generative model. ***(Top)*** Schematic of the behavioral paradigm, including instructive and feedback periods. Directional cues (oriented gratings) are more difficult for orientations close to vertical and easier further away. A long delay period ensures the engagement of working memory and temporally disassociates cue-related pupil and LC responses from saccade and feedback-related activity. Feedback tones are either positive (1000hz) or negative (400hz) depending on the correctness of the subject's choice with 100% validity. Statistical contexts are operationalized by the within-block prior probability of drawing from the set of left versus right cues. Neutral blocks are 50/50 and bias blocks are 80/20 for a given direction, and each session is counter balanced to include bias blocks in both directions with the within-session block order randomly chosen day-to-day. ***(Bottom)*** Generative model representing one plausible behavioral strategy. Context (λ_n) on trial n represents the prior probability of cue direction. On each trial n, cue (z_n) generates noisy temporal observations $x_{n0},\ldots x_{nt}$ *within* the

trial. These are combined with the current beliefs/uncertainty about the context and cue to infer cue direction. Feedback R_n is used to update beliefs/uncertainty about context, which changes *between* trials according to volatility α.

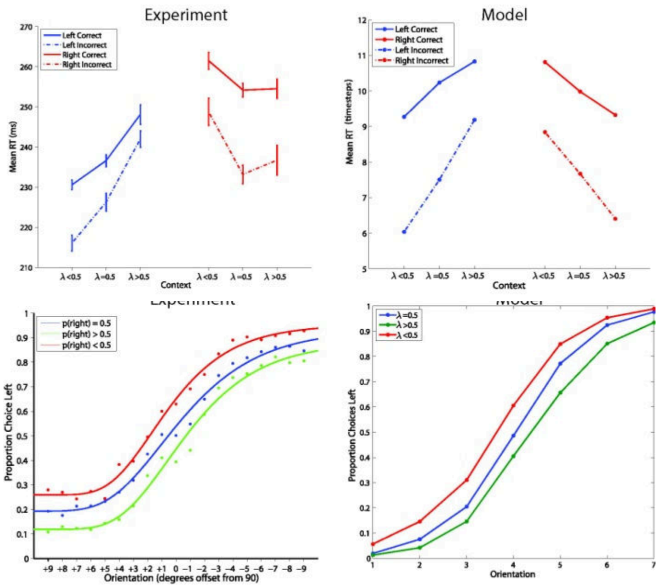
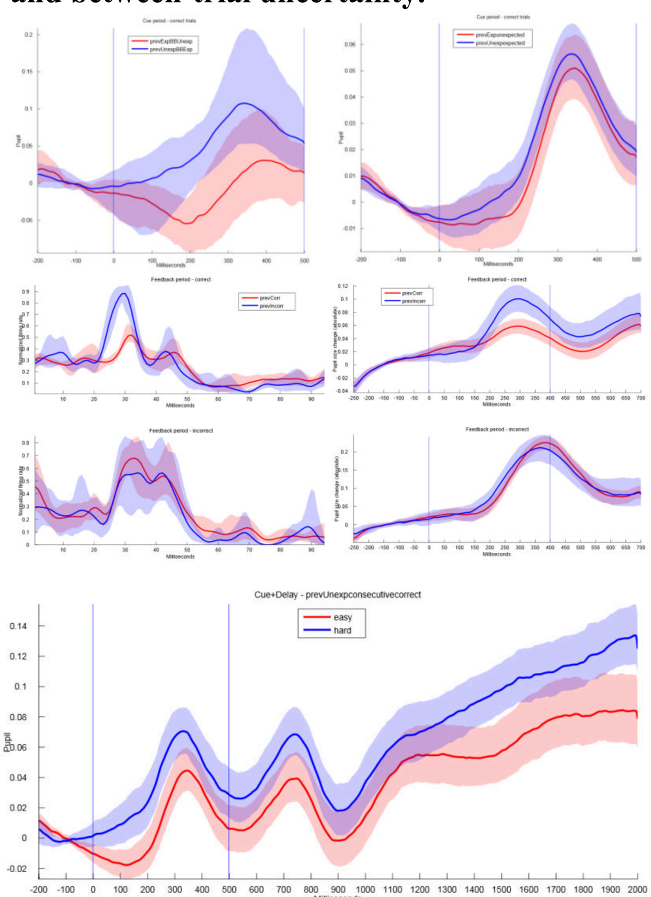
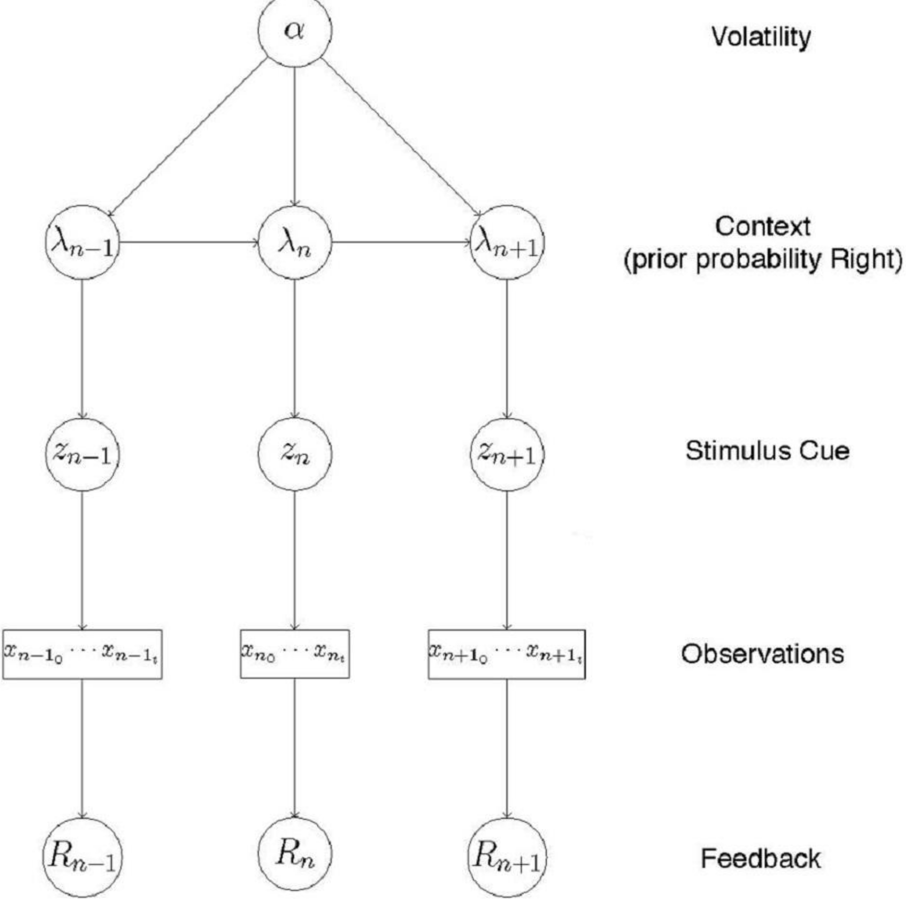


Figure 2. Candidate model qualitatively captures contextual effects in behavioral data. ***(Top)*** In an earlier reaction time version of the task, due to contextual bias, reaction times are slower on improbable/unexpected trials. The generative model captures qualitative differences in reaction times on expected and unexpected switch trials (trials in which cue direction changes from trial *n-1* to *n*). ***(Bottom)*** In an earlier version of the task with *nine* cue orientations for *each* side, our model captures the shift in the psychometric function due to contextual bias. Note that the model reaction times are collapsed into "easy", "medium" and "difficult" categories.

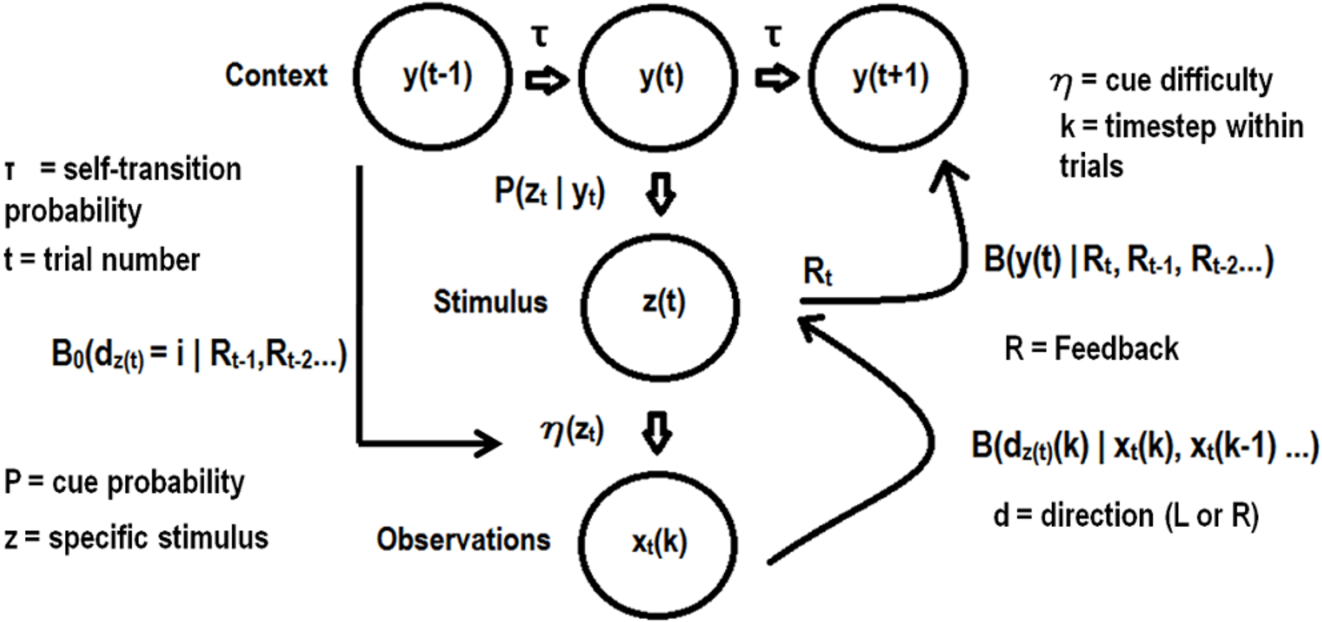
Figure 3. Preliminary LC recordings and pupillometry indicate complex effects of within- and between-trial uncertainty.



(Top) During neutral blocks that follow biased blocks, cue-related pupil dilations are larger on unexpected (*left*) versus expected (*right*) switch trials around the block boundary but not later in the same block, indicating within-trial sensitivity to contextual switches. **(*Middle*)** Both putative LC neuronal activity (*left*) and pupil diameter (*right*) demonstrate sensitivity to previous trial outcomes, with LC activation leading pupil dilation. Shown here are responses in both measurements to feedback tones when trial *n-1* was incorrect. Both pupil and LC responses to positive, but not negative, feedback tone are enhanced when the previous trial was incorrect. ***(Bottom)*** Cue difficulty and cue probability also interact with pupil diameter measurements. Shown here, when trial *n-1* was improbable, on trial *n* the pupil dilates significantly more during the cue and subsequent delay period following the presentation of *difficult* cues which indicates that pupil dilations may reflect both within- and between-trial uncertainty.



α
Volatility
λn−1
λn
λn+1
Context
(prior probability Right)
zn−1
zn
zn+1
Stimulus Cue
xn−10 ··· xn−1t
xn0 ··· xnt
xn+10 ··· xn+1t
Observations
Rn−1
Rn
Rn+1
Feedback



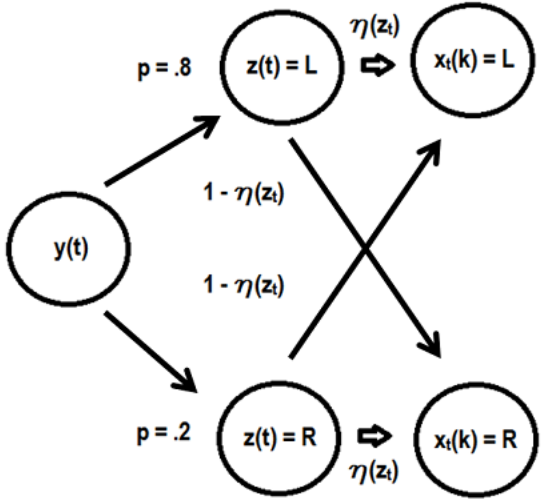
$$B(y(t) \mid R_t, R_{t-1}, R_{t-2}\ldots) \propto P(R_t \mid y(t) = i) * B(y_t = i \mid R_{t-1}, R_{t-2}\ldots)$$

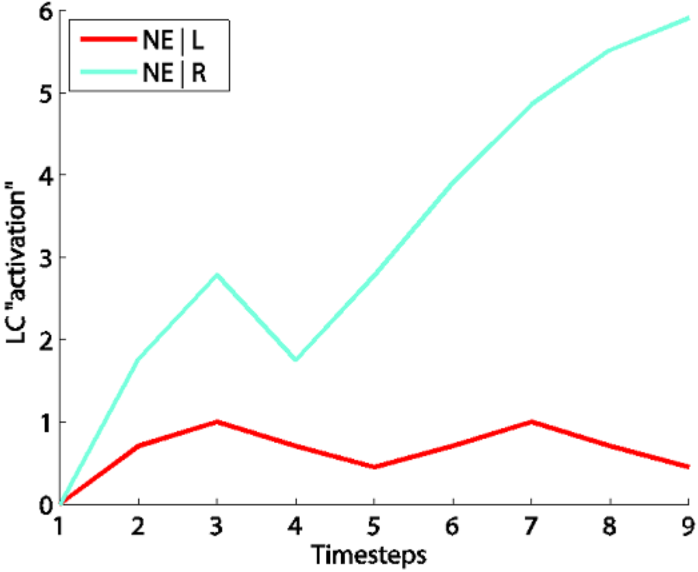
$$B_0(d_{z(t)} = i \mid R_{t-1}, R_{t-2}\ldots) \propto \sum_j L(d = i \mid y_{t-1} = j) * B(y_{t-1} = j \mid R_{t-1}, R_{t-2}\ldots)$$

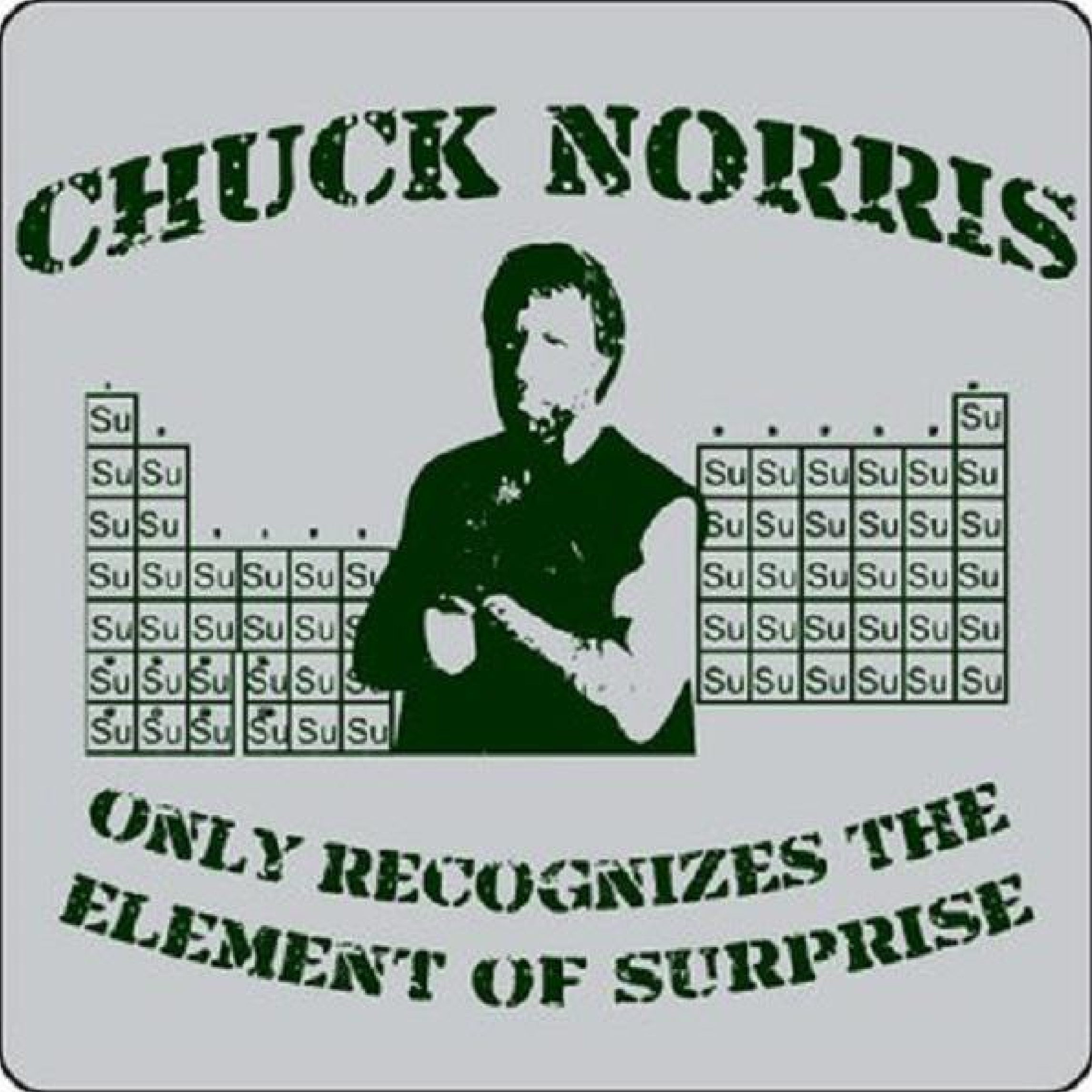
$$B(d_{z(t)}(k) \mid x_t(k), x_t(k-1)\ldots) \propto P(x_t(k) \mid d_t(k) = i) * B(d_t(k) = i \mid x_t(k-1), x_t(k-2)\ldots, R_{t-1}, R_{t-2}\ldots)$$

Predicted NE phasic activation

$$NE_{|B(yt=L)} = B(d_t = R \mid x_t(k), x_t(k-1)\ldots) \,/\, B(d_t = R)$$



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