Challenges in Delivering Novel Treatments in Depression: Glutamate, Ketamine and Beyond

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Conflicts of Interest

- Consultant: Akili Interactive
- Co-Founder: eMind Science Corp

Outline

- Depression: From Disorder to Disease
  - DSM & RDoC
  - Subdividing Depression
- Treatment of Depression: Mechanisms of Action
  - Psychotherapies
  - Pharmacotherapies
  - Devices
- Neuroscience of the Mind: Known, Unknown & Unknowable
  - Representational Maps – Sensation, Emotion, Cognition, Behavior
  - Circuits – Bottom-Up, Top-down
  - Information Theory
    - Computational process, Memory and Energy
  - Mathematical models
  - Consciousness
- Towards a New Pathophysiology of Mental Diseases
  - Novel treatments and their Discovery and Development

Depression Nomenclature

- DSM-5
  - Manifest phenomena without theoretical orientation
  - Ignores the **brain**
- Research Domain Criteria (RDoC)[1]
  - Current and future knowledge in neuroscience
  - Ignores the **mind**
- Subtypes of Depression
  - Severity
  - Course
  - Endogenous vs Reactive; Melancholic
  - Stress, Immune, Hormone, Genetic, Idiopathic

[1] http://www.nimh.nih.gov/research-funding/rdoc/

DSM-5 Depressive Disorders

- Major Depressive Disorder
- Persistent Depressive Disorder (Dysthymia)
- Premenstrual Dysphoric Disorder
- Substance/Medication-Induced Depressive Disorder
- Depressive Disorder Due to Another Medical Condition

DSM-5 Anxiety Disorders

- Generalized Anxiety Disorder
- Panic Disorder
- Agoraphobia
- Specific Phobias
- Social Anxiety Disorder (Social Phobia)
- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition

OCD and PTSD are separate from Anxiety Disorders in DSM-5

Research Domain Criteria (RDoC)	Units of Analysis						
Domains	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report
- Valence							
+ Valence							
Cognitive							
Social							
Arousal							

Emotions, Thoughts and Behaviors

EMOTIONS are feelings you experience that may be difficult to describe in words. Emotions differ from thoughts. Consider the intensity, duration, and any associated distress from emotions and whether they controlled your thinking and behavior

THOUGHTS are ideas that are usually reasoned and logical. The substance of thoughts are influenced by emotions. Intense emotions make thoughts disorganized, hard to control and decide purposely.

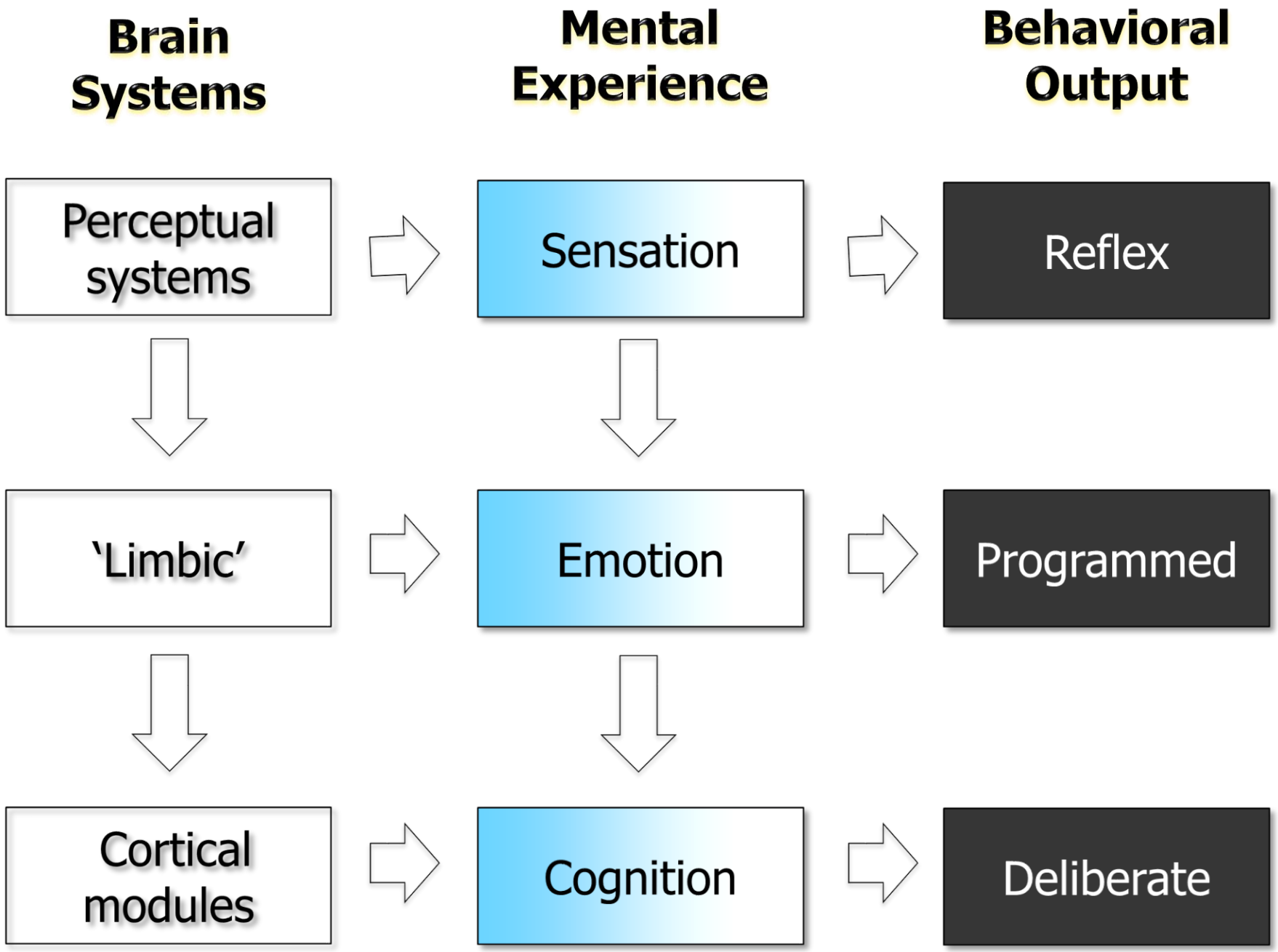
BEHAVIORS are externally observable actions. They are shaped by emotions and thoughts. Behaviors driven by intense emotions are more difficult to control and less determined and intentional.

Hierarchies to Heterarchies of the Brain

- Intrinsic, layered brain output systems
  - Sensation — reflex behaviors
  - Early response (emotions) — conditioned behaviors
  - Late response (cognitions) — willful behaviors
- Emergent brain
  - Cortical networks — executive choices

Survival by Selection

- Fundamental evolutionary systems in the brain
  - Threat response
    - Acute: Anxiety, Anger
    - Sustained: Sadness
  - Reward
    - Lack of pleasure


Brain Systems
Mental Experience
Behavioral Output
Perceptual systems
Sensation
Reflex
'Limbic'
Emotion
Programmed
Cortical modules
Cognition
Deliberate

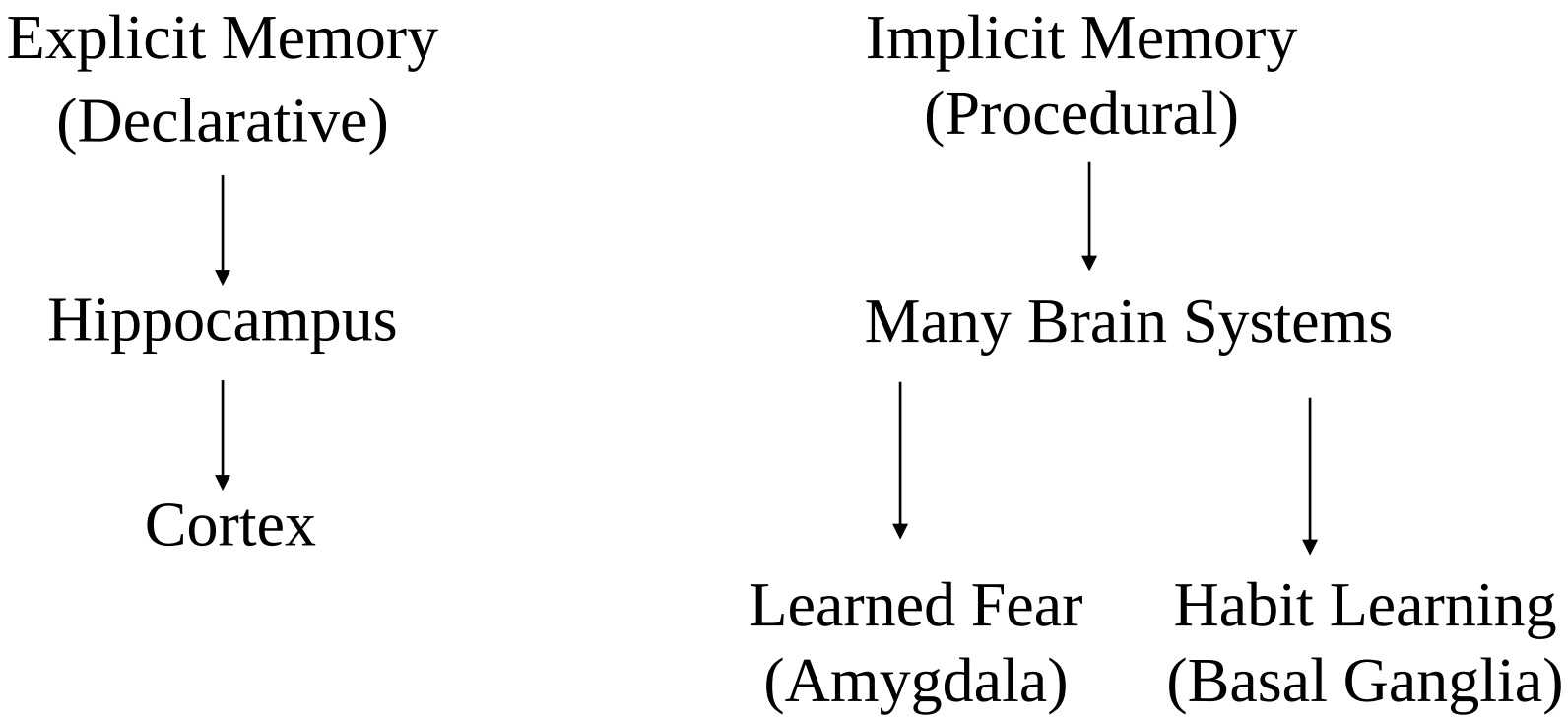
Treatments for Depression:
Symptomatic vs Disease Modifying

- Recently Approved
  - Brexanolone for Post-Partum Depression
  - Esketamine for TRD
- Somatic therapies
  - Pharmacologic
    - ‘Small molecules’
    - Biopharmaceuticals
      - Vaccines
  - Devices
- Psychotherapies

Brain Mediation of Benefits of Psychotherapies

- All psychotherapies involve brain mediated learning
- What are the mechanisms of action of different psychotherapies?
- Are there principles from neuroscience that can lead to testable hypotheses?

Types of Learning



Albright, Kandel, & Posner, 2000, *Curr. Opin. Neurobio.*, *10*, 612-624

Psychotherapies	Primary Mechanisms
Psychodynamic	Reconsolidation
Behavioral	Extinction
Cognitive	Context & habit routines
Interpersonal	Mirroring - Empathy
Mindfulness	Present experience

Pharmacotherapies

- Current psychotropics
  - Largely symptomatic treatments
  - Broad spectrum
  - Majority respond, minority remit
- Future psychotropics
  - Need to demonstrate superiority
  - Subpopulations
  - Biomarkers
  - Enhance signal detection
  - Novel trial designs

Biopharmaceuticals

- Disease modification
  - Alter disease progression
  - Alter pathophysiology
  - Stem cells
  - Prevention
- Vaccines

Boundaries of the Mind and Brain

Dimensions	Second	Millisecond	Microsecond	Nanosecond
Meter	1			
Millimeter		10^{-3} (one thousandth)		
Micrometer			10^{-6} (one-millionth)	
Nanometer				10^{-9} (one billionth)

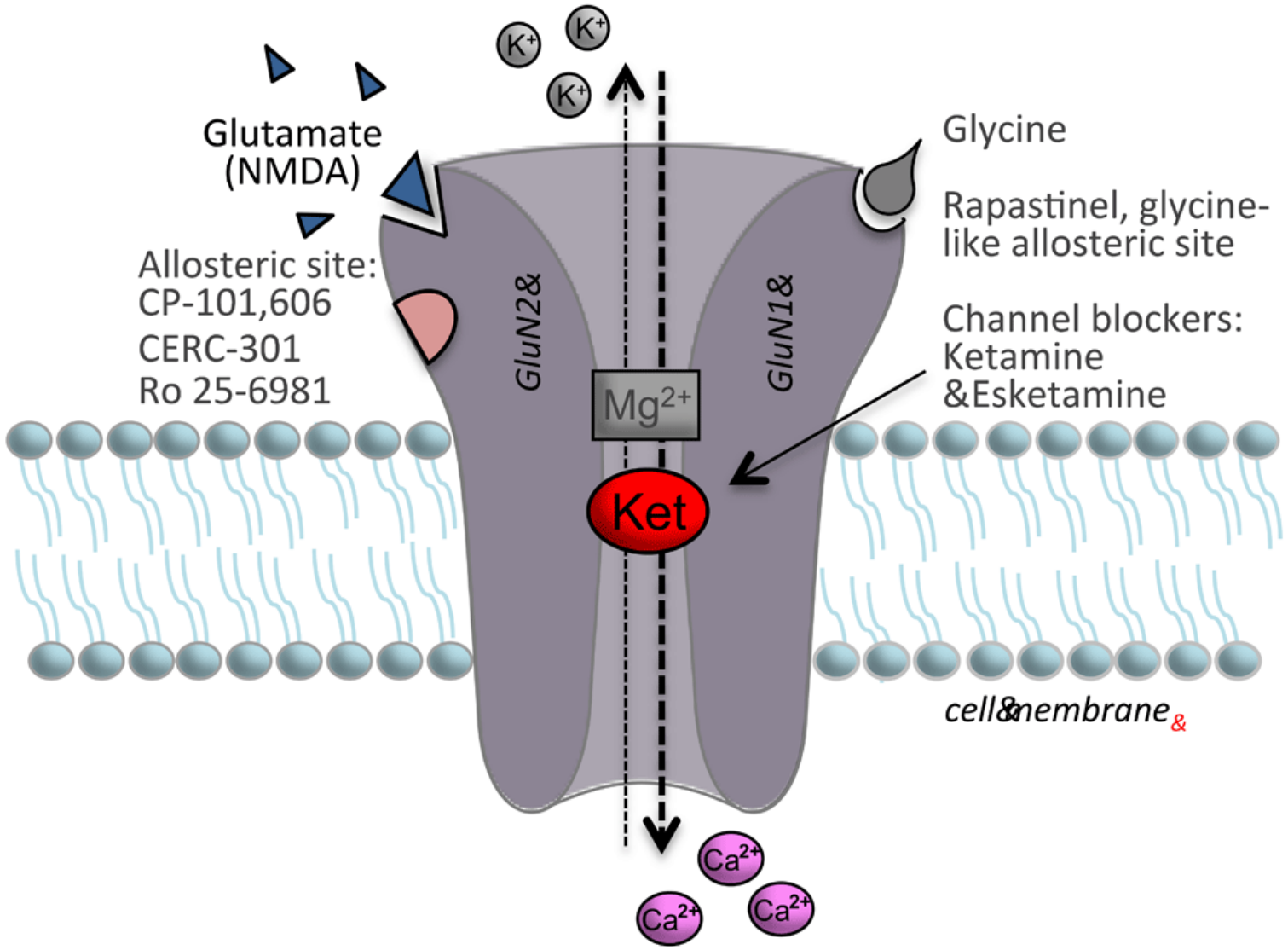
Horizons of the mind – two orders above and below the central focus
The human brain is more complex than the mind
Computation occurs at gigahertz (GHz) speed – one billion processes per second

Llinas RR. I of the Vortex. 2001. The MIT Press. Preface

Glutamate and Depression

- NR2B selective NMDA glutamate receptor antagonist

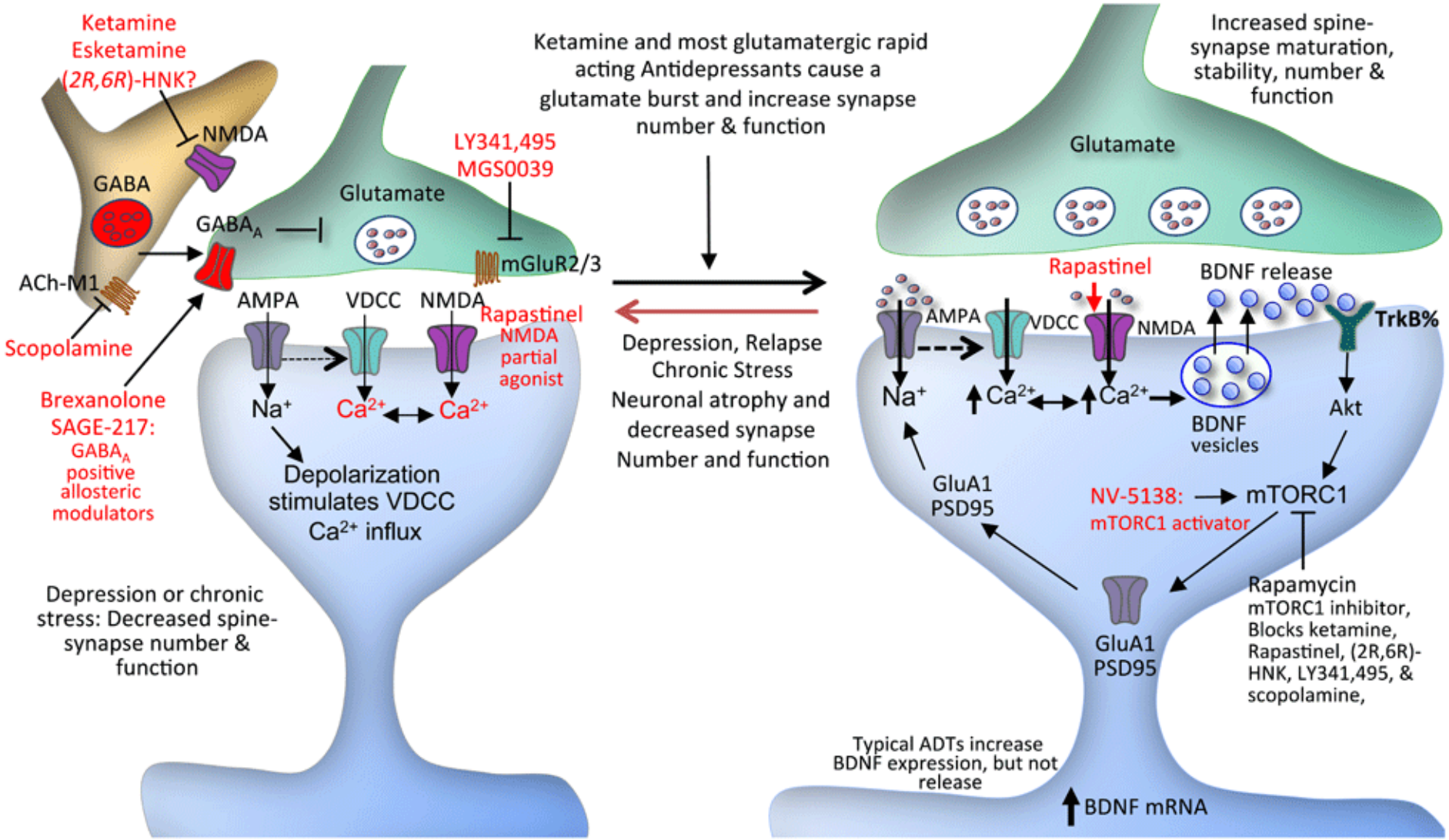
Figure 2. Model of the NMDA receptor complex and target sites of rapid-acting antidepressants.



Duman RS. Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide [version 1]. F1000Research 2018, 7:659 (doi: 10.12688/f1000research.14344.1)

F1000Research

Figure 1. Schematic model for the initial cellular target sites of rapid-acting antidepressants and subsequent...

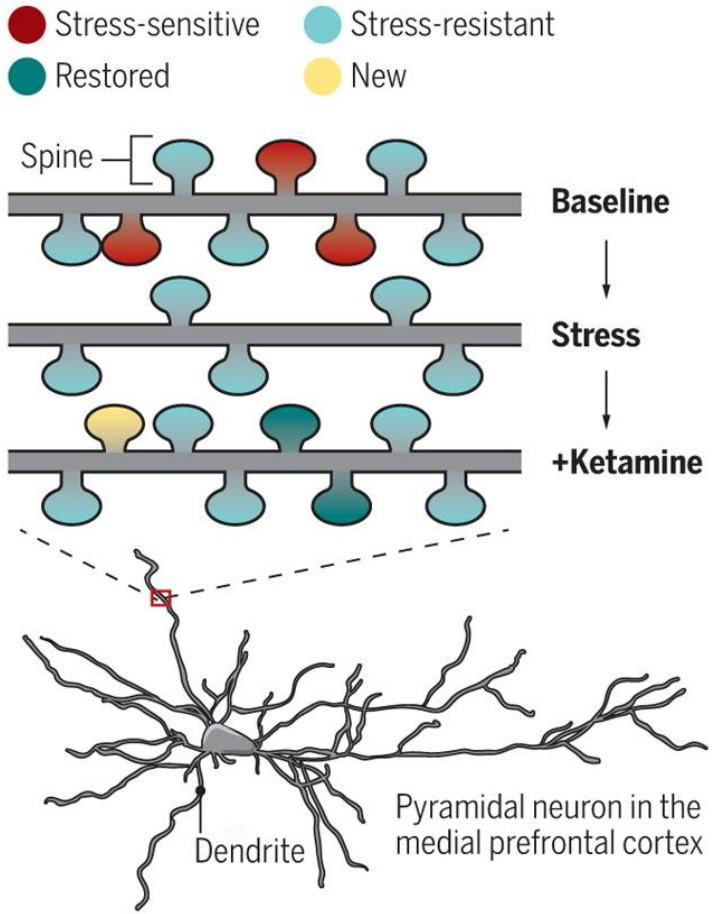


Duman RS. Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide [version 1]. F1000Research 2018, 7:659 (doi: 10.12688/f1000research.14344.1)

F1000Research

Stress and ketamine alter dendritic spines

Dendritic spines are the site of synaptic connection with other neurons. In a stress-induced model of depression-like behaviors, spines of pyramidal neurons are depleted. Treatment with the antidepressant drug ketamine restores part of the lost spines and promotes the formation of new spines.



Anna Beyeler Science 2019;364:129-130

Table 1: Summary of FDA-Approved Products for Treatment of TRD

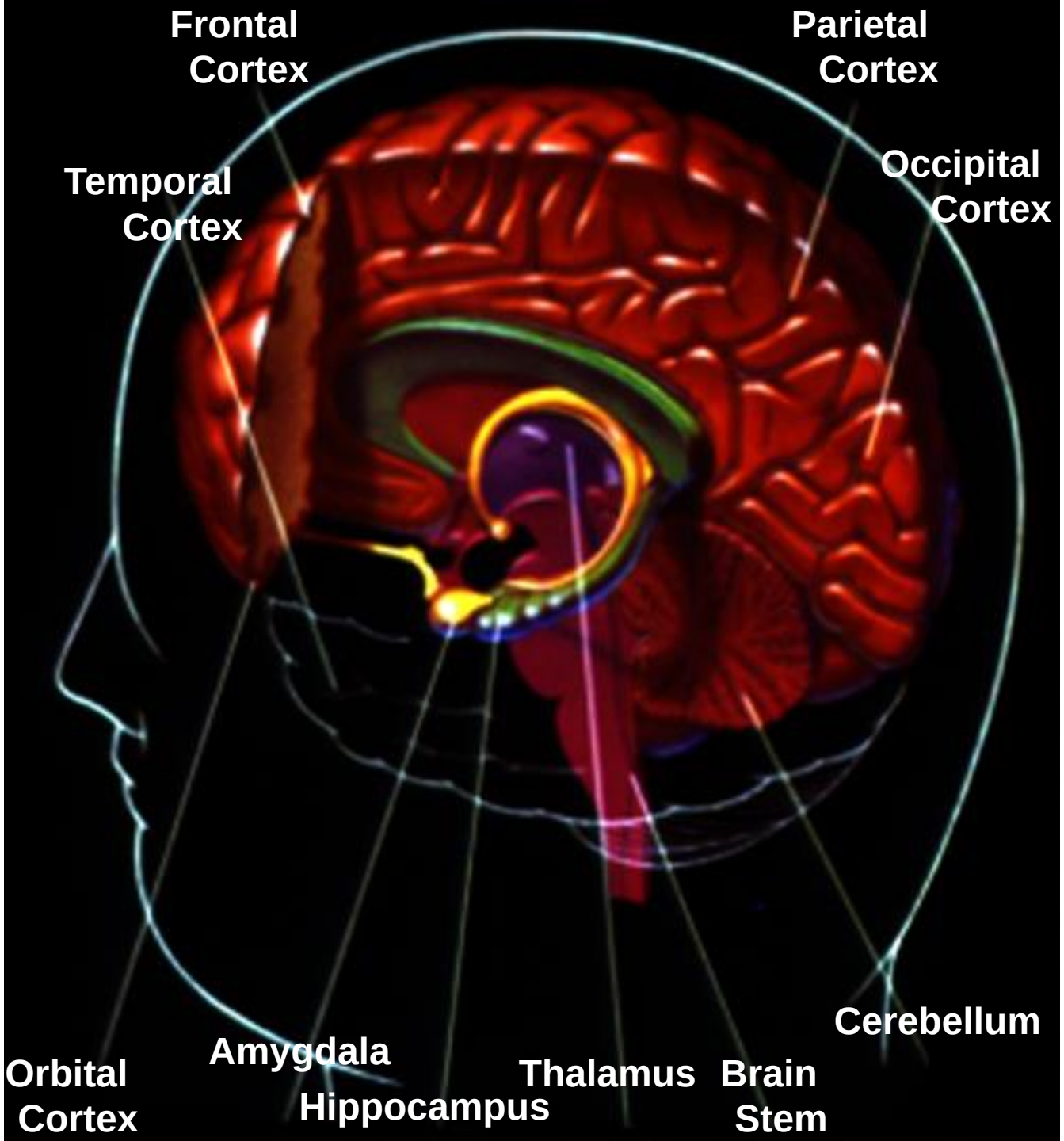
Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Authority
FDA Approved Treatments Combine by Pharmacologic Class, if relevant						
Symbyax (Fluoxetine plus Olanzapine)	TRD	2003	Oral daily	MADRS Total Score Change from Baseline of -16 vs. olanzapine -12 and placebo -10 for Study 1, -18 vs. -14 and -9 for Study 2	Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and extrapyramidal symptoms/ akathisia	CDER
ECT	TRD (associated with either MDD or Bipolar Disorder)	1976 (most recent update 2018)	Bitemporal or unilateral temporal; up to 3 times a week for 6 to 10 treatments initially	Not available; approval based on various studies from research literature.	Memory concerns, use of general anesthesia	CDRH
TMS	TRD (patients who failed only 1 anti-depressant)	2008	Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)	MADRS Total Score Change from Baseline of -6 at Week 4 and Week 6 active TMS vs. -4 at Week 4 and Week 6 sham TMS. Approval based on post-hoc analysis and responder/remission rates.	No major safety issues, limited long-term safety data	CDRH
VNS	TRD	2005	Once (surgical implant)	12-week sham placebo-controlled study not statistically significant. Approval was based on long-term open-label HAM-D responder data (30% response in 1 year versus 13% treatment as usual). 12-week open-label pilot study showed 34% MADRS responders.	Surgical intervention risks (allergies, infection, etc.)	CDRH

There are several other FDA-approved drugs for the separate indication of adjunctive treatment for partial response in MDD: quetiapine XR, aripiprazole, and brexpiprazole. From a regulatory standpoint, the adjunctive treatment indication applies to patients who have insufficient but partial response to their current oral antidepressant and may benefit from add-on treatment. This population is usually less severely ill than for the TRD population; these patients are frequently on their first antidepressant and adjunctive

Table 9: MADRS Score Change from Baseline for Prior Approved Antidepressants

Indication	Antidepressant	MADRS LS Mean CFB at Primary Endpoint Range	MADRS LS Mean CFB Difference from Placebo/Active Control	Baseline MADRS Score
MDD	Vortioxetine	-13 to -20	-2.8 to -7.1	31 to 34
	Vilazodone	-9.7 to -13	-2.5 to -3.2	31 to 32
	Levomilnacipran	-14 to -17	-1.3 to -4.9	30 to 36
Adjunctive MDD	Aripiprazole	-8.5 to -8.8	-2.8 to -3.0	31 to 32
	Brexpiprazole	-7.7 to -8.5	-1.3 to -3.1	33 to 35
	Quetiapine XR	-14 to -17	-1.6 to -4.1	28 to 32
TRD	Olanzapine + Fluoxetine (fixed-dose combination)	-8.6 to -14	n/a	23 to 30
	Fluoxetine (vs. Olanzapine + Fluoxetine)	-1.2 to -11	-1.4 to -12	"
	Olanzapine (vs. Olanzapine + Fluoxetine)	-2.8 to -10	-0.8 to -11	"
	Esketamine	**-10.1 to -20.8**	**-3.2 to -4.1**	**37 to 38 adult, 35 geriatric**

Source: DPP Antidepressant Study Database from Previously Approved NDAs


Frontal Cortex
Parietal Cortex
Temporal Cortex
Occipital Cortex
Cerebellum
Orbital Cortex
Amygdala
Hippocampus
Thalamus
Brain Stem

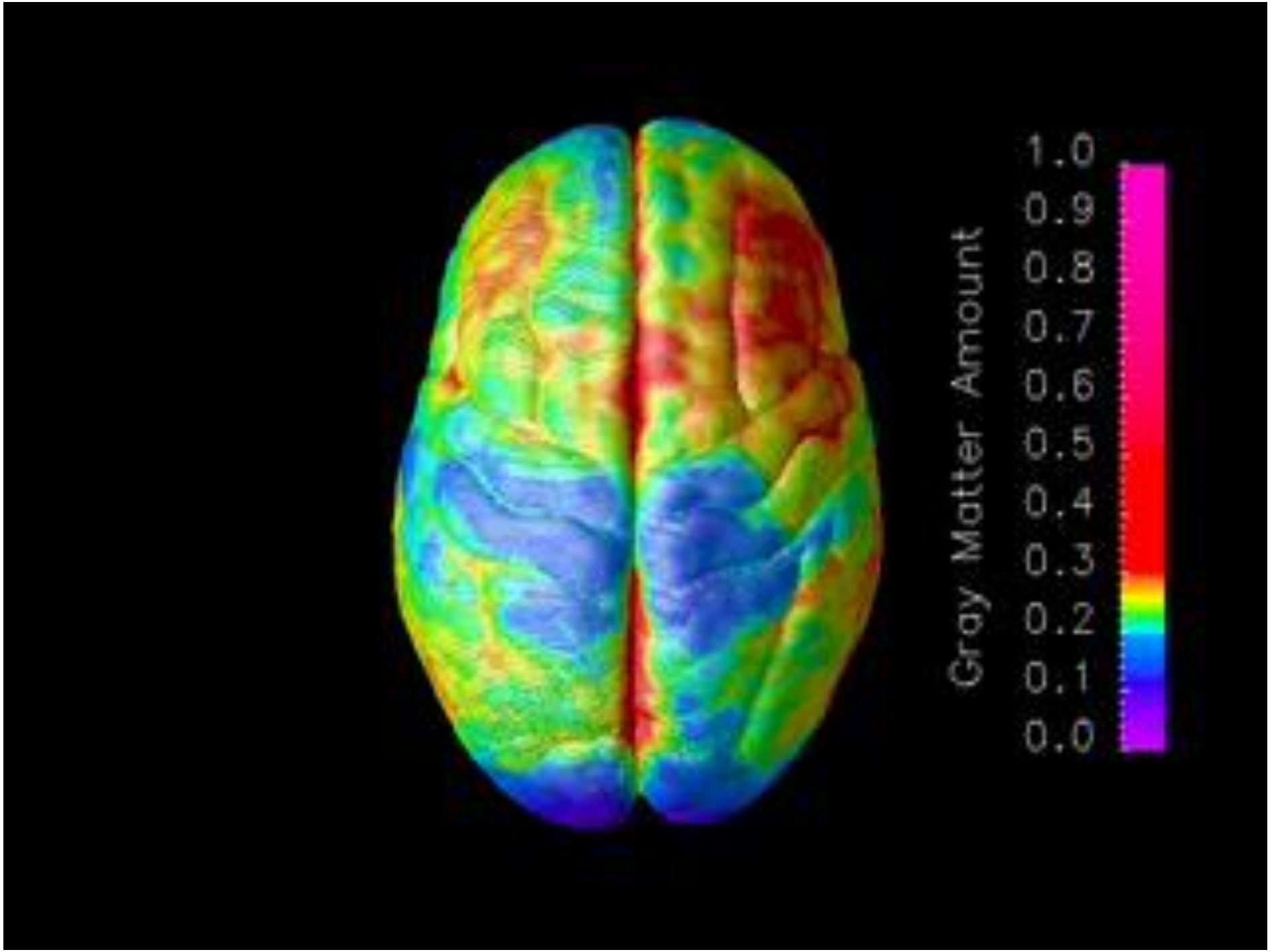
Brain & Mind

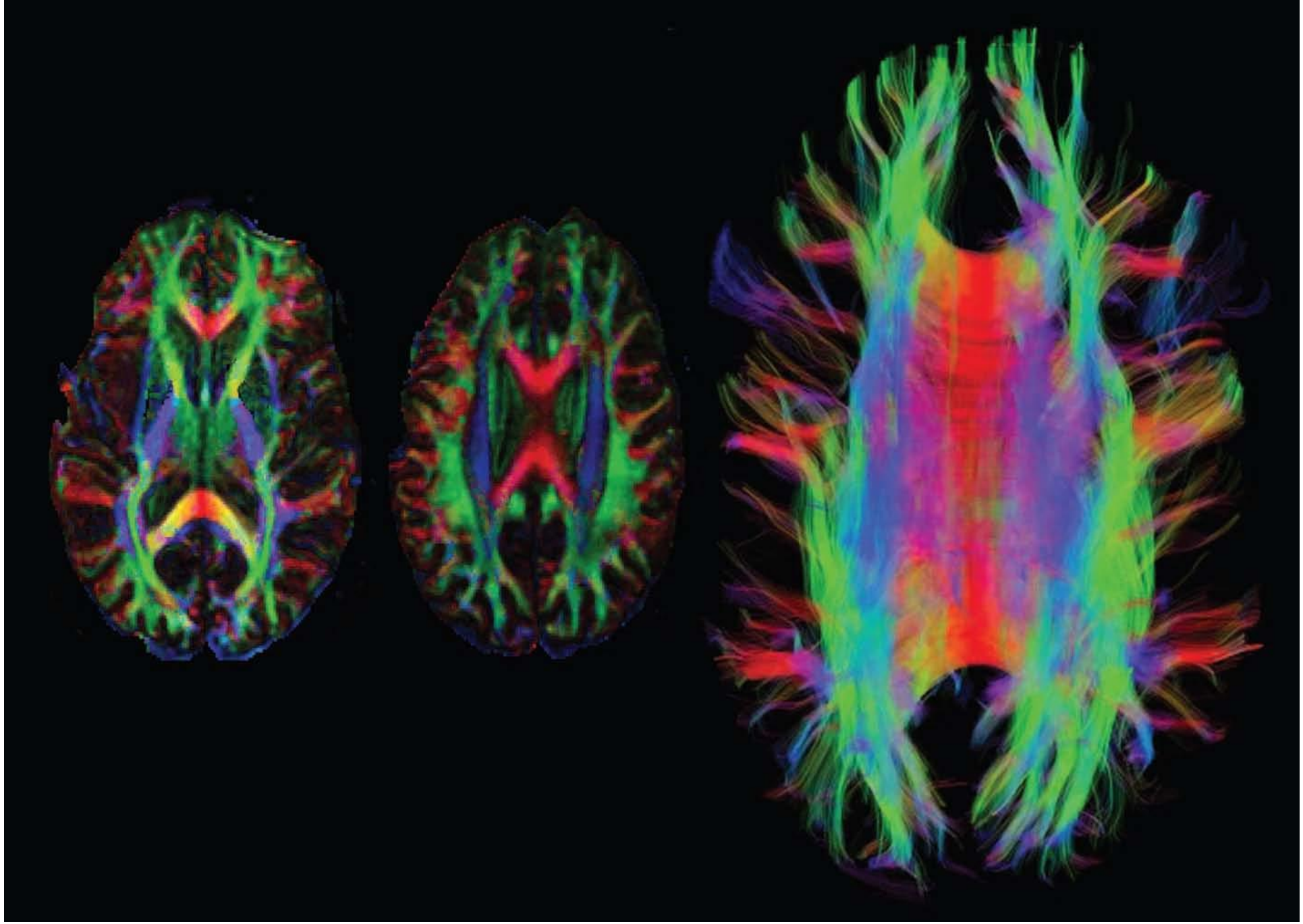
- Human brain is the most complex structure in the known universe
- Human mind emerges from the activities of the brain
  - “The mind is what the brain does” *
  - “The map is not the territory” **

* The Primordial Emotions. Derek Denton 2009
** Alfred Korzybski 1931

Humans have Two Minds

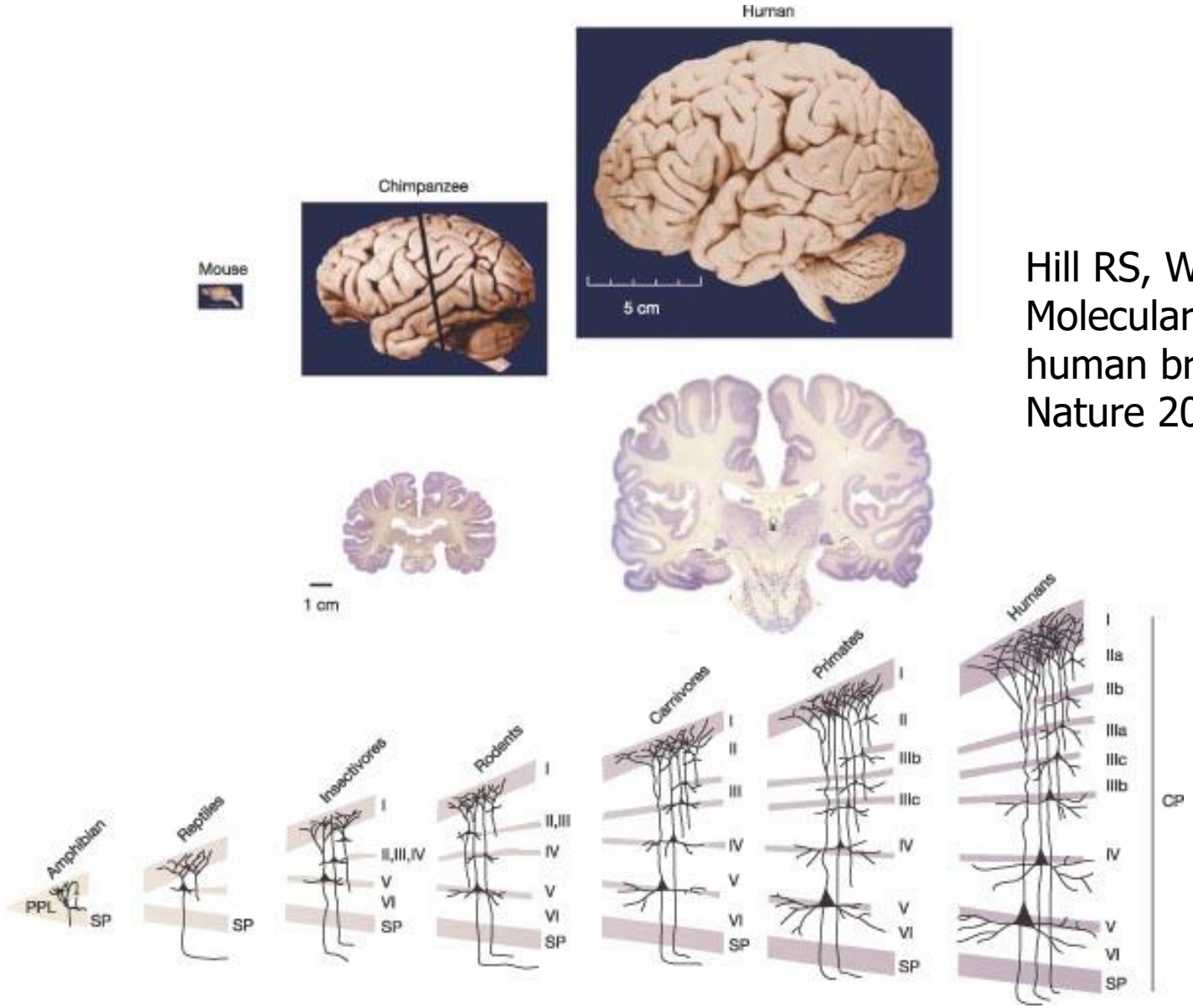
- Intrinsic mind
  - Behavior driven by bottom up processing
    - Sensation ⟹ Emotion ⟹ Cognition
    - Threat (Amygdala-centric) and Reward (Accumbens-centric) systems
  - Exists in the present experience
  - Neural circuits – open loop
- Emergent mind
  - Behavior driven by top down processing
  - Agency of ‘self ’
    - Self-referential feedback loop
  - Creation of a ‘simulated’ virtual reality
  - Neural networks – closed loop


Gray Matter Amount
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0



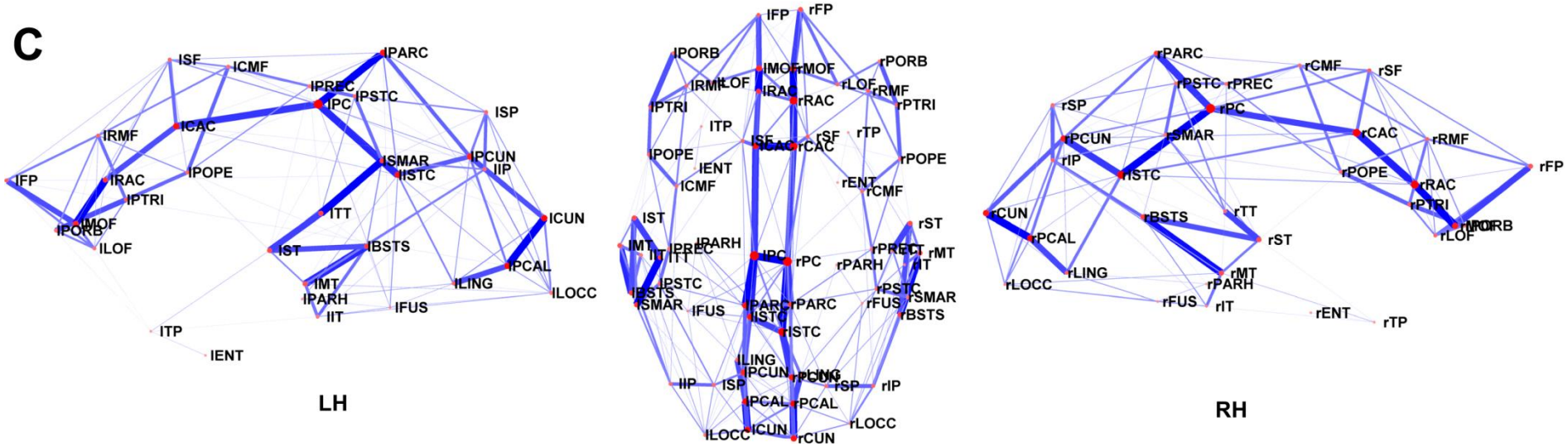
DeFelipe J. Science 2010;330:11980 1201

Evolution of Cortical Mantle



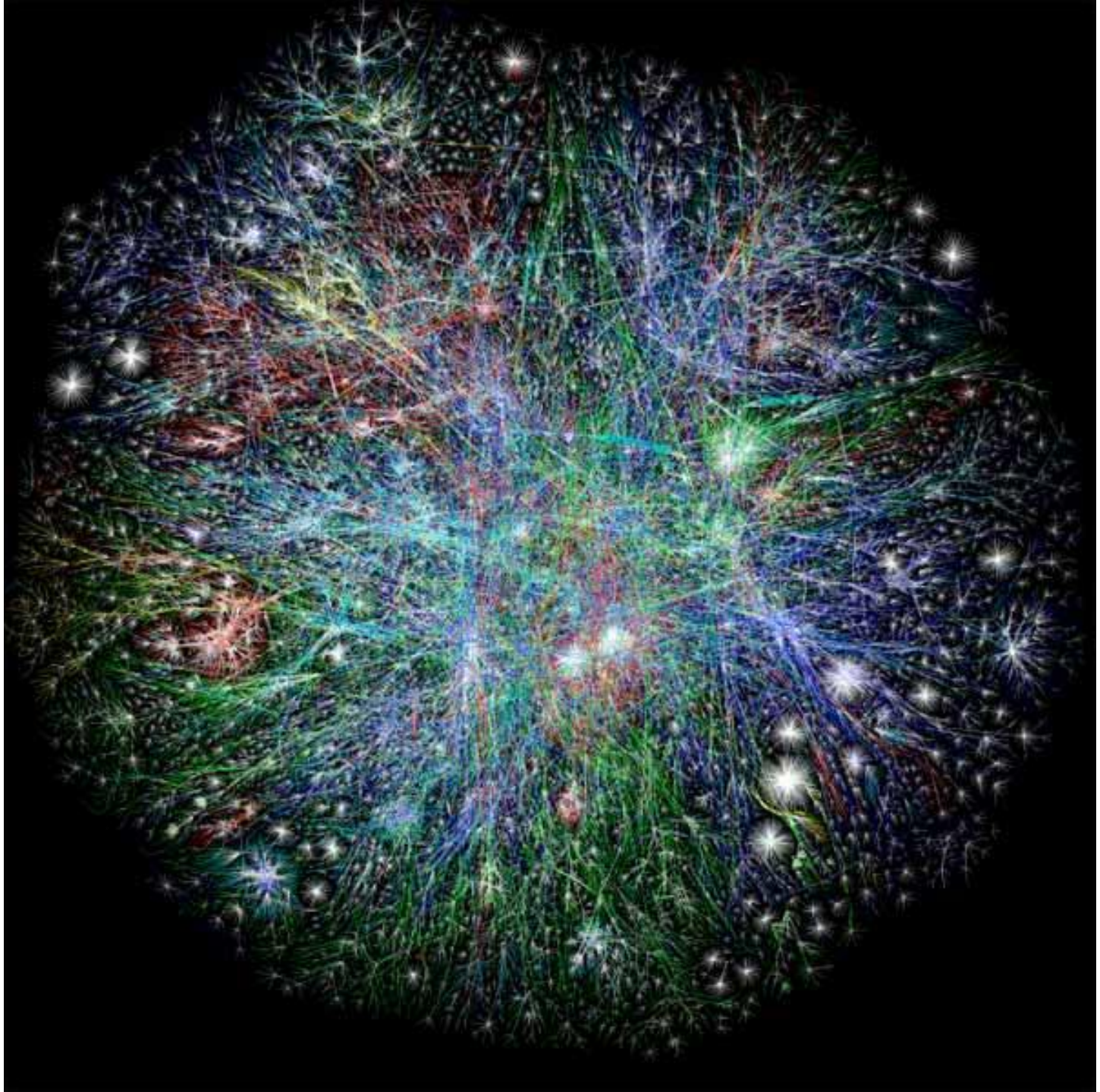
Hill RS, Walsh CA. Molecular insights into human brain evolution. Nature 2005;437:64-67

Connectivity Backbone



Hagmman P et al PLOS Biol 2008;6:1479-1493

Global Internet Traffic



Intrinsic Mind: Cognition

Cognition is a higher order synthesis of information

- Proportionate, logical, reasoned - analogous to the premotor vectors for movement
- Summation of implicit parallel, pre-cognitive processing leading to explicit, serial processing
- Time sequenced - context provided by the past/present
- Goal directed
- Language - value of nuanced differentiations
- Allows willful control and choice

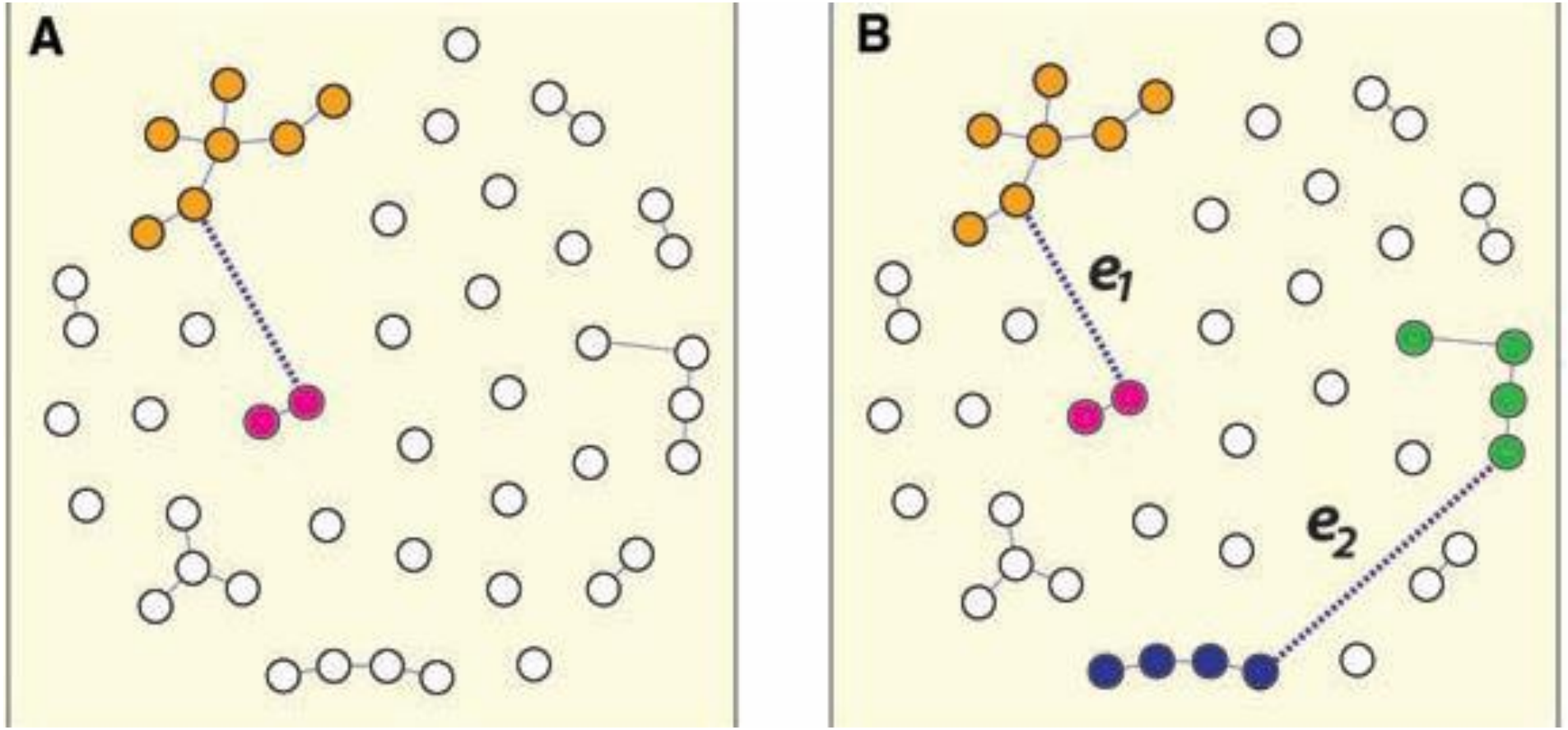
Linas RR. I of the Vortex: From Neurons to Self. Cambridge, MA: The MIT Press; 2002
Ninan PT, et al. Psychopharmacology Bull 2002;36(suppl 3):67-78

Structure for the Virtual Mind

- Cortical circuits permit the crafting of networks
- Connectome
  - Mapping structural connections in the human brain
  - Functional and effective connectivity
  - Quantitative analysis of brain connectivity with the mathematical tools of network science
  - Edges, Nodes and hubs

Olaf Sporns. Networks of the Brain 2011 MIT Press, Cambridge

Network Evolution: Nodes & Edges



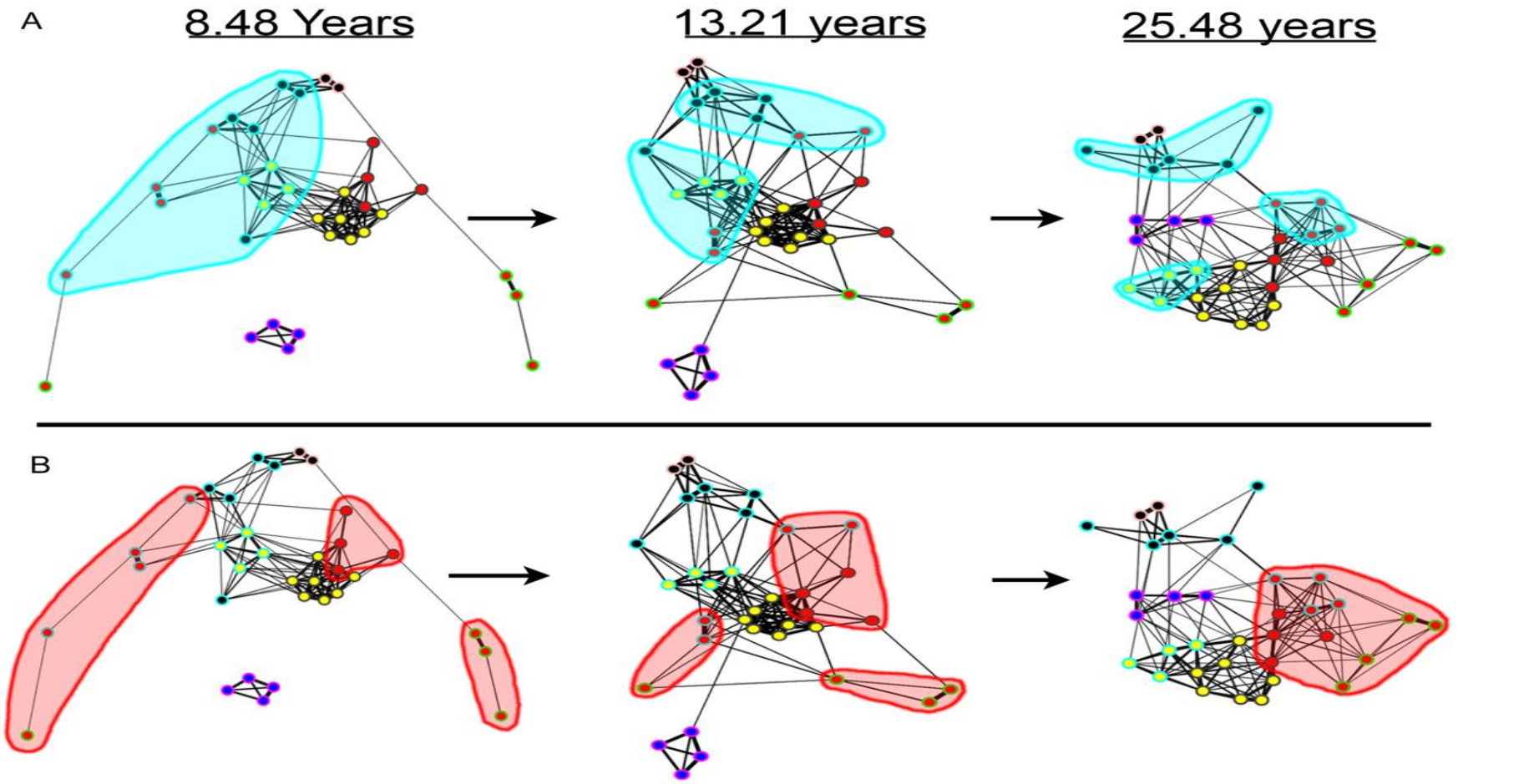
Achlioptas D et al. Science 2009;323:1453-1455

Properties of Networks

- A network is a collection of nodes with links joining some pairs of nodes
  - Few links compared to nodes results in large number of isolated components
    - Phase transitions can result in abrupt and explosive behaviors
    - An uncommon property now becomes very likely
    - Delaying the phase transition increases the violence of the explosion
  - Increasing the links randomly >50% of nodes
    - Results in an emergent ‘giant’ component during phase transitions
    - The giant component grows to cover the entire network
    - The transition to the giant component can be smooth or abrupt

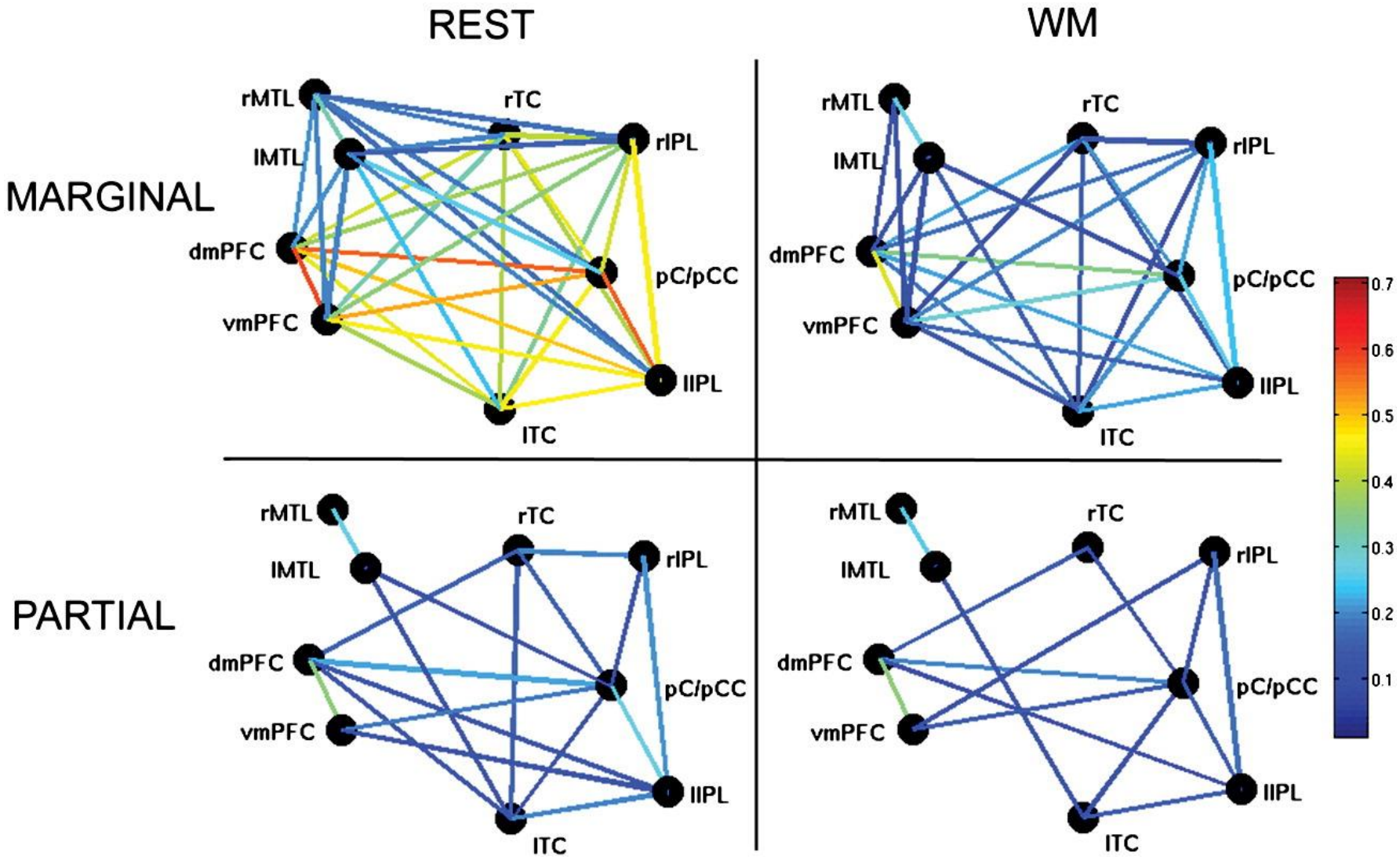
Janson S. Science 2011;333:298-299
Bohman T. Science 2009;323:1438-9

Development : Local to Distributed Networks



Fair DA et al.
PLOS Comput Biol
2009;5:1-14

Default Mode Network



Fransson P et al. Neuroimage 2008;42:1178-1184

The Virtual Mind

- Prefrontal network
  - Functional agency of ‘self ’
- The Default Mode Network permits the creation of an internal ‘simulated’ reality
  - Subjective personal and private
    - Infinite experiences
  - Retrieval and display of declarative memories
  - Simulation of events
    - Fantasy
    - Future
  - Augmented reality

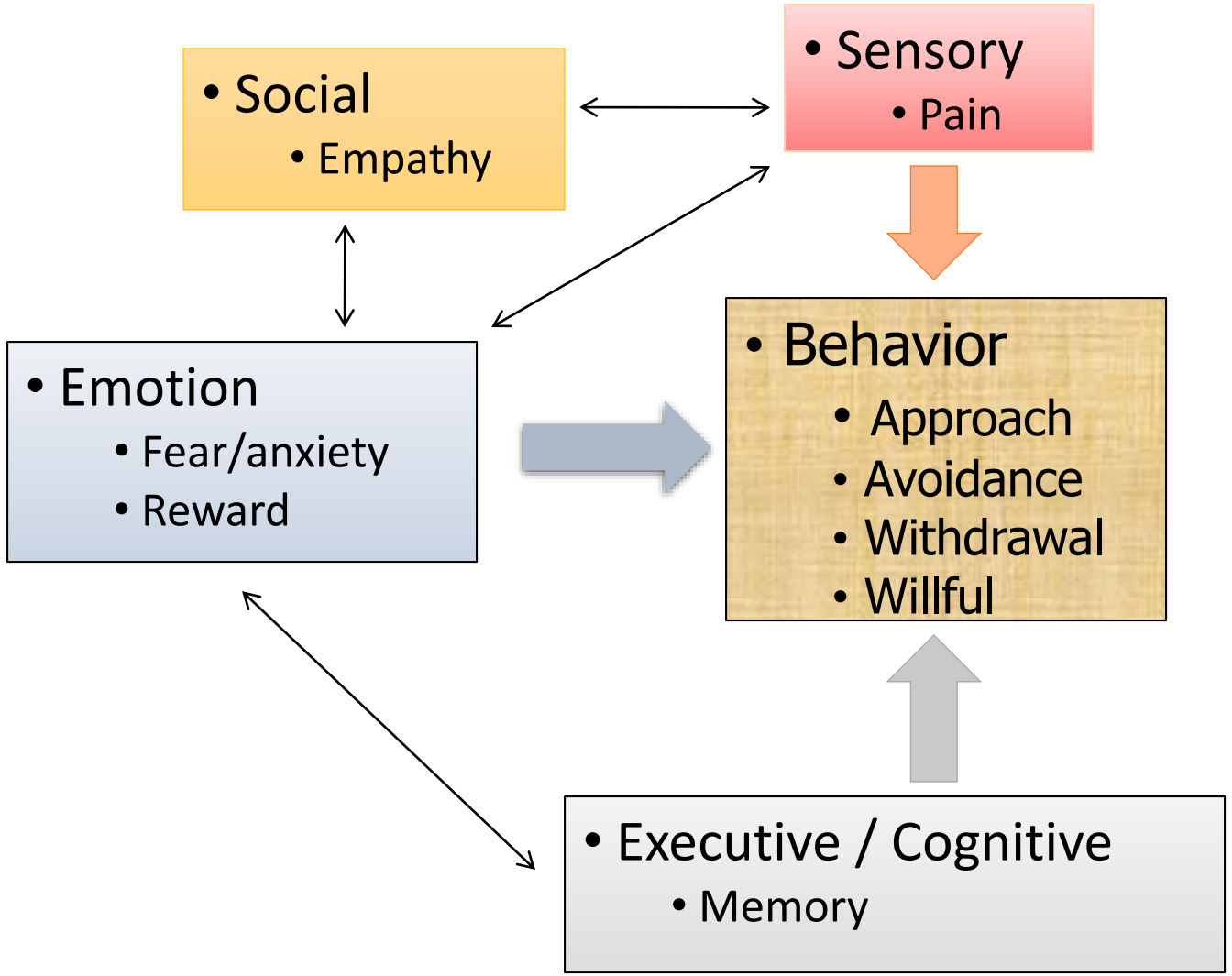
Neural Networks: Implications

- Networks permit synthesis and emergent properties
- Psychosis results from lower ratio of nodes to edges in key circuits
  - Lack of insight
  - Hallucinations
  - Delusions of control
- Wisdom from age

Brain and consciousness

- Consciousness associated with distributed simultaneously across different neuronal groups in different brain regions
- These groups of neurons interact rapidly and reciprocally through reentry
- Loss of diversity of neuronal repertoire (e.g. sleep, epilepsy) is associated with loss of consciousness

Temporal Sequence of Information Processing



Levels of Behavior

I. Innate
   - Reflex
   - Instinctive/Programmed

II. Procedural
   - Automated
   - Conditioned

III. Consciously chosen
   - Willful
   - Effortful

Summary

- Explanatory model of how the human mind emerges from brain activity
  - Experiencing vs. Reporting self
- Psychiatric nomenclature
  - Modeling psychopathologies
- Mechanism of action of treatments
  - Discovering novel treatments