Psychiatric Disorders and Neural Mechanisms: How are They Connected?

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Mechanism and Disease

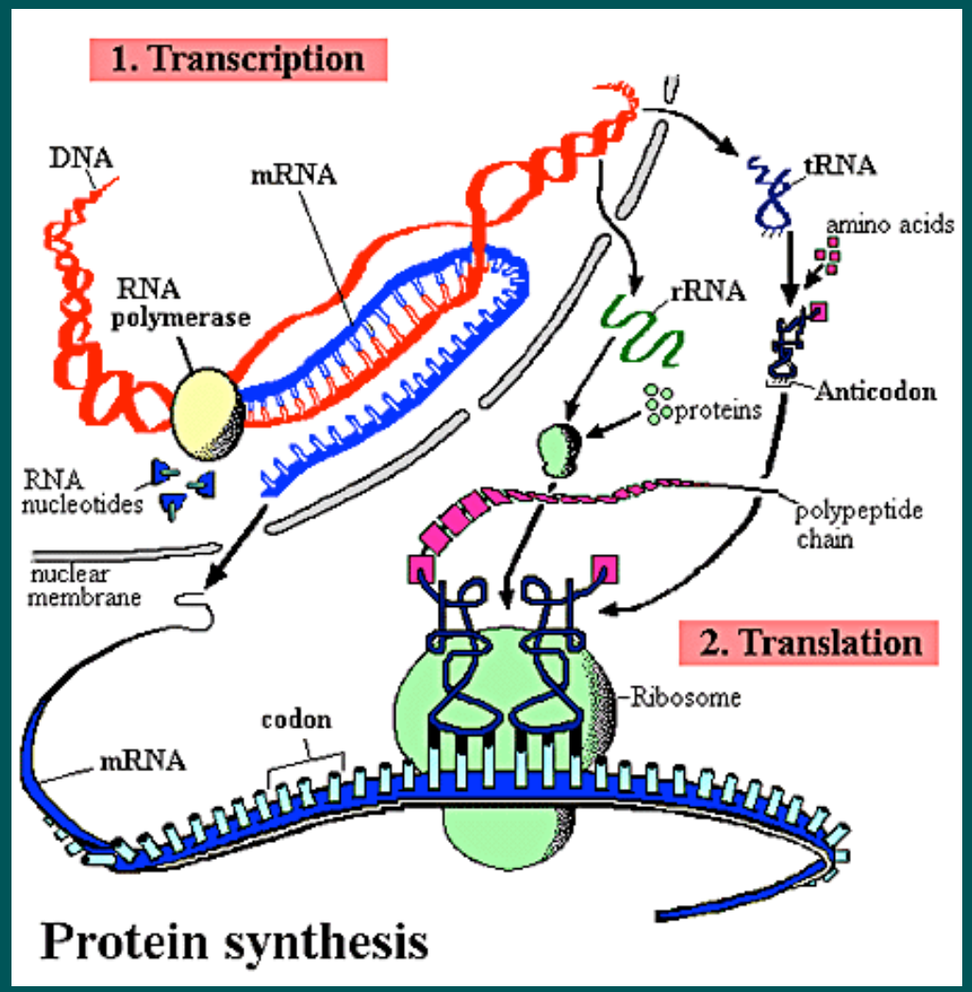
- “New mechanism” has become the focus of philosophical discussions of explanation in biology
  - Not everyone embraces it (and “mechanism” means different things to its various advocates and opponents)
- The framework has been applied to phenomena in normally functioning organisms
  - seldom to disease
- Challenge: how to apply the framework to pathological conditions
  - In particular, how to apply it to major depression

Outline

1. Mechanisms and Disease
2. Productive and Control Mechanisms
3. Seeking Control Mechanisms for Major Depression
4. The Serotonin Hypothesis
5. Circadian Mechanisms and Depression
6. Conclusions

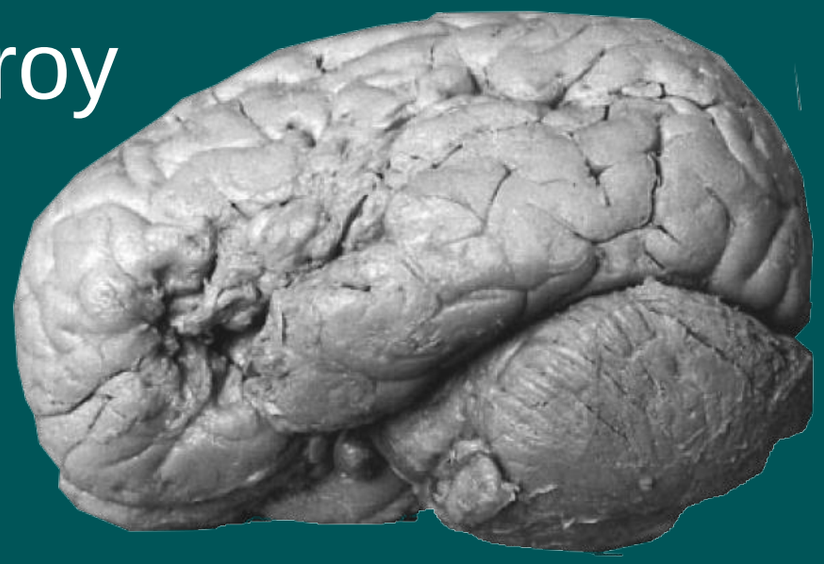
New Mechanism

- Start with reasonably well delineated phenomena
- Relate a given phenomenon to a mechanism
- Decompose the mechanism into its component parts, operations, and organization
- Recompose the mechanism (either actually, conceptually, or through simulation)



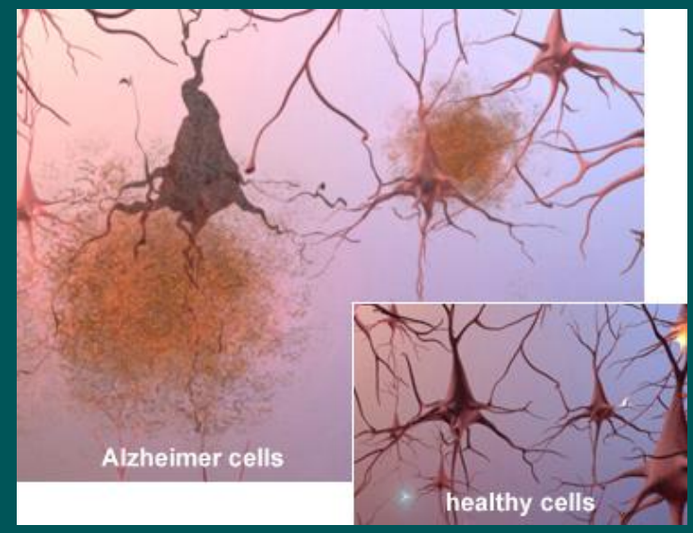
Pathology as a Discovery Heuristic

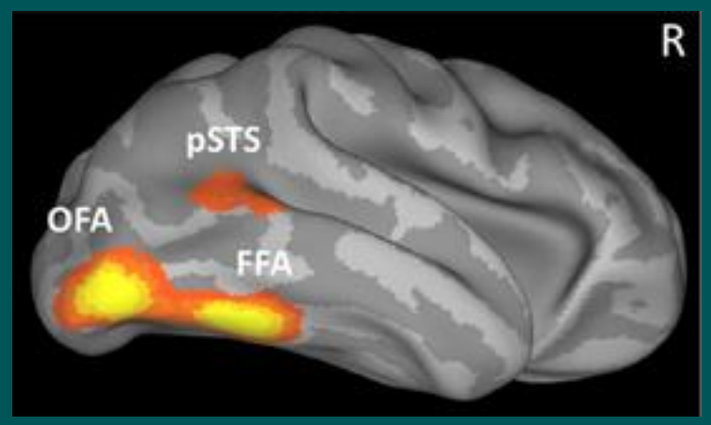
- Mechanistic research commonly makes use of damaged or pathological conditions as a tool for discovery
  - Simon: normally operating systems don't reveal their parts—one must consider how they break down
- Both experiments of nature and actual experiments that damage or destroy a mechanism or its parts help investigators infer what they contribute to normal function



Mechanism and Disease

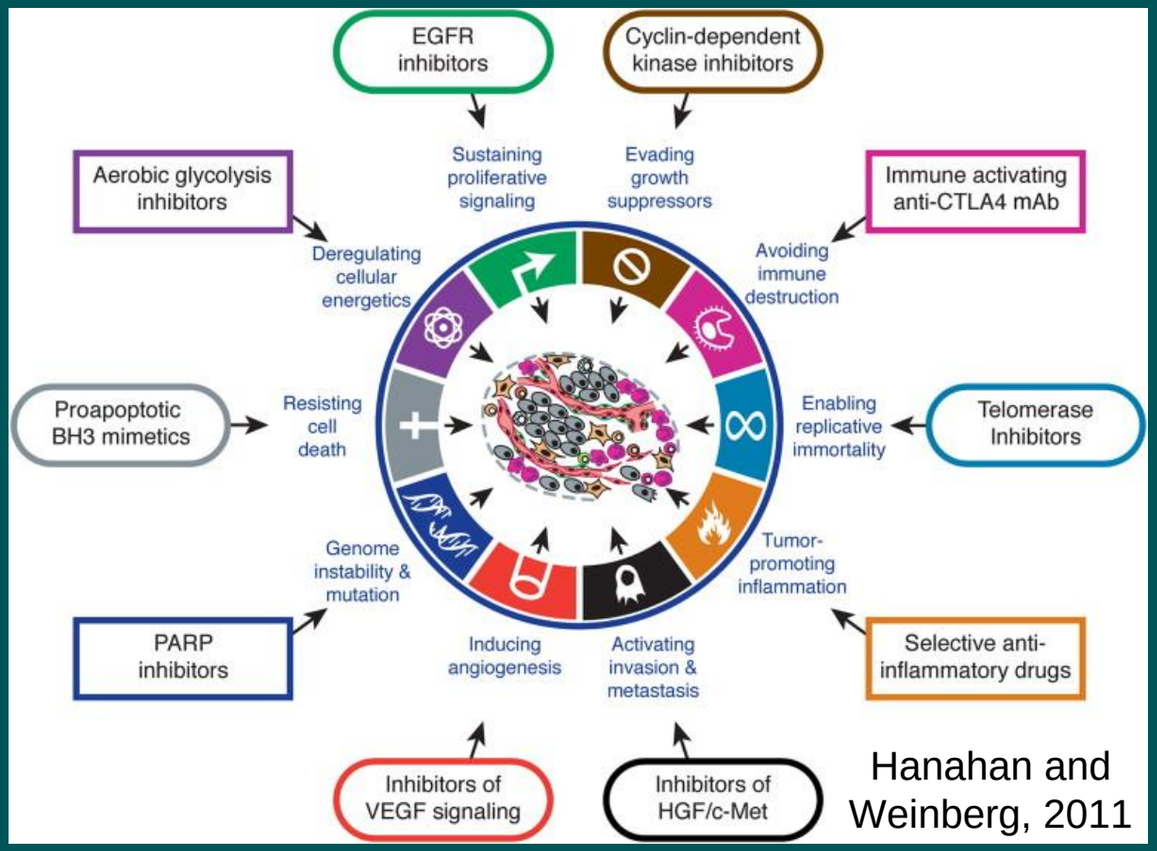
- Three strategies for relating the mechanistic perspective to disease?
  - **Disease mechanisms**: mechanisms that generate disease phenomena
    - Generation of plaques and tangles in Alzheimer's Disease
  - **Broken mechanisms**: diseases explained in terms of breakdown of mechanisms
    - Damaged fusiform face area in Prosopagnosia
  - **Altered control mechanisms**: resulting in altered functioning of a network of control mechanisms





Disease and Altered Control

- Many diseases make use of the same mechanisms as operate in healthy organisms
  - But use these mechanisms to different ends
- The hallmarks of cancer involve cancer cells activating or inhibiting mechanisms of normal cells
- Distinguish productive and control mechanisms



Hanahan and Weinberg, 2011

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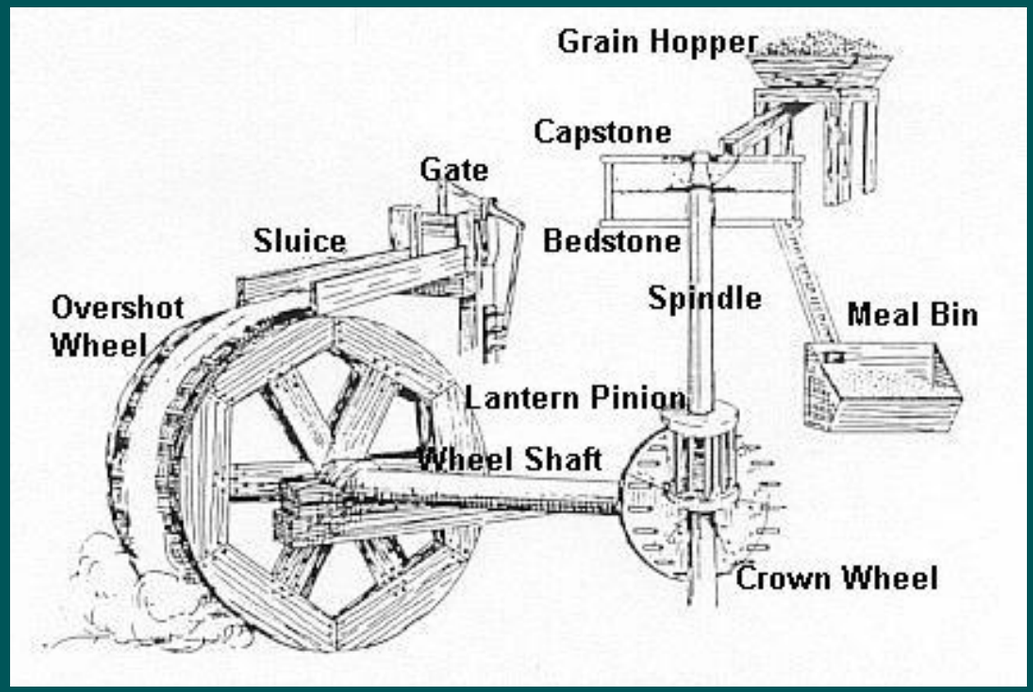
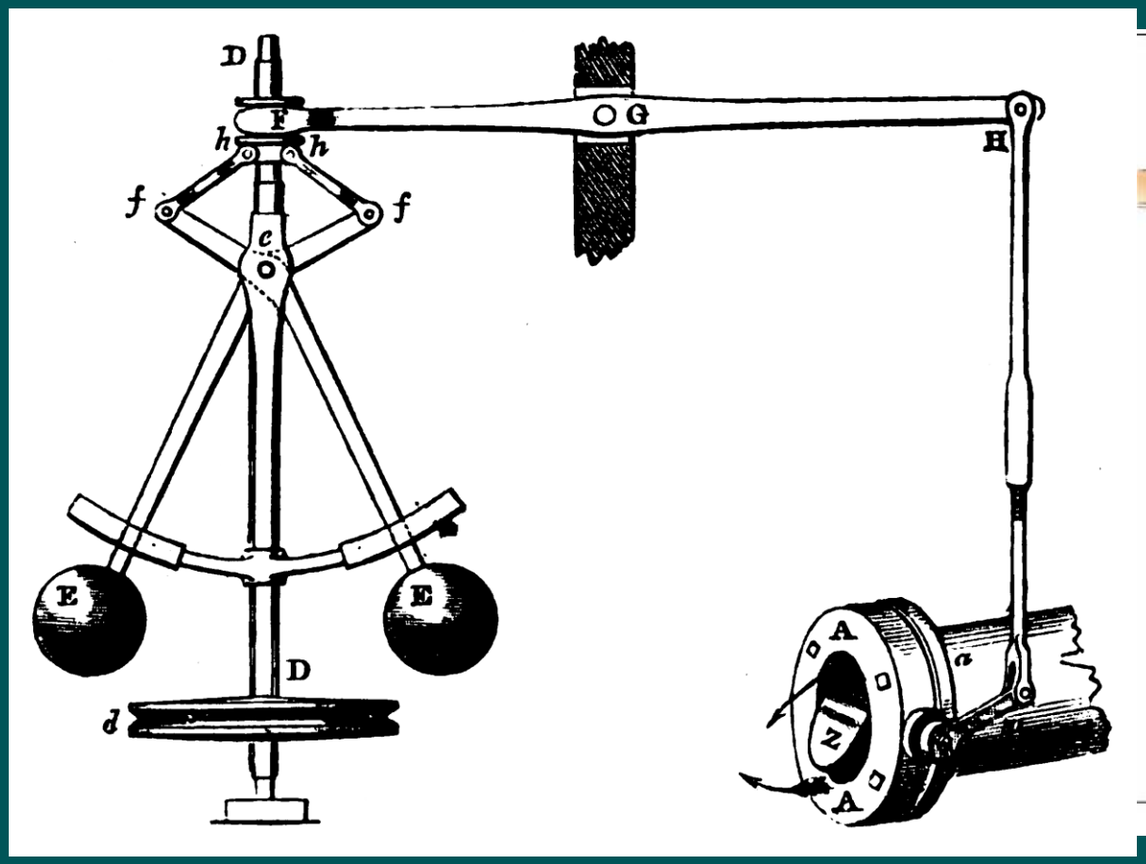
Extending the Mechanistic Framework

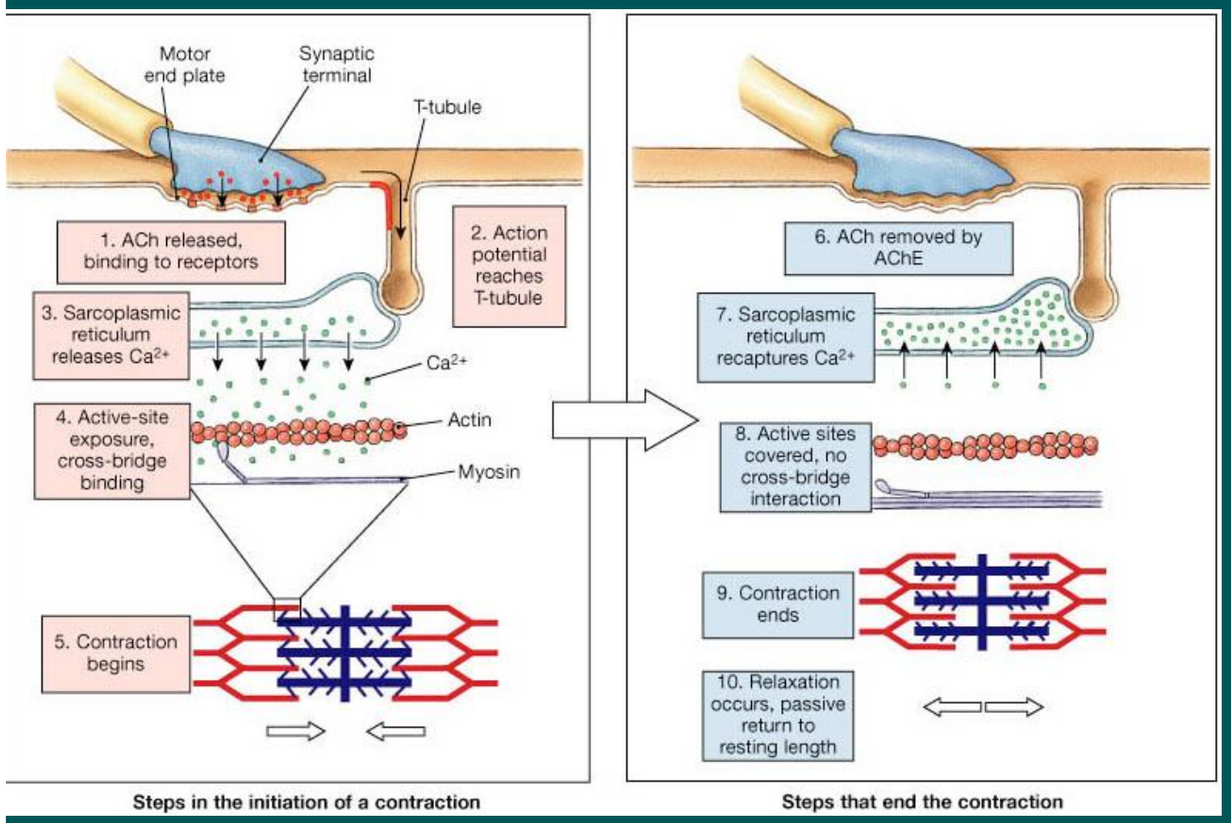
- The focus on the composition of mechanisms leaves out an important element: how they are controlled
- A different perspective on mechanisms
  - they perform work
  - by constraining the flow of
  - free energy
- The parts and operations in the mechanist's account constrain energy flows



Flexible vs. Fixed Constraints

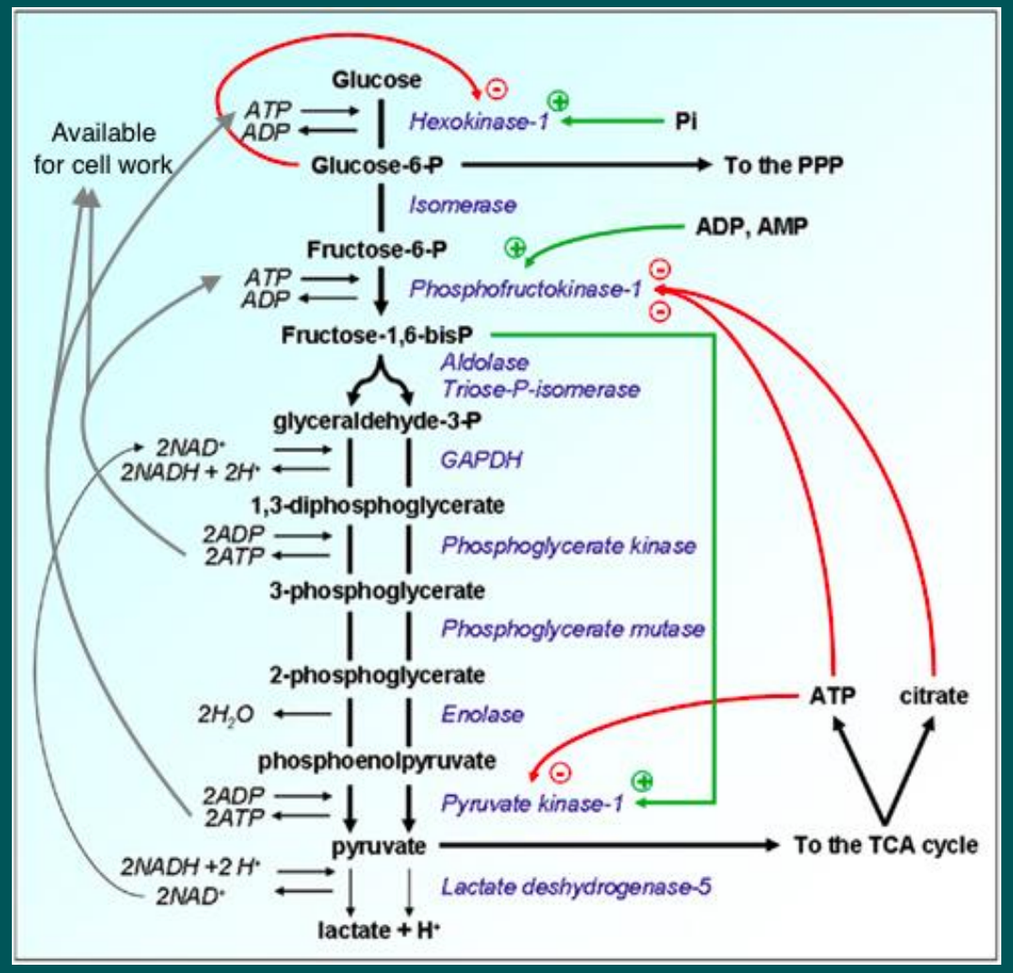
- Many of the constraints in a mechanism are fixed
- Some are flexible
  - they can be operated on by other (control) mechanisms





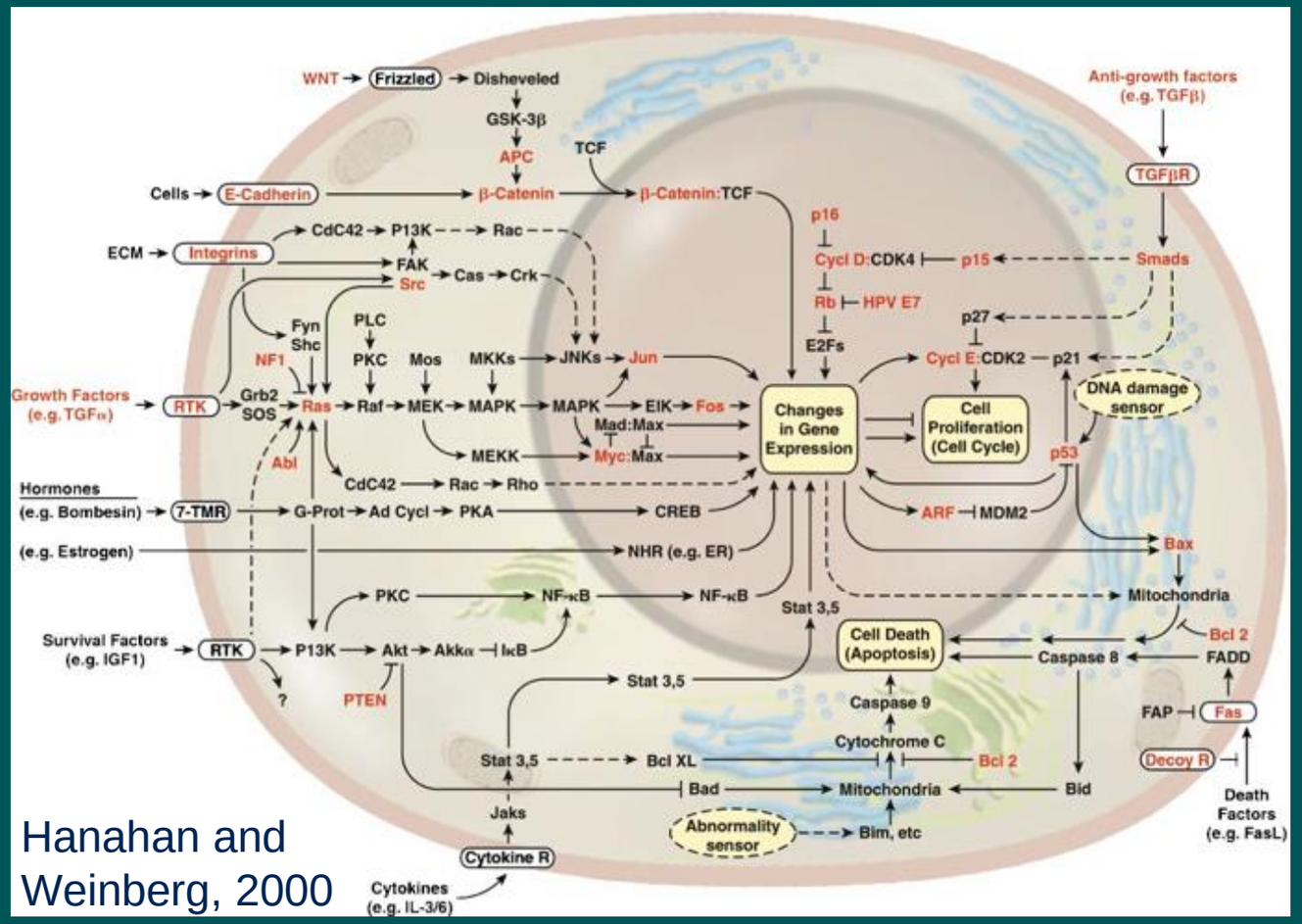
Control Mechanisms

- Control mechanisms, like productive mechanisms, perform work (although generally the amount of work performed is far less than that performed by productive mechanisms)
  - and so require energy and often material inputs
- But in order for control to be effective, control mechanisms also require information
  - In glycolysis ATP is both
    - a material/energetic input
    - an information input



The Ubiquity of Control Mechanisms

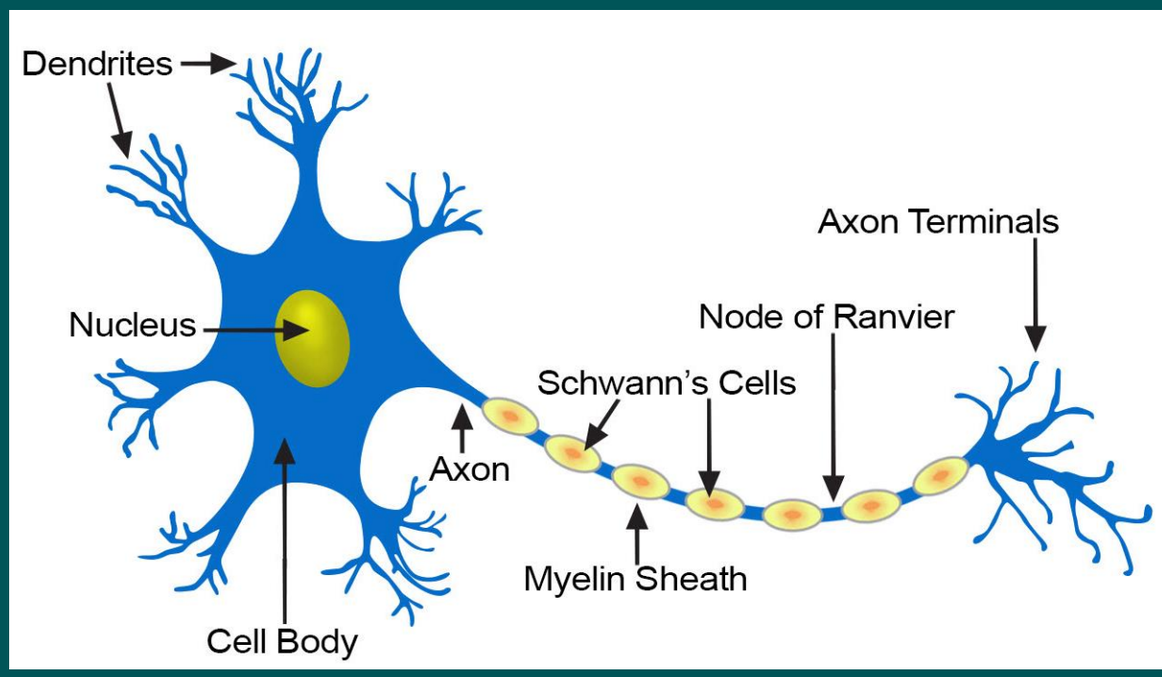
- Even within individual cells, control mechanisms vastly outnumber productive mechanisms
- Investigating the hallmarks of cancer has revealed a multitude of control mechanisms that when altered, can redirect the cell's productive mechanisms to serving the needs of the cancer cell

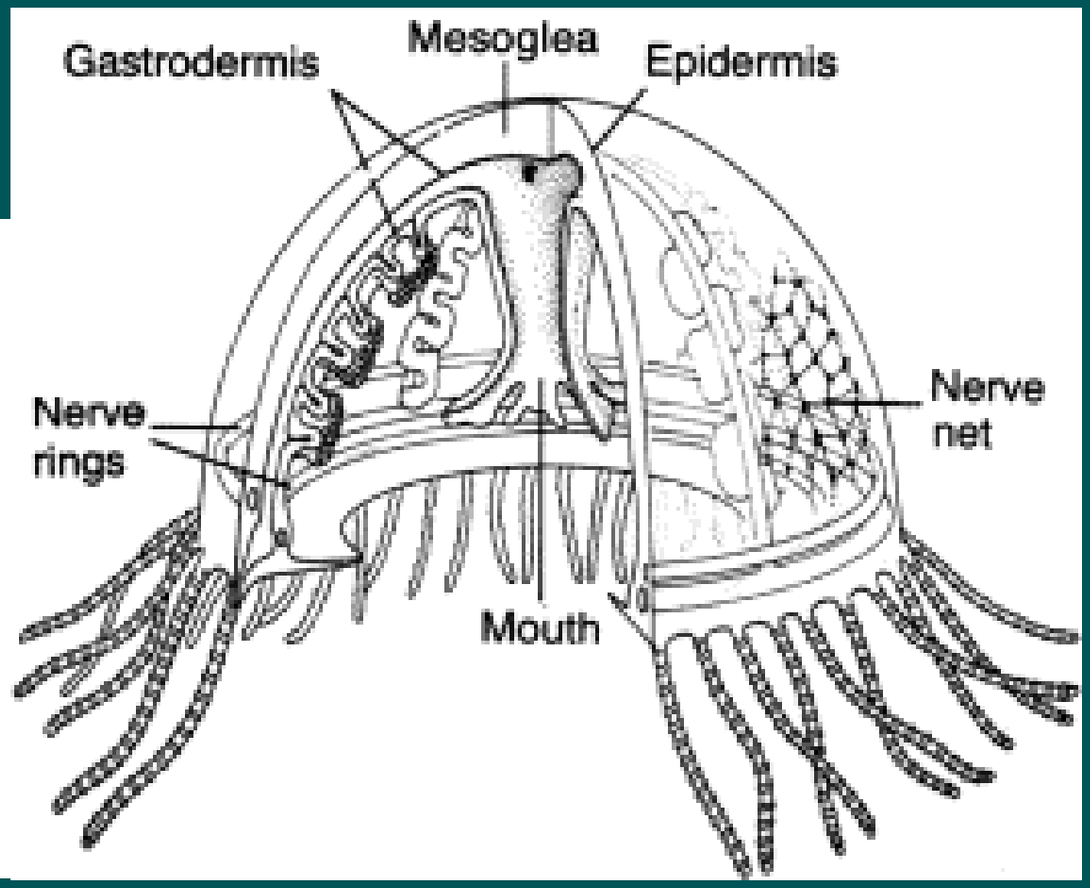


Hanahan and Weinberg, 2000

Neurons as Control Mechanisms

- Electrical transmission of information predates neurons
  - which, in all likelihood, evolved as control mechanisms to coordinate muscle contraction (Keijzer's skin brain hypothesis)



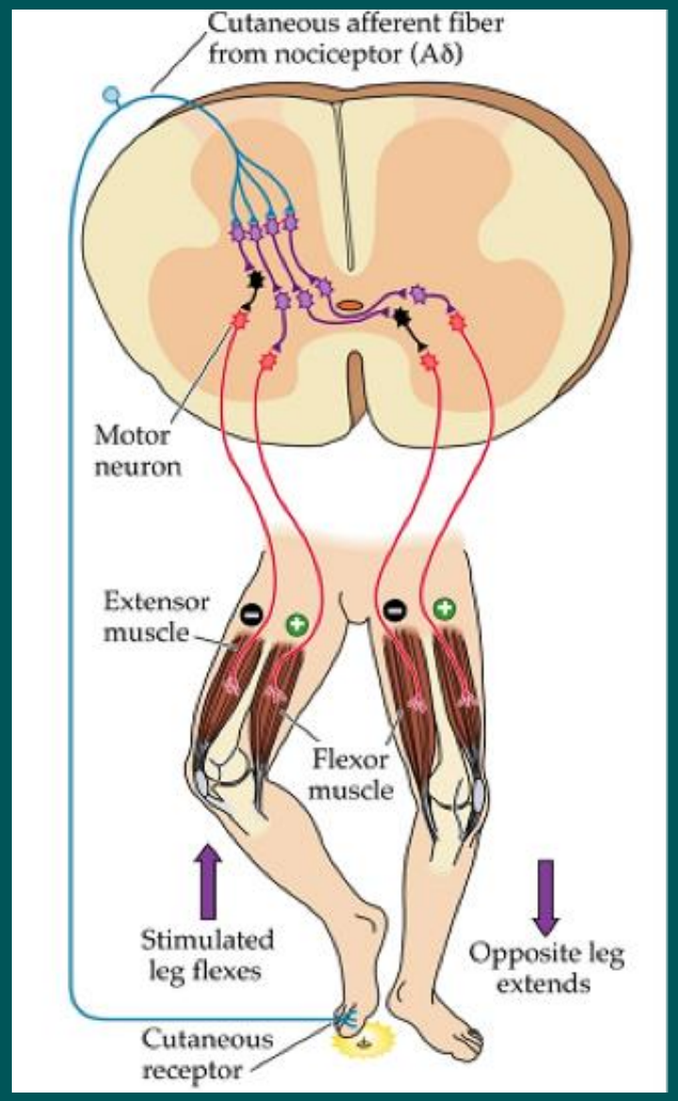


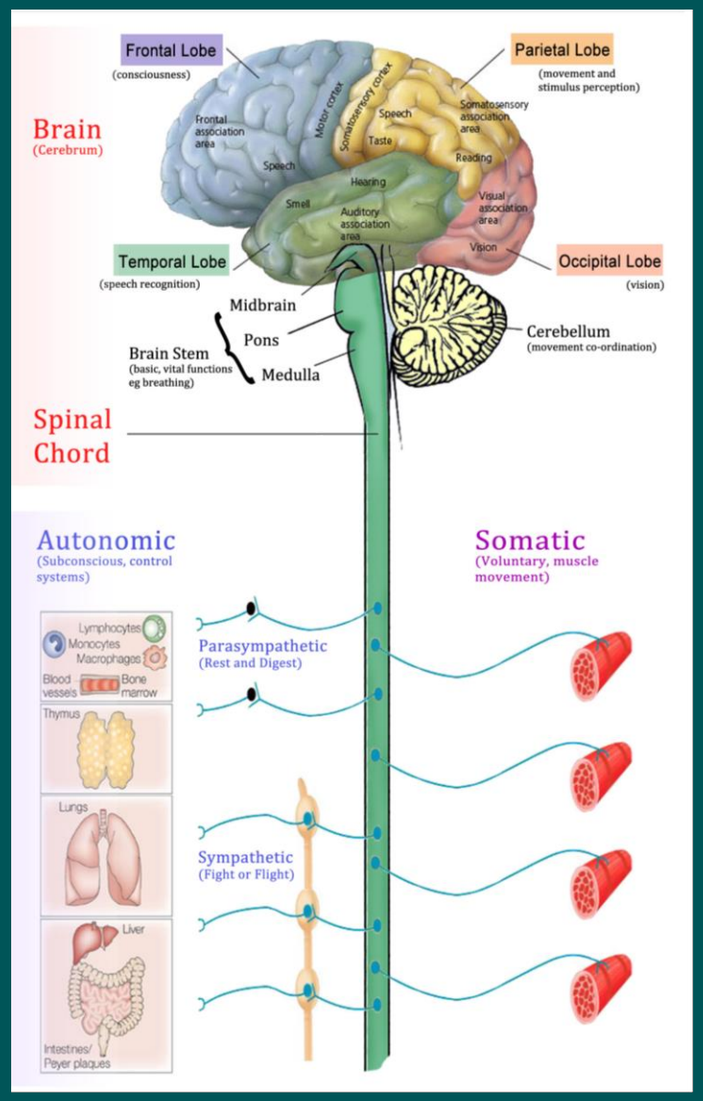
Control Mechanisms Modulate Productive Mechanisms

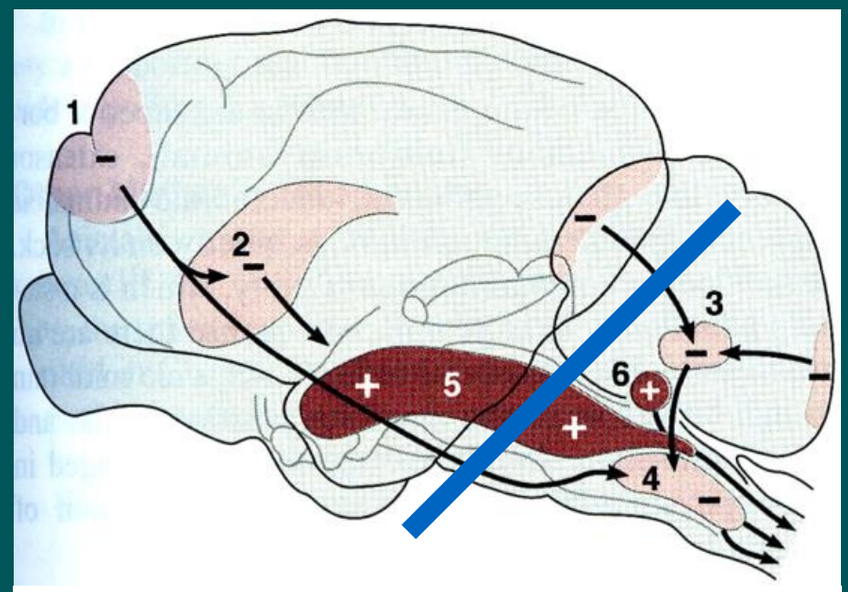
- When control mechanisms act on productive mechanisms they don't instruct their activities, but modulate their endogenous activities
  - enabling overall coordinated behavior
- Most machines and biological mechanisms are designed to perform work when materials and free energy are available
  - accordingly, most control is inhibitory, restricting the mechanism to operating when its output is required
  - many higher-level control mechanisms inhibit inhibitory mechanisms

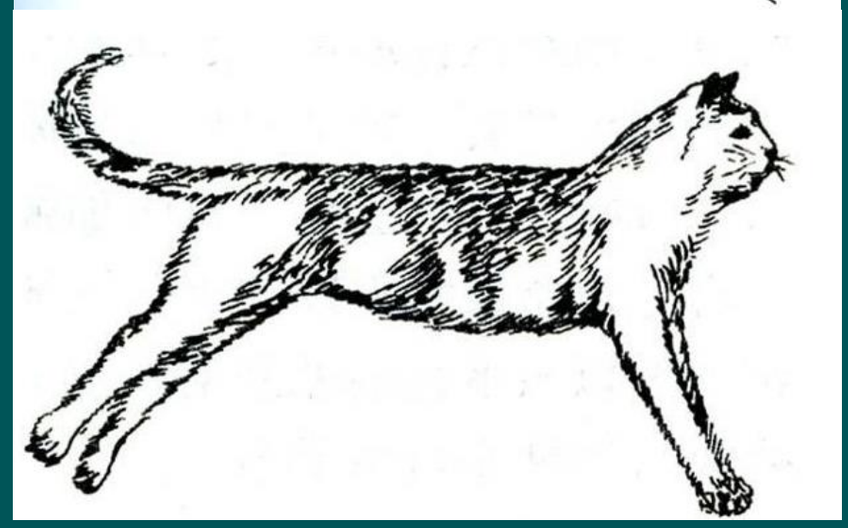
Multiple Levels of Neural Control

- The neocortex doesn't operate on its own, but serves to control and organize mechanisms that, lacking such regulation, still perform behaviors



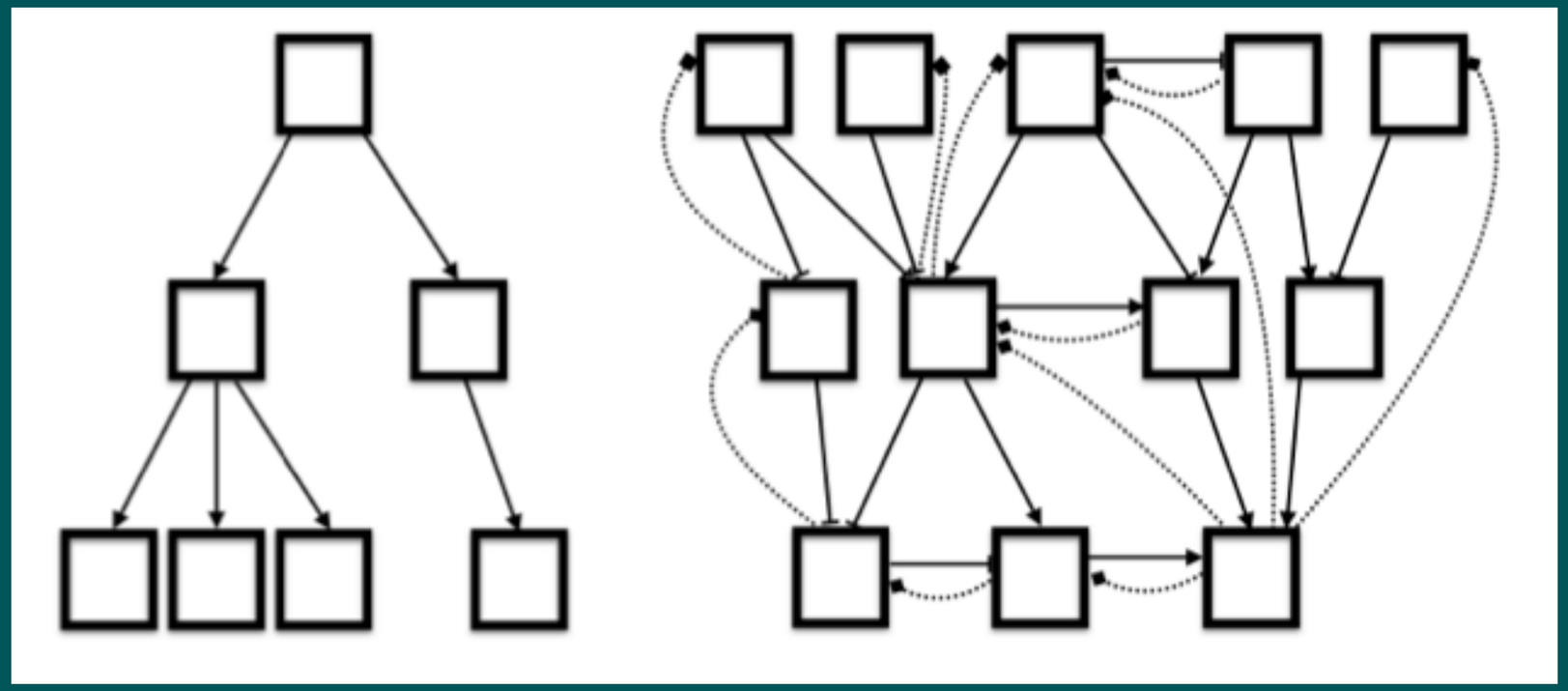






Heterarchical Control

- We often think of control as hierarchical, with the highest level directing all the others
- But in biological control is often heterarchical
  - Individual productive (or control) mechanisms may be controlled by several control mechanisms
- Without an executive overseeing everything



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The Phenomenon of Major Depression

- Major depression is characterized in the DSM as requiring 5 of 9 symptoms
  - depressed mood
  - anhedonia
  - significant weight loss
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or guilt
  - inability to concentrate and indecisiveness
  - thoughts of death or suicide.

Heterogeneity and Reconstituting the Phenomenon

- The heterogeneity might seem to be an obstacle to any integrated account of depression
- But sometimes the search for mechanisms can provide order to what seems like unsystematic variation
  - Cancer research faced an even greater heterogeneity problem (in cancers affecting specific organs, no genes are mutated in all patients and there is a long-tailed of infrequently mutated genes)
  - Network analysis has often resulted in grouping mutated genes into clusters that have provided a basis for differentiation of different types of cancer

Heterogeneity of Major Depression

- Patients with minimally overlapping symptoms are all diagnosed as depressed
- Different neural control mechanisms are responsible for each of these various traits
- Making it unlikely that there is a single mechanism
  - generating major depression
  - or broken in all instances of depression
- Instead, this heterogeneity suggests looking for higher-level control mechanisms that when altered affect a host of other control mechanisms

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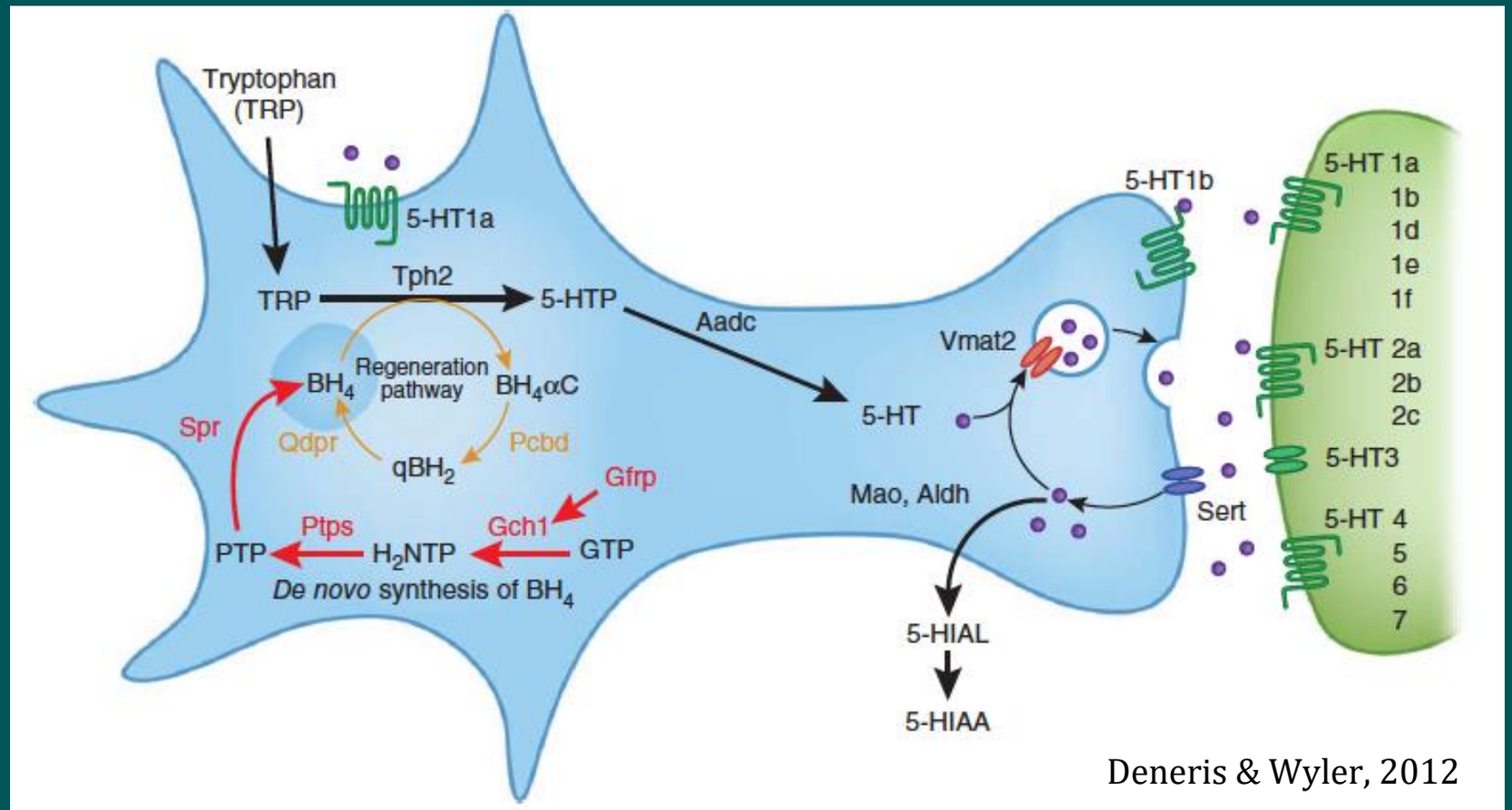
The Serotonin Hypothesis

- Developed in the 1960s in response to the apparent efficacy of drugs in treating cases of depression
  - and reinforced by the apparent efficacy of SSRIs such as Prozac (Fluoxetine)
- Subsequent studies have raised doubts about these efficacy claims
  - Challenge of testing the central assumption that depression results from low serotonin levels
    - measurements are indirect
  - Any effects of SSRIs on depression occur much later than effects on serotonin levels
- Yet many researchers still view serotonin as playing a causal role in depression even if it is not *the* cause

Serotonin Could Be a High-Level Controller

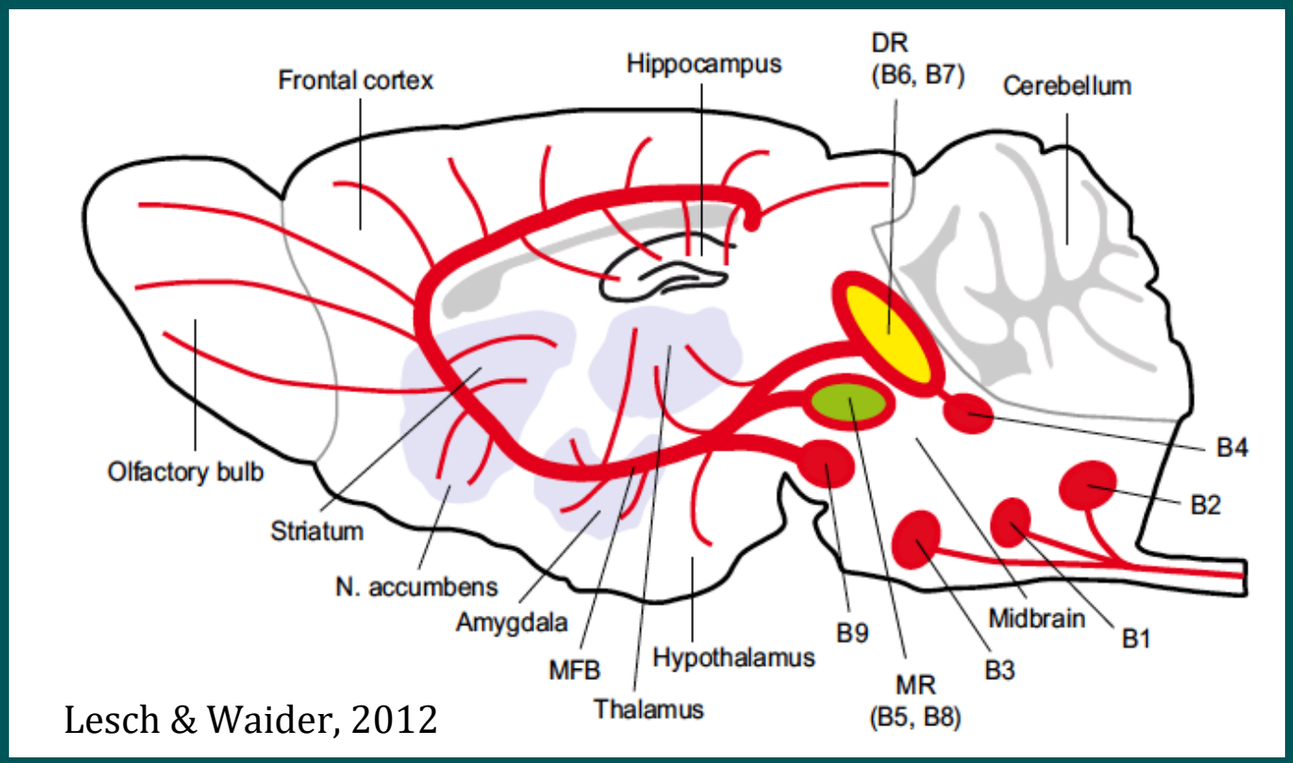
- There is detailed understanding of both the synthesis of serotonin and its receptors
  - Seven classes of receptors for which there is detailed knowledge of how they affect post-synaptic cells



Deneris & Wyler, 2012

Serotonin Widely Distributed

- Serotonin is only synthesized in the brain in the 9 raphe nuclei of the mid-brain
  - B1-B3 project to the brain stem
  - B4-B9 project broadly to the forebrain including the hypothalamus, thalamus, amygdala, hippocampus, and frontal cortex



Lesch & Waider, 2012

How Might It Function as a Control Mechanism?

- While wide distribution is compatible with a high-level control mechanism, the challenge is to link it to the mechanisms responsible for specific traits of depression
- The different classes of receptors might provide a needed bridge, but they too seem extremely diverse
  - 5-HT 1a receptors are found in frontal cortex, hippocampus, entorhinal cortex, septum, and amygdala
  - have effects on addiction, appetite, blood pressure, heart rate, cardiovascular function, memory, pain sensitivity, respiration, penile erection and sexual behavior, sleep, and thermoregulation, as well as mood and related phenomena such as anxiety

Diverse Functions of Serotonin

- Serotonin predates neurons
  - appears to have evolved in cyanobacteria, which created the molecular oxygen needed for its synthesis but also the demand for antioxidants (a function serotonin serves)
  - occurs in plants, in which it functions in growth and mitosis
- In *C. elegans* it modulates sensory responses to the repellant stimulus octanol
- In *Aplasia* in affects synaptic plasticity, enhancing LTP
- In the medicinal leech, it is a transmitter that acts on neuron 208, which biases decision making towards swimming rathe than crawling

What is Lacking in the Serotonin Story

- Research in bacteria, plants, and invertebrates
  - shows the versatility of serotonin
  - indicating how it might act on specific productive or control mechanisms in the case if depression
- Reveals the gap in the serotonin hypothesis for depression
  - We are lacking accounts of how it carries out specific, selective actions on control mechanisms responsible for depression
- If this gap is to be filled, it will likely be through finding appropriate model organisms in which specific control activities of serotonin can be identified
  - mouse is already too complex

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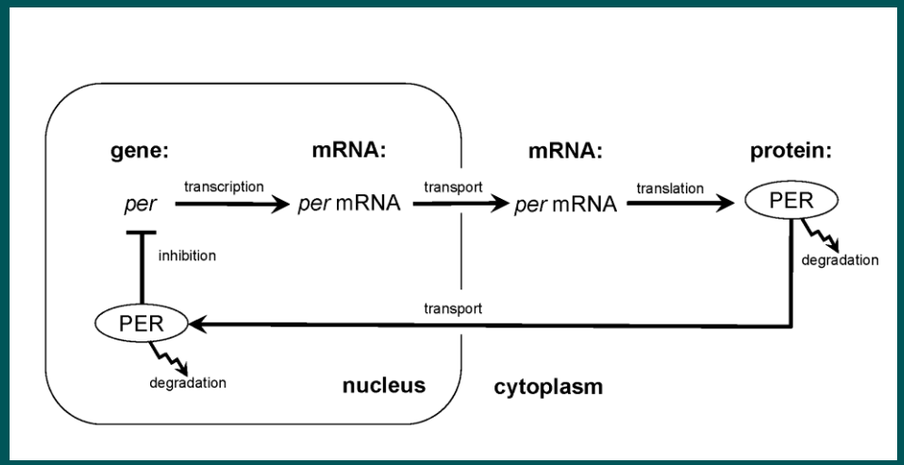
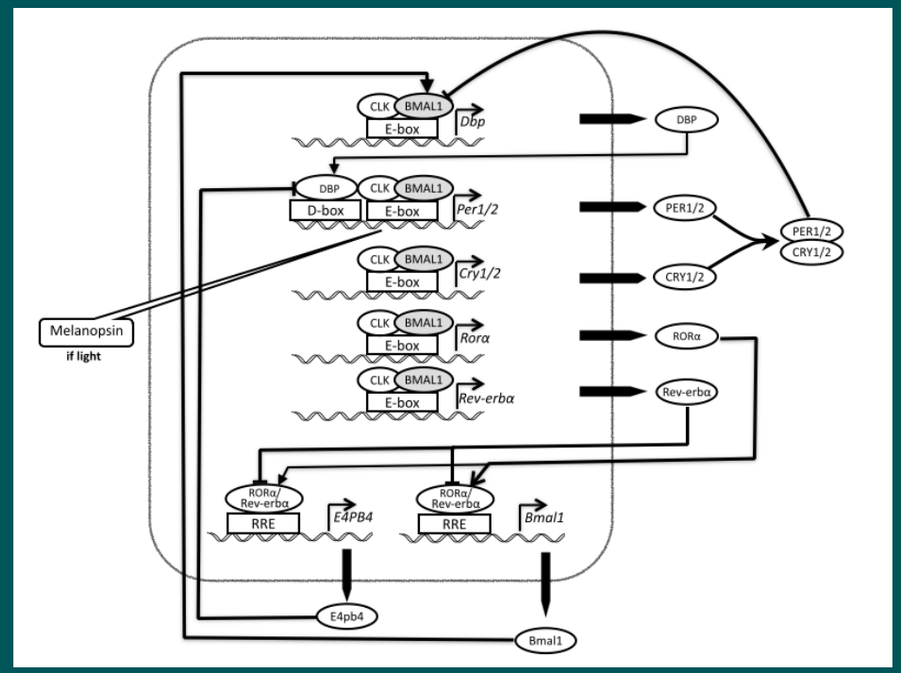
Circadian Basics

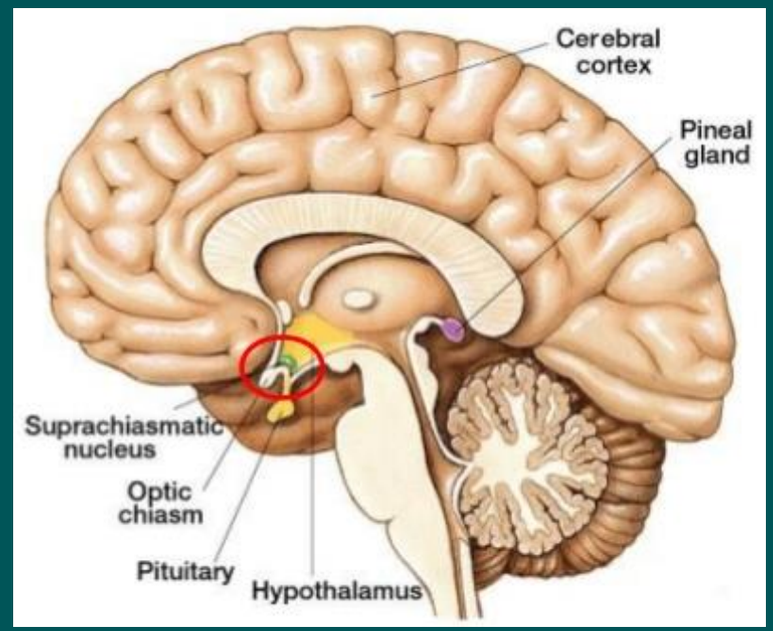
- Circadian clocks are reasonably well-understood mechanisms
- Konopka and Benzer (1971) identified in fruit flies the first gene—*period* or *per*—that, when mutated, eliminated or altered the period of circadian behavior
- Hardin, Hall, and Rosbash (1990) showed a phase delay in expression and proposed a transcription, translation feedback loop
- Subsequent, many more feedback loops with more components have been identified





Circadian Basics - 2

- Central clock in mammals is located in the suprachiasmatic nucleus (SCN)
  - SCN lesions result in loss of circadian rhythms
  - Transplant of an SCN to the ventricle can restore many circadian behaviors



- But the clock mechanism is present in each cell of the body
  - The SCN is required to synchronize these clocks
- These peripheral clocks affect behavior through regulating expression of other genes

Long History of Attempts to Link Circadian Rhythms to Depression

- First studies focused on altered sleep in depressed patients, but sleep is only partly under circadian control
  - In 1997 Boivin et al. desynchronized sleep from circadian rhythms and showed a purely circadian association
- Bright light therapy for seasonal affective disorder
  - bright light around dawn can reset the circadian clock
- Agomelatonine, synthetic version of melatonin, acts on both melatonin and serotonin receptors and is claimed to have antidepressant effects

Pseudo Time-series Study of Dampened Rhythms in Depressed Patients

- To really demonstrate altered circadian oscillations of gene expression, need time-series data
- Li et al., 2013, used time of death as a proxy and showed significant reduction in circadian rhythms in depressed patients

1
0.8
0.6
0.4
0.2
0

Symbol	DLPFC	AnCg	HC	AMY	NAcc	CB
ARNTL*	0.0005	0.0005	0.001	0.001	0.0005	0.0005
PER2*	0.001	0.0005	0.0005	0.005	0.008	0.0005
PER3*	0.0005	0.0005	0.0005	0.094	0.0005	0.001
NR1D1*	0.0005	0.0005	0.0005	0.102	0.0005	0.008
DBP*	0.0005	0.0005	0.003	0.066	0.002	0.001
SFPQ	0.0005	0.152	0.013	0.134	0.001	0.029
ITIH5	0.0005	0.021	0.009	0.577	0.007	0.027
LDLR	0.001	0.002	0.004	0.014	0.561	0.204
PER1*	0.0005	0.005	0.008	0.559	0.044	0.071
INSIG1	0.007	0.003	0.001	0.025	0.727	0.183
SLC39A14	0.007	0.0005	0.029	0.067	0.077	0.262
NFIL3*	0.011	0.0005	0.104	0.181	0.03	0.198
SNTB2	0.023	0.038	0.17	0.001	0.013	0.368
PDZRN3	0.002	0.001	0.037	0.333	0.207	0.195
BHLHE40*	0.0005	0.014	0.147	0.42	0.02	0.127
BHLHE41	0.005	0.003	0.997	0.751	0.051	0.003

1
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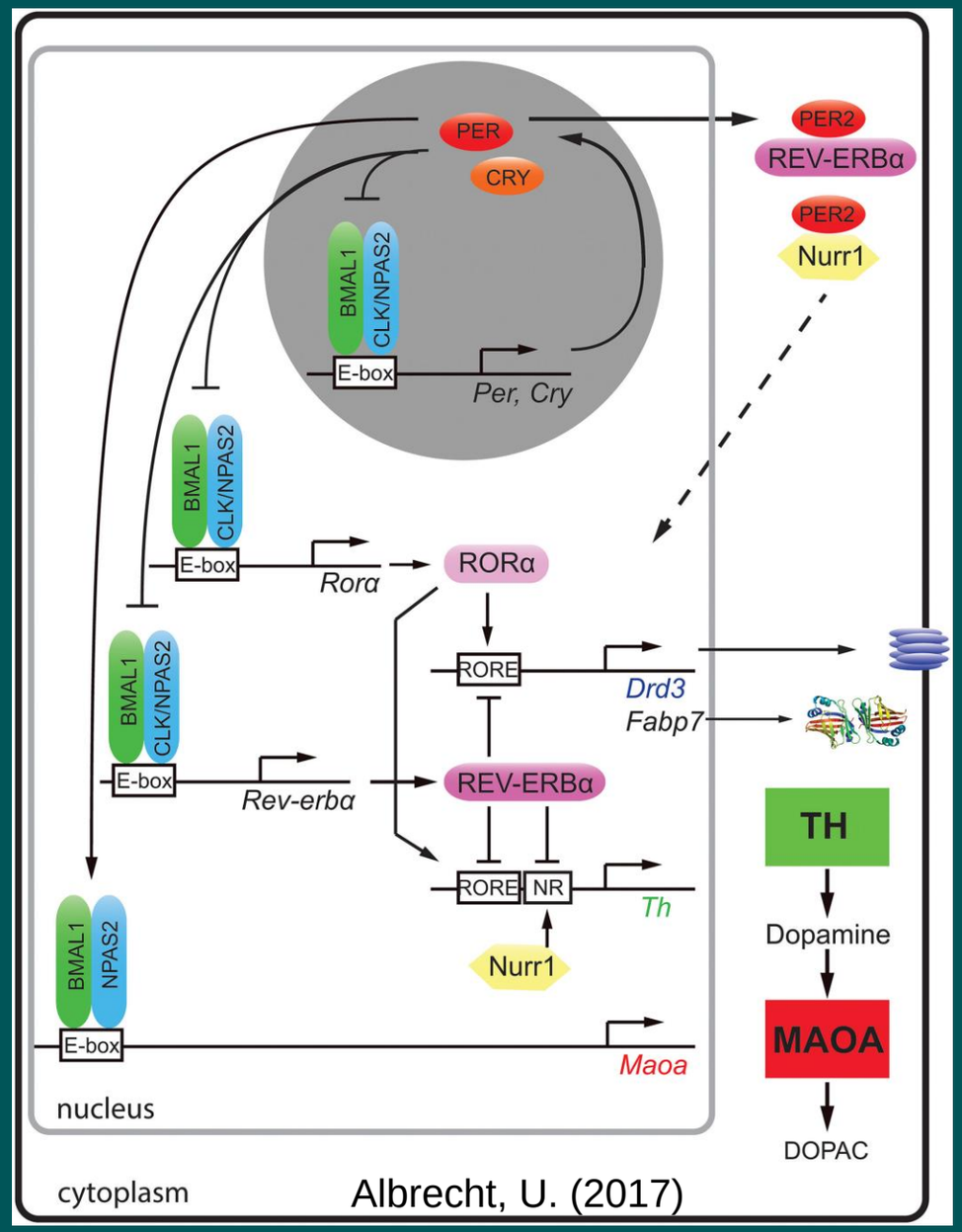
	DLPFC	ACG	HC	AMY	NACC	CB
ARNTL	0.121	0.072	0.732	0.084	0.005	0.141
PER2	0.015	0.083	0.213	0.342	0.075	0.582
PER3	0.42	0.652	0.432	0.999	0.29	0.531
NR1D1	0.04	0.029	0.285	0.097	0.003	0.111
DBP	0.102	0.236	0.025	0.79	0.121	0.118
SFPQ	0.135	0.124	0.165	0.265	0.047	0.089
ITIH5	0.936	0.47	0.117	0.603	0.15	0.832
LDLR	0.012	0.385	0.315	0.307	0.005	0.028
PER1	0.006	0.21	0.137	0.619	0.124	0.061
INSIG1	0.056	0.534	0.668	0.869	0.318	0.88
SLC39A14	0.641	0.21	0.301	0.393	0.157	0.354
NFIL3*	0.565	0.326	0.633	0.478	0.179	0.617
SNTB2	0.928	0.194	0.123	0.765	0.365	0.293
PDZRN3	0.13	0.003	0.503	0.229	0.075	0.139
BHLHE40	0.19	0.897	0.433	0.963	0.14	0.009
BHLHE41	0.497	0.781	0.754	0.433	0.875	0.246

How Could the Clock Produce Depression Symptoms

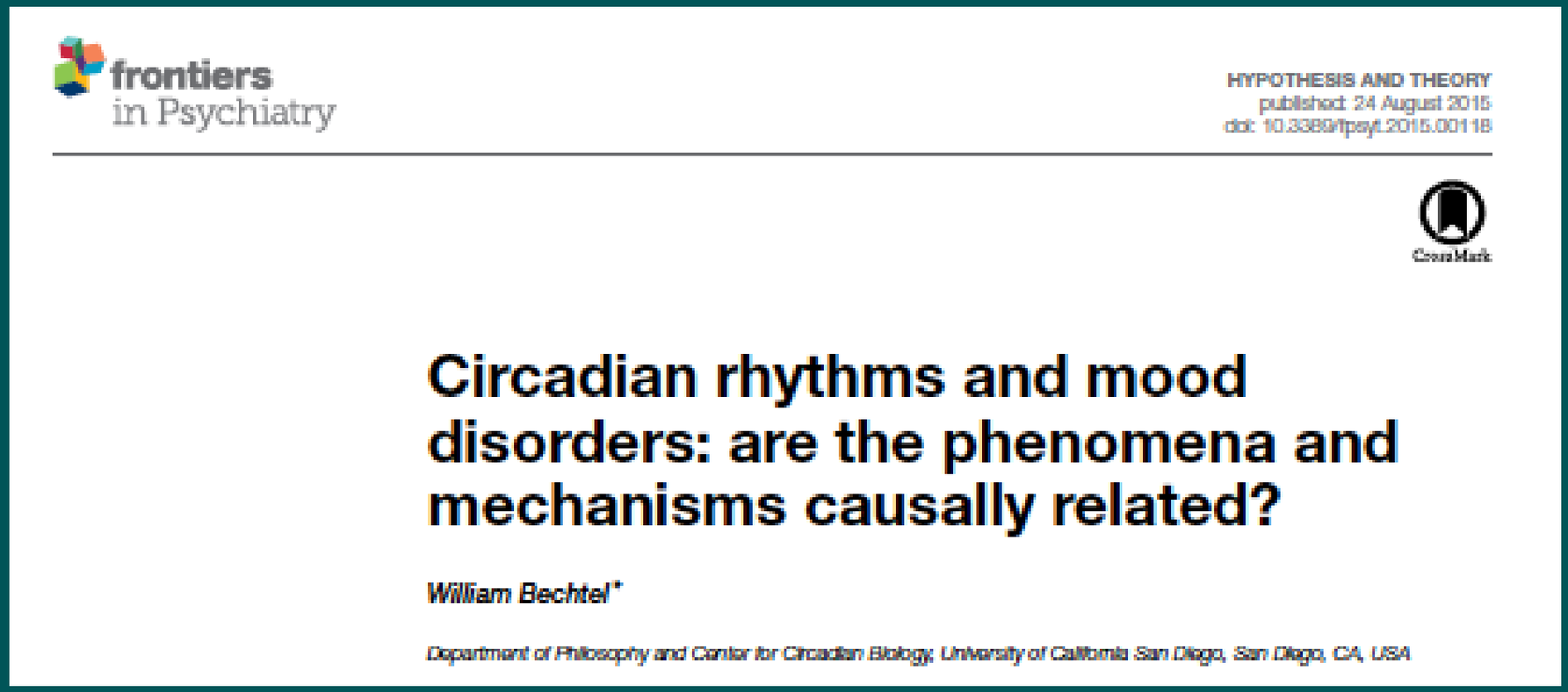
- Most molecules implicated in depression (monoamines, glucocorticoids) exhibit circadian expression
- Many of the molecules involved in their synthesis have E-boxes (to which the circadian protein BMAL1 binds) or ROR elements (to which RORα or REV-ERBα bind) on their promoters



Albrecht, U. (2017)

Causation vs. Pleiotropy

- Showing that circadian genes are involved in monoamine or glucocorticoid metabolism (or otherwise connected to depression) doesn't show that they do so in their circadian capacity
  - Effects could be pleiotropic (Landgraf et al. 2014)
  - Or results of a common cause (Lazzerini et al., 2017)



frontiers in Psychiatry

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Circadian rhythms and mood disorders: are the phenomena and mechanisms causally related?

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Specific Effects of SCN on Depression

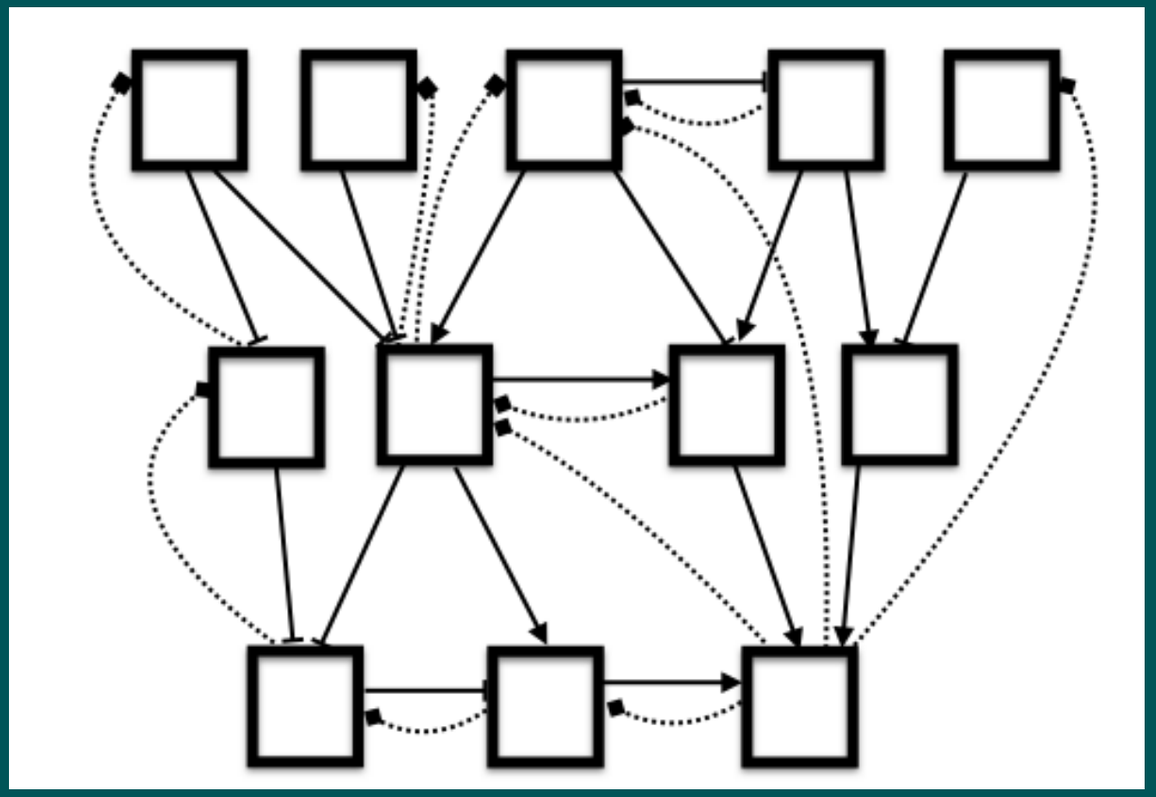
- Landgraf et al. (2016) showed a variety of depression-like effects in mice with a specific knockdown of the required circadian gene *Bmal1* in the SCN
  - longer latencies and more failures in escaping aversive stimulus
  - increased immobility in tail suspension test
- Demonstrated effects on cortisol levels and proposed this as an intermediary

A Mechanism Sketch with Gaps

- As with the serotonin hypothesis, there are major gaps in the claimed effects of altered circadian rhythms on depression (as there are with all circadian regulated behaviors)
- But together with the evidence of altered circadian rhythms in depressed patients, the ability to manipulate the SCN specifically and produce depression-like symptoms offers a sketch of a mechanism
  - with some guidance as to how it might be filled in

Circadian Rhythms as Potential Component of Heterarchical Control

- The circadian clock is not a mechanism for generating depression
- When it is altered, it has effect on a host of behaviors
  - it is not specific for regulating mood
- It is, however, a control mechanism that regulates many other control mechanisms and can interact with them and act together on more specific control mechanism
  - as part of a network of heterarchical control mechanisms



Conclusions

- Although in some cases diseases may be explained in terms of disease mechanisms or broken mechanisms, in many cases they involve altered operation of control mechanisms
- Control mechanisms perform work on productive (or other control mechanisms) in response to information
- The serotonin hypothesis of depression has the appropriate character to explain depression as the result of altered control mechanisms
  - but little has been done so far to fill in the explanatory sketch
- Circadian clocks are reasonably well understood control mechanisms that operate on many productive mechanisms
  - and research is beginning to demonstrate causality and fill in details about how it affects behaviors related to depression
- But at best circadian clocks are one of many heterarchically organized control mechanisms that figure in depression