Neuromodulators and the Neural Representation of Uncertainty

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Computational Neuromodulation

- **general**: excitability, signal/noise ratios
- **specific**: prediction errors, uncertainty signals
Learning and Inference

the world

Bayes’ Rule

inference

observations

\[ w_1, w_2, t_1, t_2 \]
Bayesian Uncertainty

• arises from:
  – stochasticity
  – ignorance
    • transient
    • possibility of ongoing change

• affects:
  – learning (the more the merrier)
  – inference (the less the merrier)
ACh & NE have similar **physiological** effects

- **suppress** recurrent & feedback processing  
  *(e.g. Kimura *et al*, 1995; Kobayashi *et al*, 2000)*
- **enhance** thalamocortical transmission  
  *(e.g. Gil *et al*, 1997)*
- **boost** experience-dependent plasticity  
  *(e.g. Bear; Shulz; Merzench)*

ACh & NE have distinct **behavioral** effects:

- ACh **boosts** learning to stimuli with uncertain consequences  
  *(e.g. Bucci, Holland, & Gallagher, 1998)*
- NE **boosts** learning upon encountering global changes in the environment  
  *(e.g. Devauges & Sara, 1990)*
Learning

- Learning: predict; control

\[
\Delta \text{weight} = \alpha (\text{error}) \times (\text{learning rate}) \times (\text{stimulus})
\]

- **dopamine**
  - phasic prediction error for future reward
- **serotonin**
  - phasic prediction error for future punishment

- **acetylcholine**
  - expected uncertainty boosts learning
- **norepinephrine**
  - unexpected uncertainty boosts learning
Conditioning

reward given

prediction weights

where

output noise

allowable drift
Single Stimulus

Intuition

window model: $w_L$ is the average of last three rewards:

**mean** goes like

**standard deviation** goes like

- more data $\Rightarrow$ more certain
- use of 3 rewards controls speed of adaptation
- asymptotic sd shouldn’t ignore changes in $r$
Multiple Stimuli

Competition for prediction error between L and S:

sound should ‘win’ since less well established
Formally: Kalman Filter

observation: $r = \mathbf{w} \cdot \mathbf{x} + \epsilon$
state: $\mathbf{w}' = \mathbf{w} + \eta$

$$\mathbf{w} \sim \mathcal{N}[\hat{\mathbf{w}}, \Sigma]$$

$$\delta = r - \hat{\mathbf{w}} \cdot \mathbf{x}$$

$$\hat{\mathbf{w}}' = \hat{\mathbf{w}} + \delta \frac{\sum \cdot \mathbf{x}}{\rho^2 + \mathbf{x} \cdot \sum \cdot \mathbf{x}}$$

$$(\mathbf{w}' = \mathbf{w} + \delta \alpha \mathbf{x} \text{ delta rule})$$

- like the delta rule, bar compression and rotation
- compression is competition for learning

$$\Sigma_{ii} / (\rho^2 + \sum_j \Sigma_{jj})$$

- $\rho^2$ sets learning rate according to noise (KKT)
- rotation allows backwards blocking
- update for $\Sigma$

$$\Sigma' = \Sigma + \sigma^2 \mathbb{I} - \frac{\sum \cdot \mathbf{x} \cdot \mathbf{x} \cdot \sum}{\rho^2 + \mathbf{x} \cdot \sum \cdot \mathbf{x}}$$

$\Delta$ weight $\alpha$ (error) x (learning rate) x (stimulus)
ACh and Learning

• Holland; Gallagher showed

amygdala CEN → nBM → ACh → parietal cortex

to be critically involved in boosted learning

• hippocampal/ACC ACh involved in suppressed learning

(Bucci, Holland, & Galllagher, 1998)
Learning and Inference

- Posner task with unsignalled cue/validity changes
  
  ACh

- `Reversal` task with stable validities
  
  NE
Formal Framework

NE

variability in **identity** of relevant cue

\[ 1 - \lambda_t^* \]

cues: vestibular, visual, ...

\[ \mu_t^* = i \]

\[ P^*(\mu_t^* | D_t) = \lambda_t^* \]

\[ P^*(\mu_t = j \neq i | D_t) = \frac{1 - \lambda_t^*}{h - 1} \]

target: stimulus location, exit direction...

ACh

variability in **quality** of relevant cue

\[ 1 - \gamma_t^* \]

ACh & NE are part-synergistic, part-antagonistic:

avoid representing full uncertainty

Sensory Information
Phasic NE: A-J; Sara
detect and react to a rare target amongst common distractors

- elevated tonic activity for reversal
- activated by rare target (and reverses)
- not reward/stimulus related? more response related?

Clayton, et al
Vigilance Model

- variable time in start
- _______ controls confusability
- one single run
- cumulative is clearer
- exact inference
- effect of 80% prior
Phasic NE

- NE reports **uncertainty** about current state
  - state in the **model**, not state of the model
  - **divisively** related to prior probability of that state

- NE measured relative to **default state sequence**
  - start _ distractor

- **temporal** aspect - start _ distractor

- **structural** aspect target **versus** distractor
Phasic NE

- onset response from timing uncertainty (SET)
- growth as $P(\text{target})/0.2$ rises
- act when $P(\text{target})=0.95$
- stop if $P(\text{target})=0.01$
- arbitrarily set NE=0 after 5 timesteps

(small prob of reflexive action)
Four Types of Trial

fall is rather arbitrary
Response Locking

slightly flatters the model – since no further response variability
- set $\_ = 0.65$ rather than 0.675
- information accumulates over a longer period
- hits more affected than cr’s
- timing not quite right
Interrupts/Reset (Shulz)
Discussion

• phasic NE as unexpected state change within a model
• relative to prior probability; against default
• interrupts ongoing processing
• tie to ADHD?
• close to alerting (AJ) – but not necessarily tied to behavioral output (onset rise)
• close to behavioural switching (PR) – but not DA
• close to instability (EB)
• phasic ACh: aspects of known variability within a state?
Neuromodulation and Uncertainty

- ACh/NE as expected/unexpected uncertainty signals
- experimental psychopharmacological data replicated by simulations
- implications from complex interactions between ACh & NE
- predictions at the cellular, systems, and behavioral levels
- activity vs weight vs neuromodulatory vs population representations
- irreducible uncertainty vs ignorance
Simulation Results: Posner’s Task

nicotine

scopolamine

VE \propto (1-)(NE - ACh)

concentration

concentration

(Phillips, McAlonan, Robb, & Brown, 2000)

no unexpected change

% normal level

% normal level
Simulation Results: Maze Navigation

Rats reaching criterion:

No. days after shift from spatial to visual task

(Devauges & Sara, 1990)

No invalidity
ACh/NE

Typical Run

Simulated Pharmacology
Summary

• single framework for understanding ACh, NE and some aspects of attention and learning

• ACh/NE as expected/unexpected uncertainty signals

• experimental psychopharmacological data replicated by model simulations

• implications from complex interactions between ACh & NE

• predictions at the cellular, systems, and behavioral levels

• activity vs weight vs neuromodulatory vs population representations of uncertainty

• Kalman filter; added ‘shock’ process; also competitive combination

• irreducible uncertainty vs ignorance
ACh in Hippocampus

Given **unfamiliarity**, ACh:
- **boosts** bottom-up, suppresses recurrent processing

Hippocampus, CA1, CA3, DG, MS

ACh in Conditioning

Given **uncertainty**, ACh:
- **boosts** learning to stimuli of

<table>
<thead>
<tr>
<th>Treatment condition (groups)</th>
<th>Phase 1: consistent L-T relation</th>
<th>Phase 2: experimental change in L-T relation</th>
<th>Phase 3: test of conditioning to L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent (CTL-C, PPC-C)</td>
<td>L → T → food; L → T</td>
<td>L → T → food; L → T</td>
<td>L → food</td>
</tr>
<tr>
<td>Shift (CTL-S, PPC-S)</td>
<td>L → T → food; L → T</td>
<td>L → T → food; L</td>
<td>L → food</td>
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(Hasselmo, 1995) (Bucci, Holland, & Gallagher, 1998)
Cholinergic Modulation in the Cortex

Electrophysiology Data

Examples of Hallucinations Induced by Anticholinergic Chemicals

<table>
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<tr>
<th>Anticholinergic Chemical</th>
<th>Effect on Hallucinations</th>
<th>Study</th>
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<tbody>
<tr>
<td>Scopolamine in normal volunteers</td>
<td>Integrated, realistic hallucinations with familiar objects and faces</td>
<td>Ketchum et al. (1973)</td>
</tr>
<tr>
<td>Intravenous atropine in bradycardia</td>
<td>Intense visual hallucinations on eye closure</td>
<td>Fisher (1991)</td>
</tr>
<tr>
<td>Local application of scopolamine or atropine eyedrops</td>
<td>Prolonged anticholinergic delirium in normal adults</td>
<td>Tune et al. (1992)</td>
</tr>
</tbody>
</table>

**ACh agonists:**
- **facilitate** TC transmission
- **enhance** stimulus-processing

**ACh antagonists:**
- **induce** hallucinations
- **interfere** with stimulus-processing
Norepinephrine

Something similar may be true for NE (Kasamatsu et al, 1981)

(Hasselmo et al, 1997)

NE specially involved in novelty, confusing association with attention, vigilance, selective attention

(Devauges & Sara, 1990)
Approximation

approximation is not catastrophic compared with a simpler, algorithm