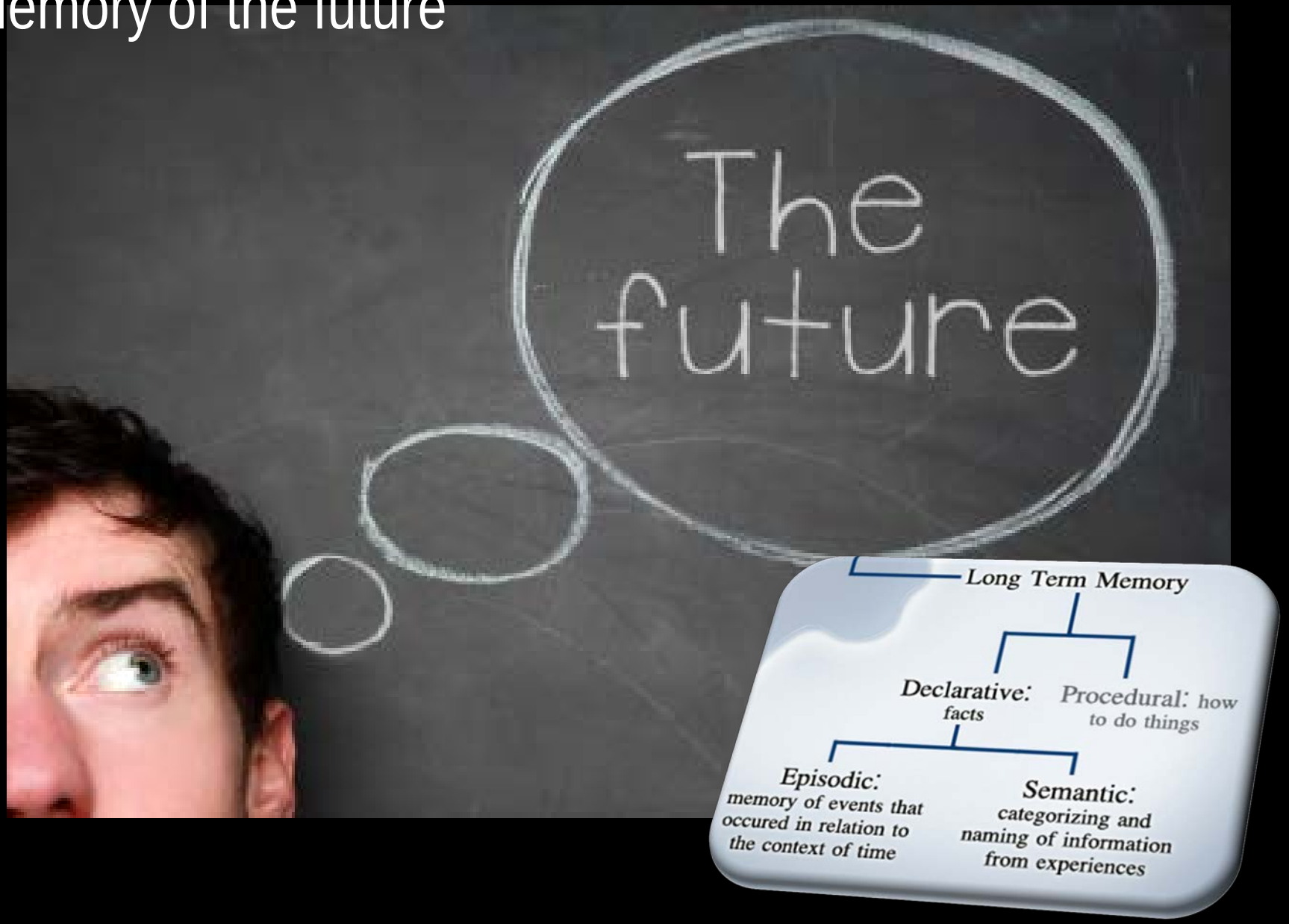
The moving brain: On stress, prediction, consciousness, and alpha7 nicotinic receptors

Albert Gjedde

University of Southern Denmark

Memory of the future



Outline

1

Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia

Definitions of stress

A first definition of stress was made by Hans Selye in 1936. According to Selye, stress is ”the non-specific response of the body to any demand for change". The definition turns out to be useful to recent understandings of brain function in humans.

Example:
First day of school or work.

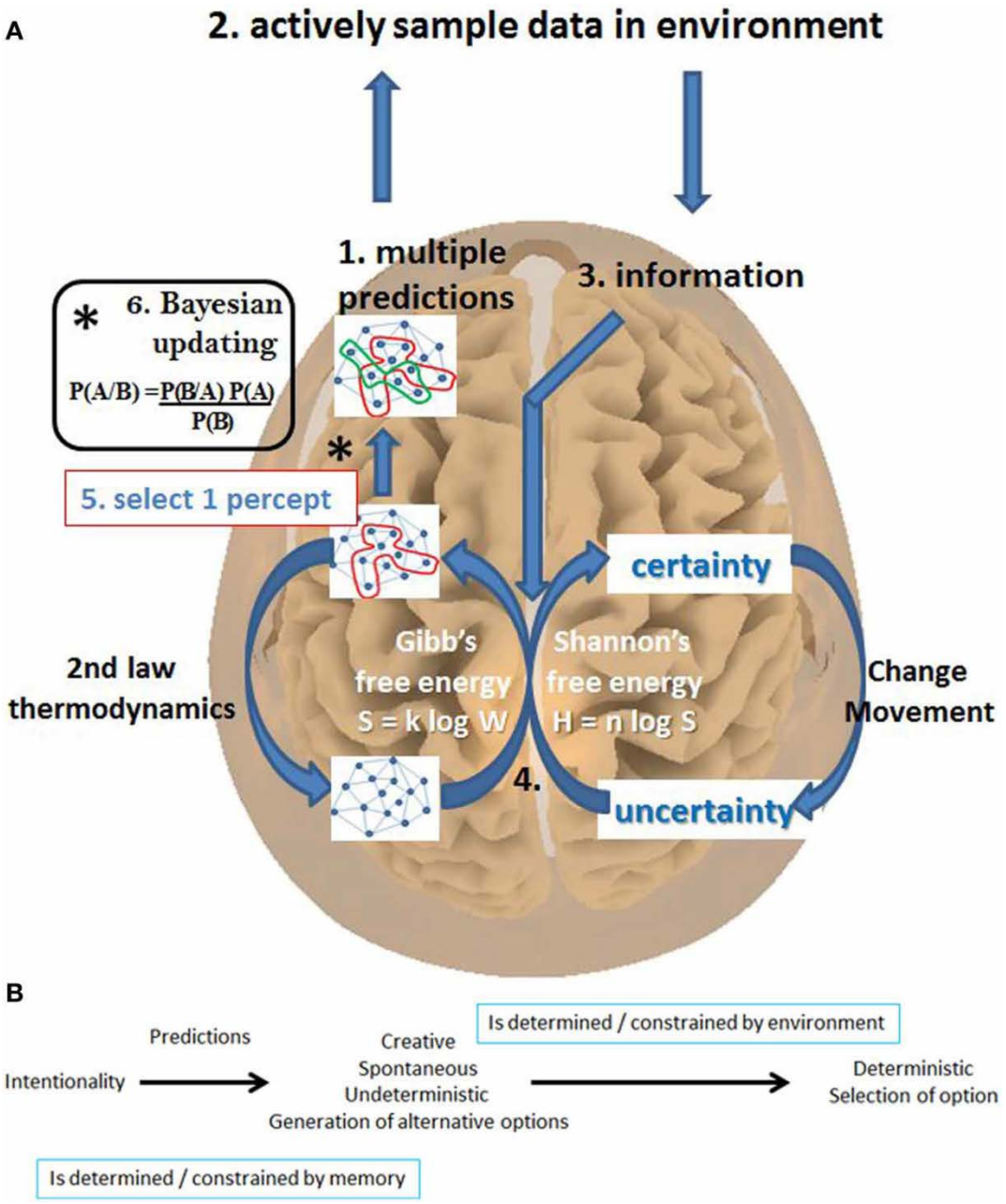
Example:
Loss of family member, but with supportive buffers in place.

Example:
Witnessing domestic violence in the home, chronic neglect.[2]

Definitions of stress

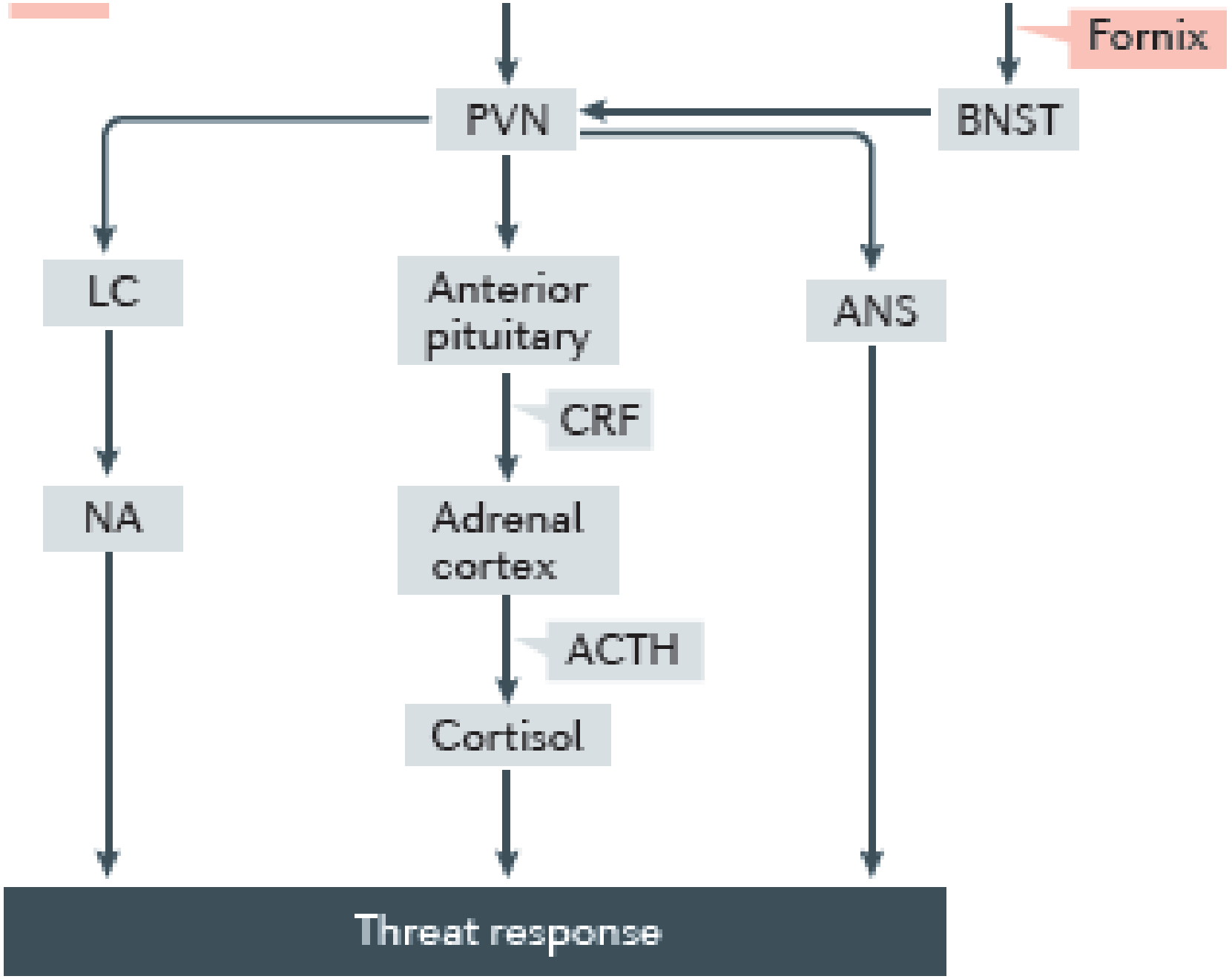
Selye's definition allows us to work from the claim that stress is not a reaction to adversity as such, but rather any reaction to changes in circumstance that require (physical) action. This definition is independent of the body's specific kind of response.

Ridder et al. 2013



Definitions of stress

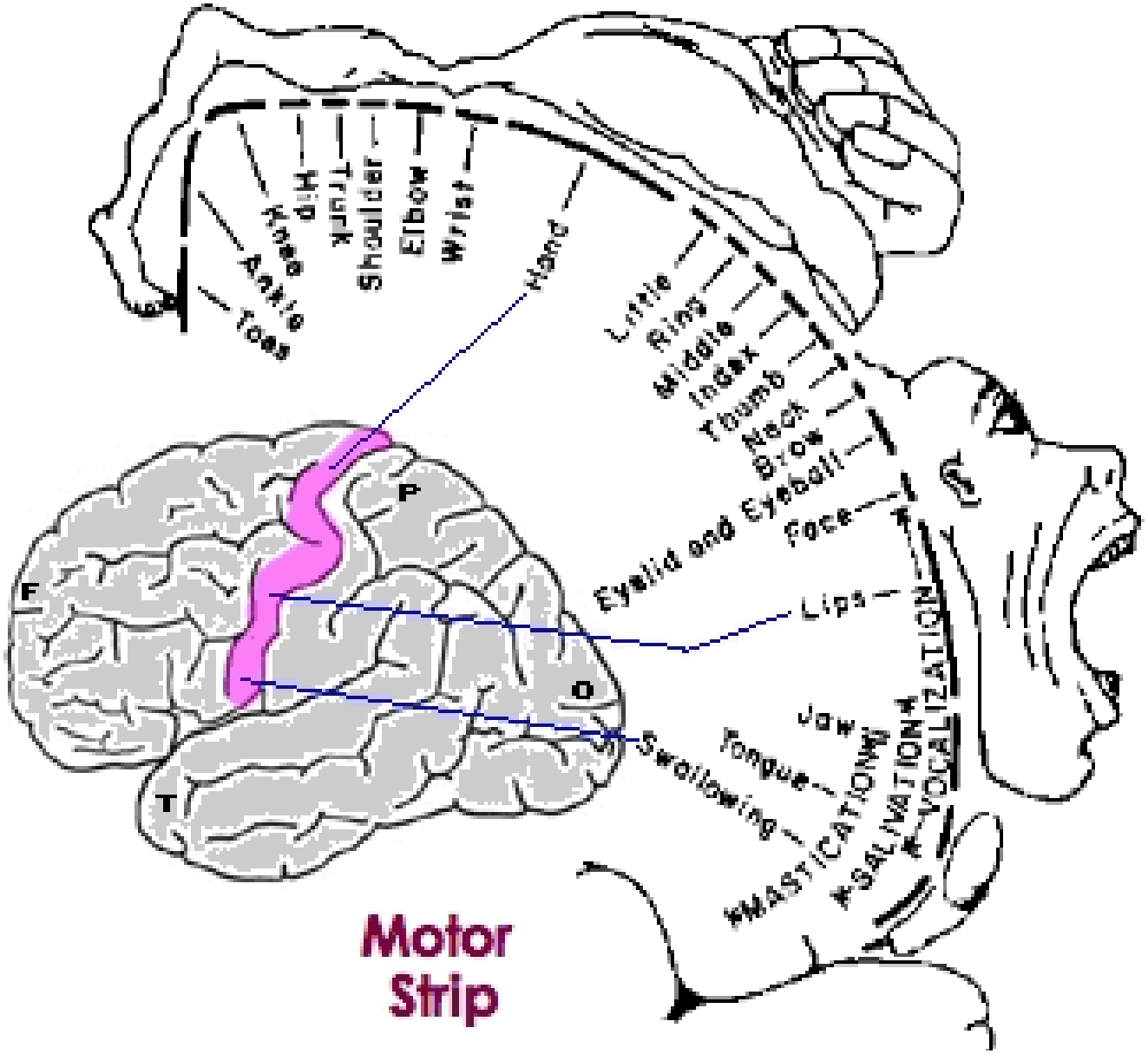
Specifically, stress is a combined "physical, mental, and emotional strain or tension“, generated by a change of circumstance. In order for stress to form, whether from good or bad circumstance, a stressor must be present for the tension to appear.


Fornix
PVN
BNST
LC
Anterior pituitary
ANS
CRF
NA
Adrenal cortex
ACTH
Cortisol
Threat response

Outline

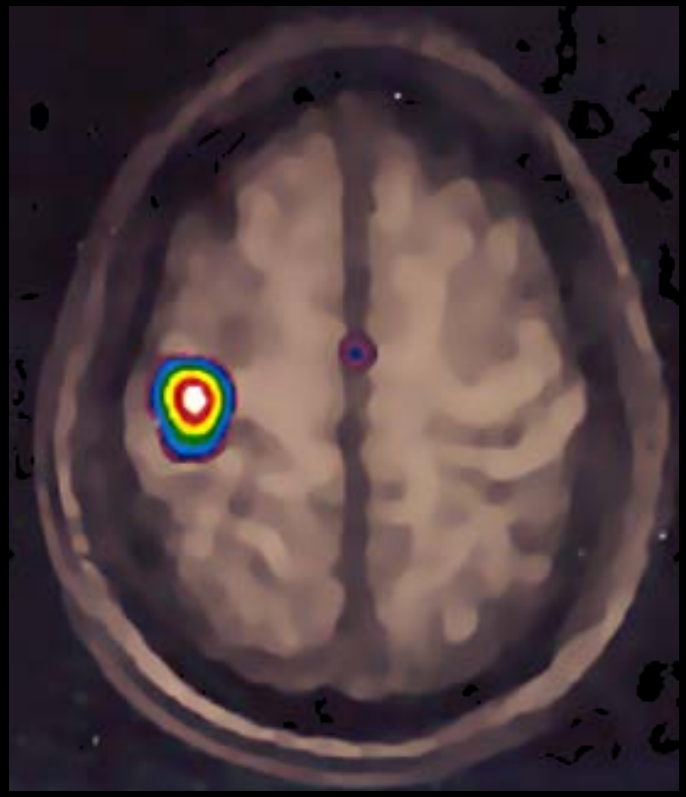
2

Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia

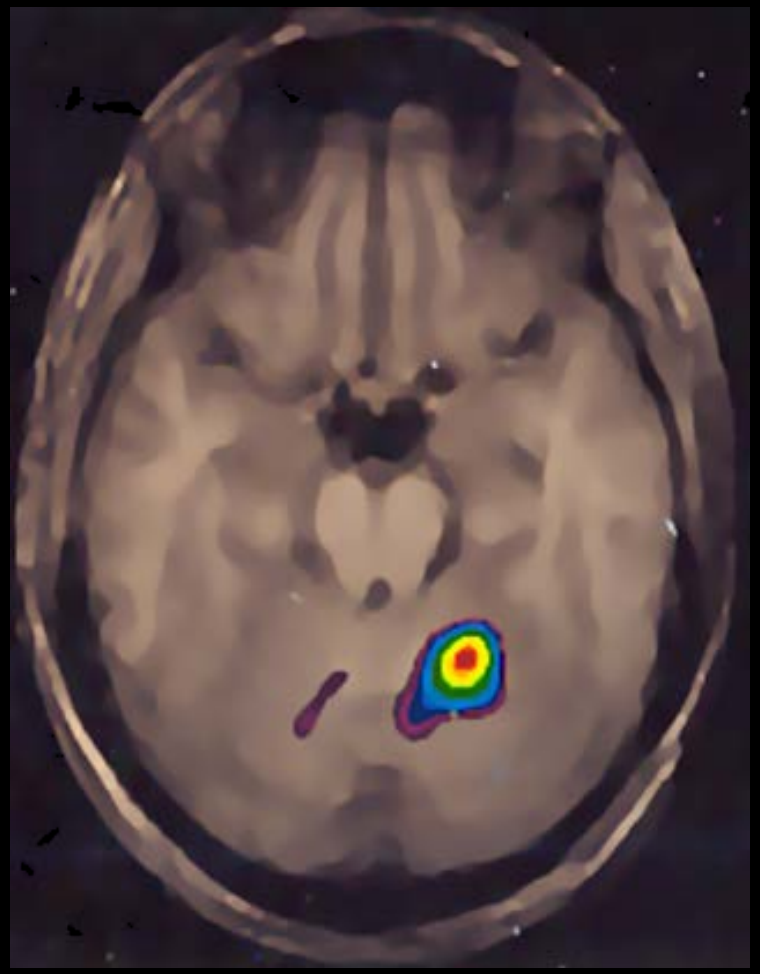

Hip
Knee
Ankle
Toes
Trunk
Shoulder
Elbow
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Neck
Brow
Eyelid and Eyeball
Face
Lips
Jaw
Tongue
Swallowing
MASTICATION
SALIVATION
VOCALIZATION
F
P
O
T
Motor Strip

Repetitive motion of right index finger

Left Right

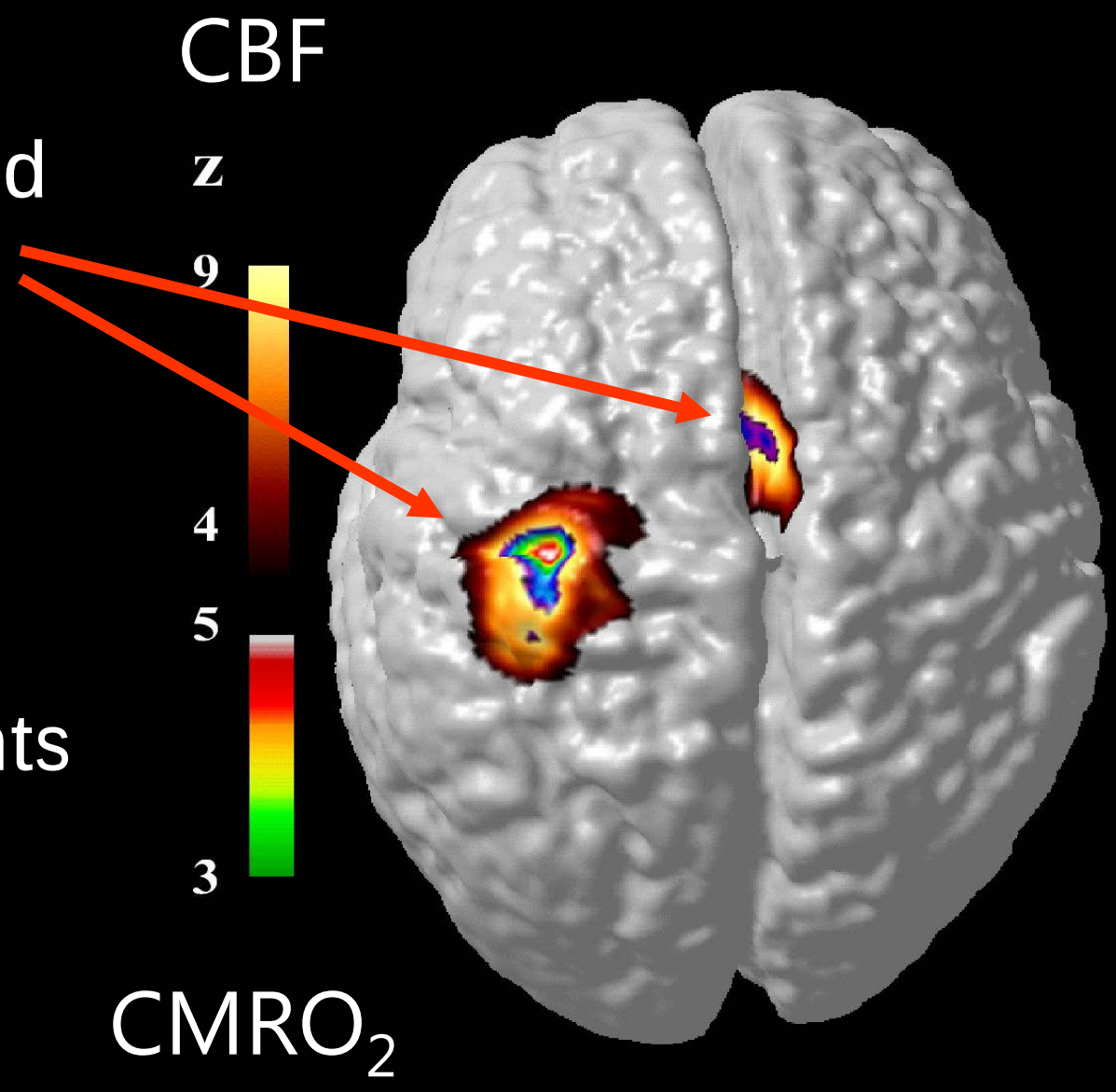


z=61 mm



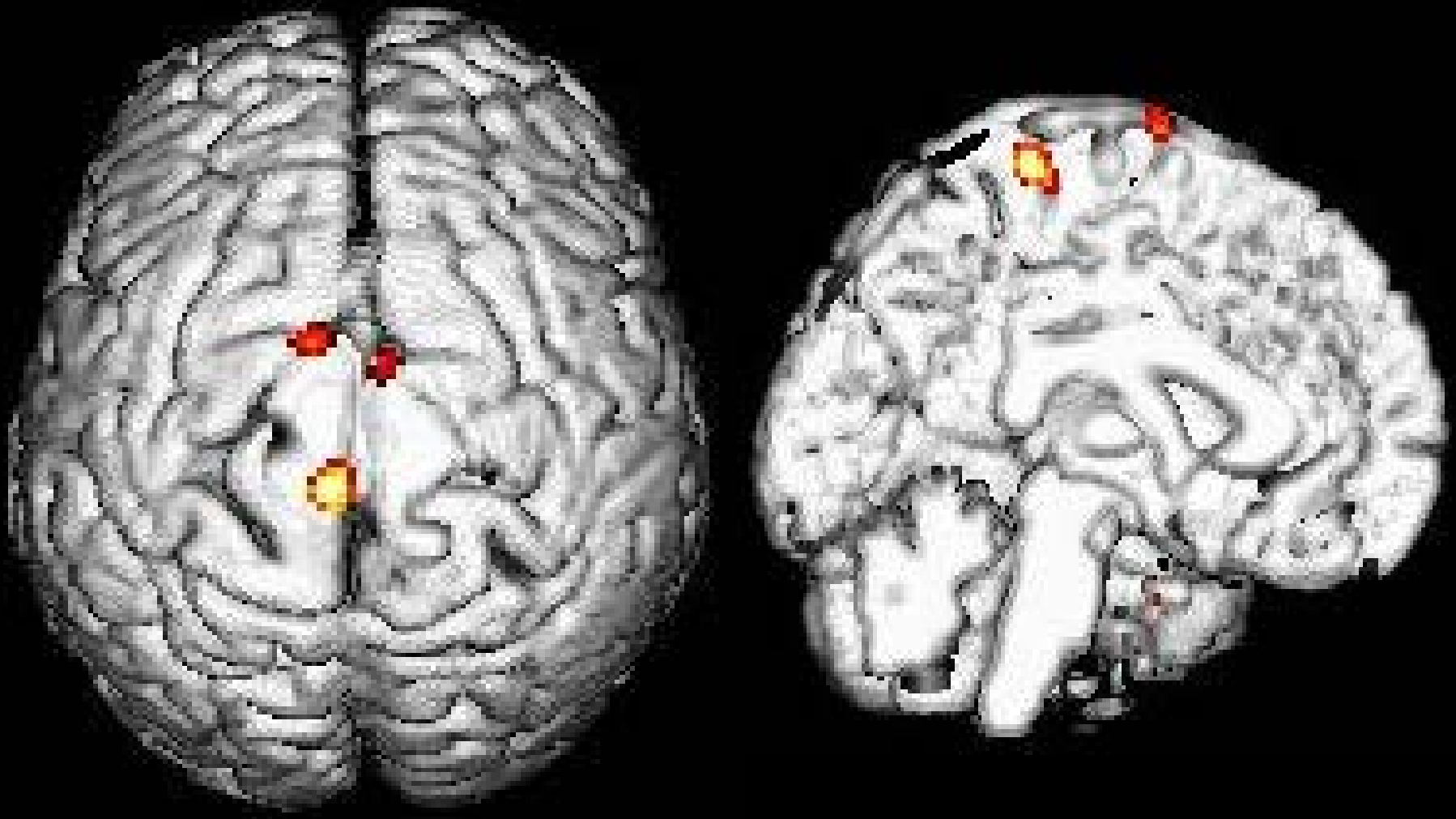
z=21 mm

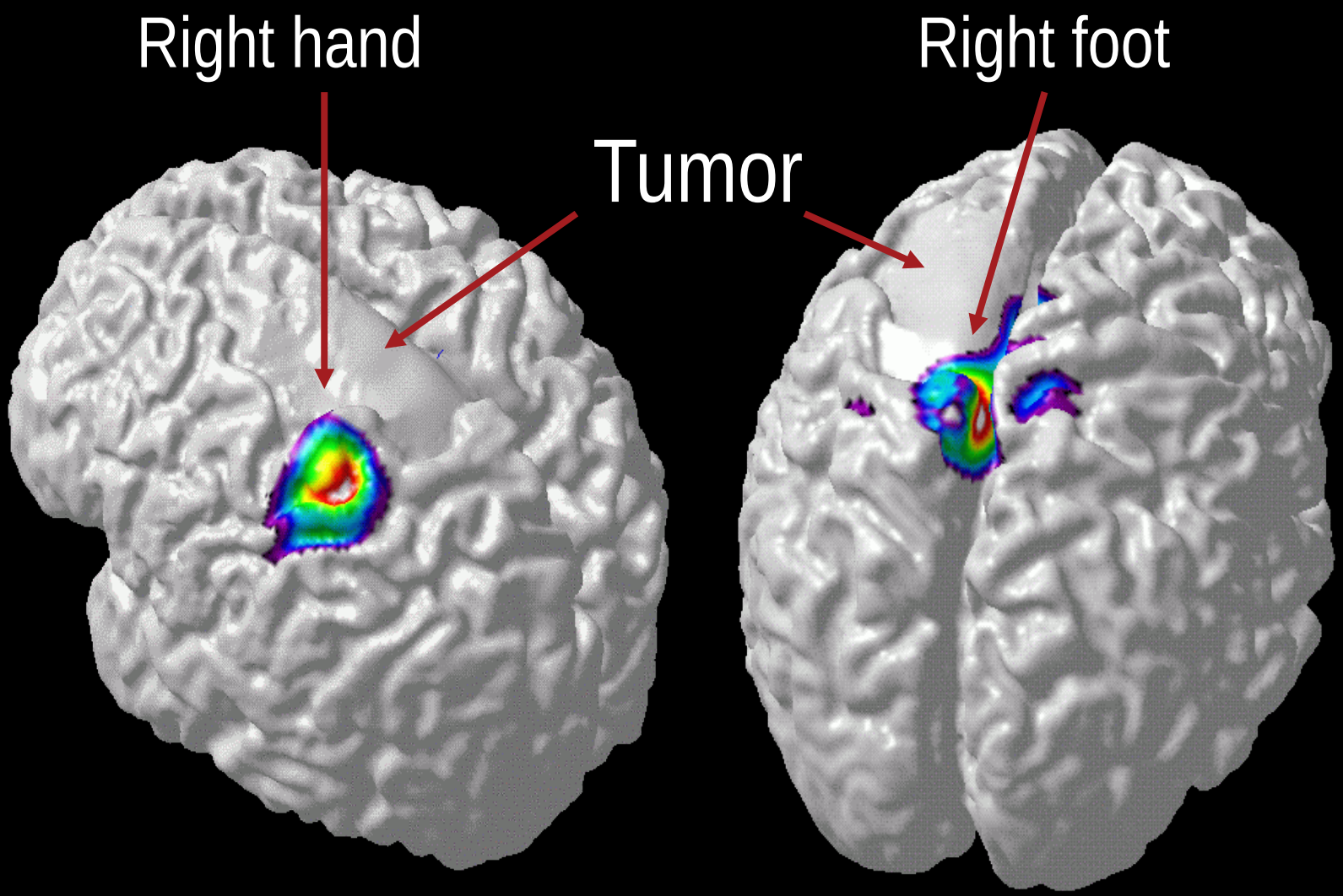
Right hand SMA, M1 and S1, mapped during finger movements

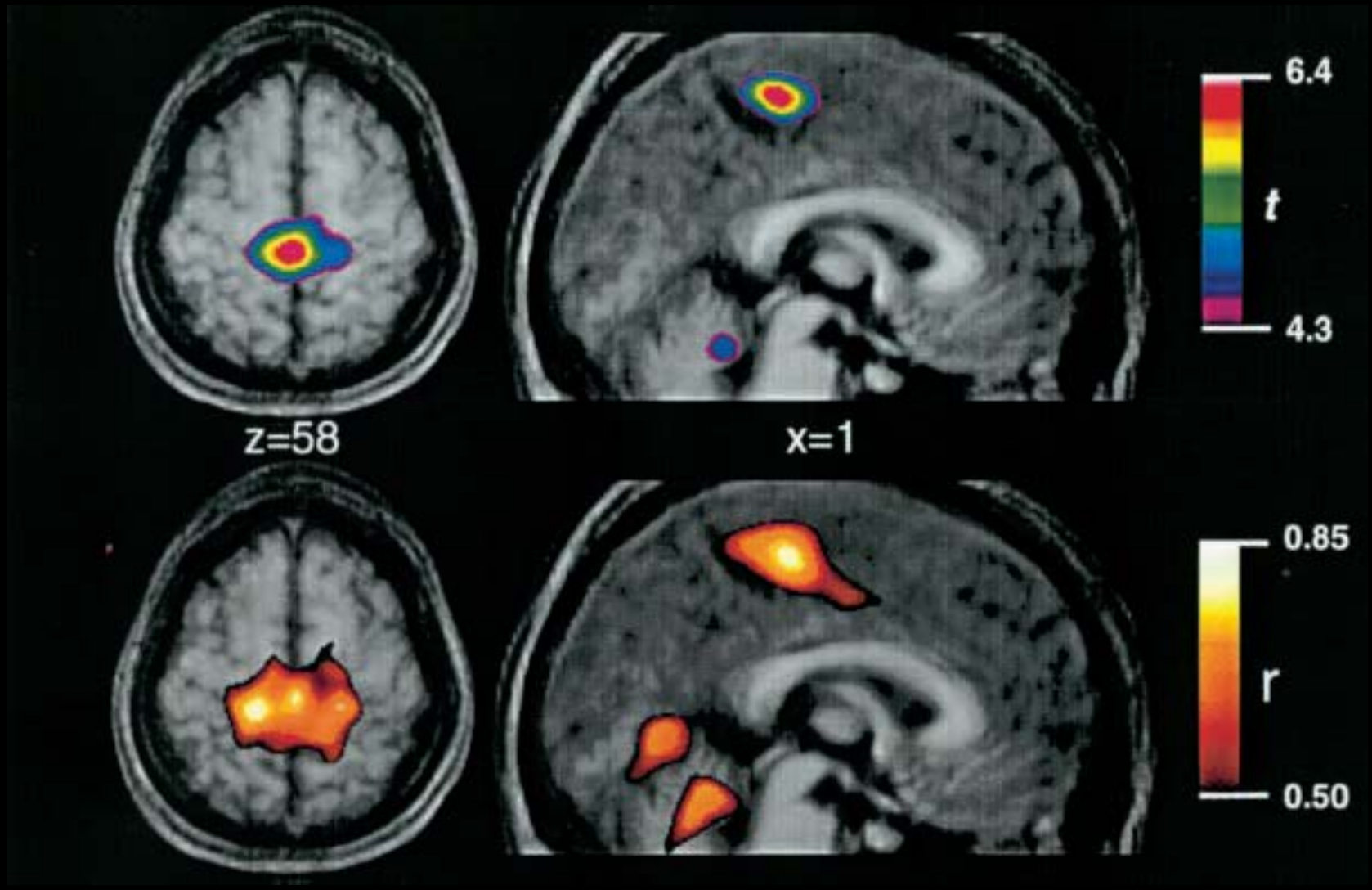


Vafaee et al. 2012

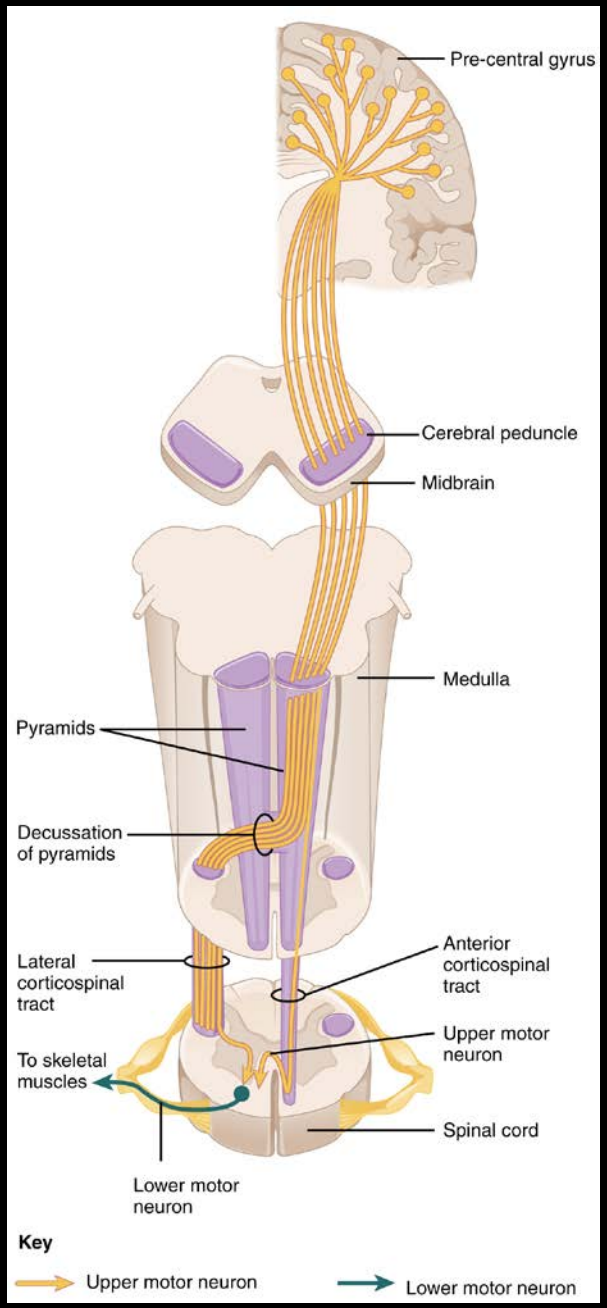
Right foot

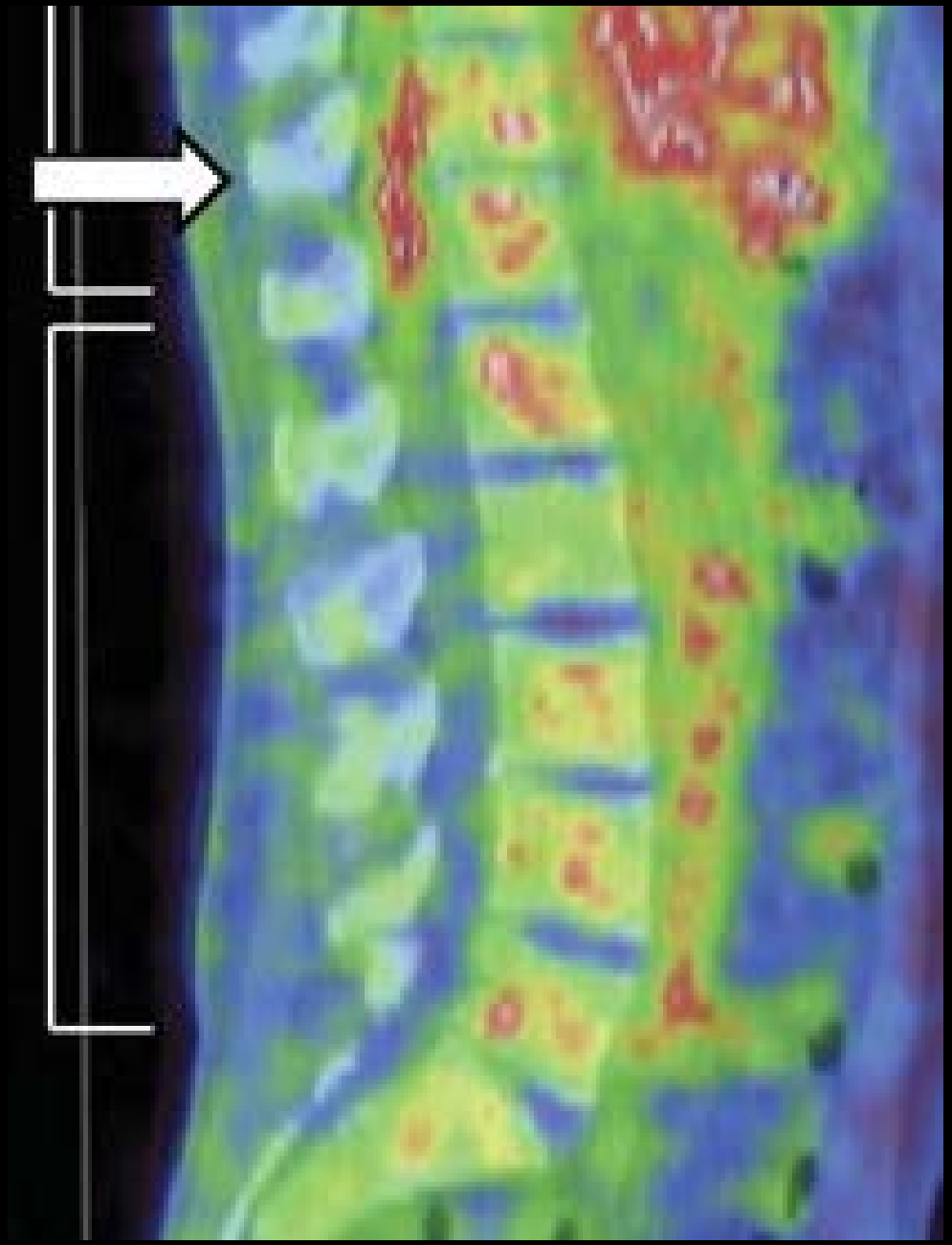



Right hand
Tumor
Right foot

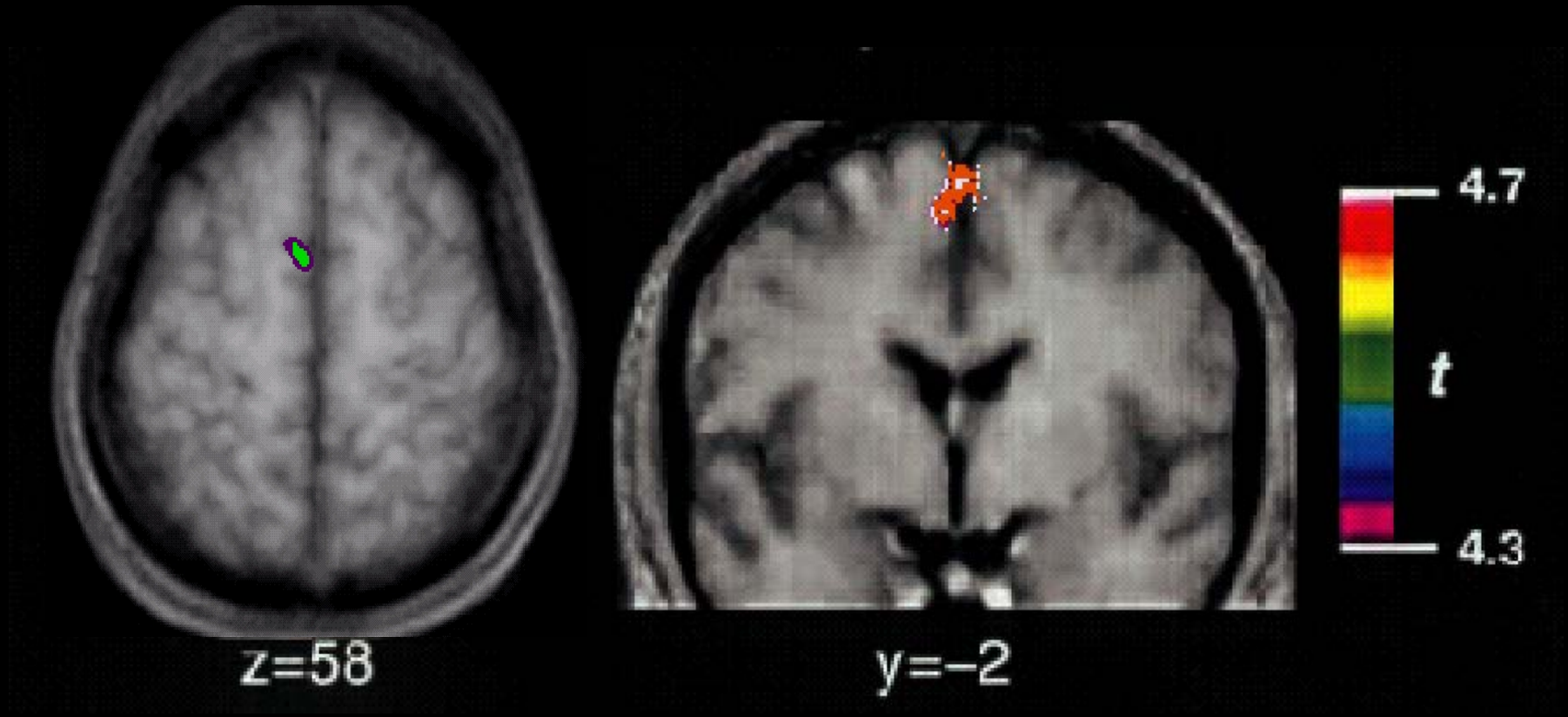


Christensen et al. 2000: Bicycle motion


Pre-central gyrus
Cerebral peduncle
Midbrain
Medulla
Pyramids
Decussation of pyramids
Lateral corticospinal tract
Anterior corticospinal tract
Upper motor neuron
To skeletal muscles
Spinal cord
Lower motor neuron
Key
Upper motor neuron
Lower motor neuron



Imagination of bicycle motion

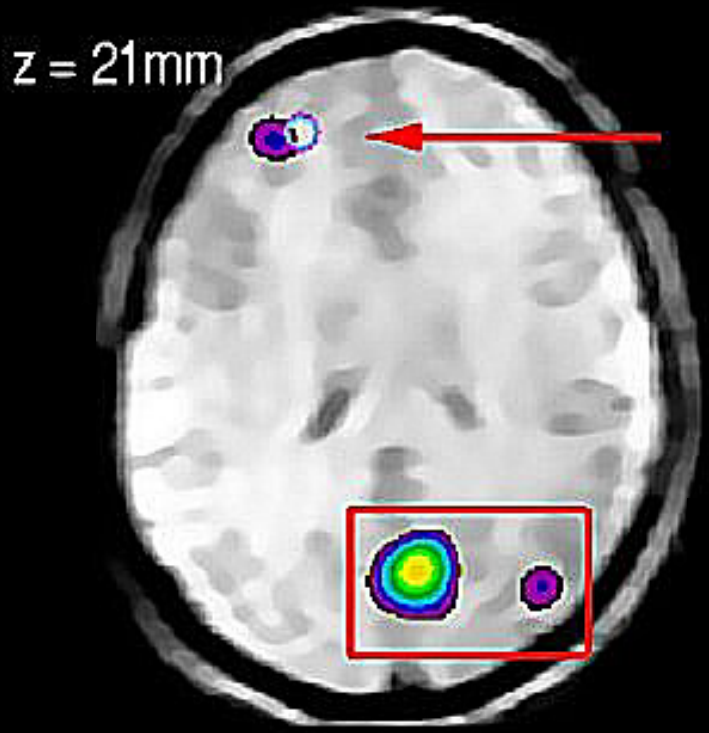


Outline

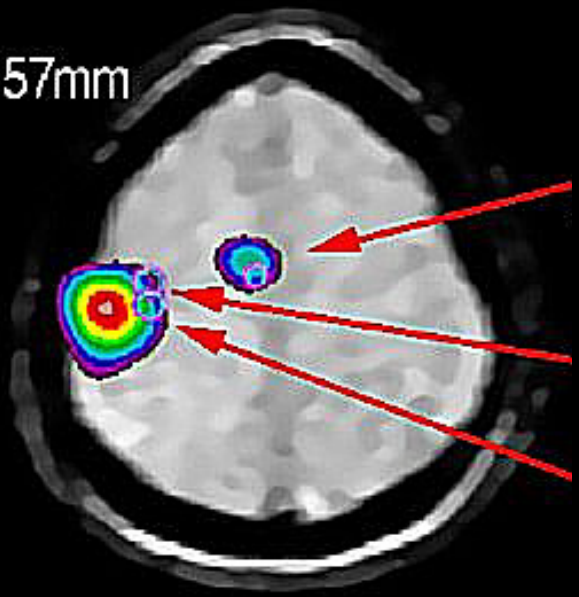
3

Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia

PET & MEG maps on MR images
Time = 0 ms at movement onset



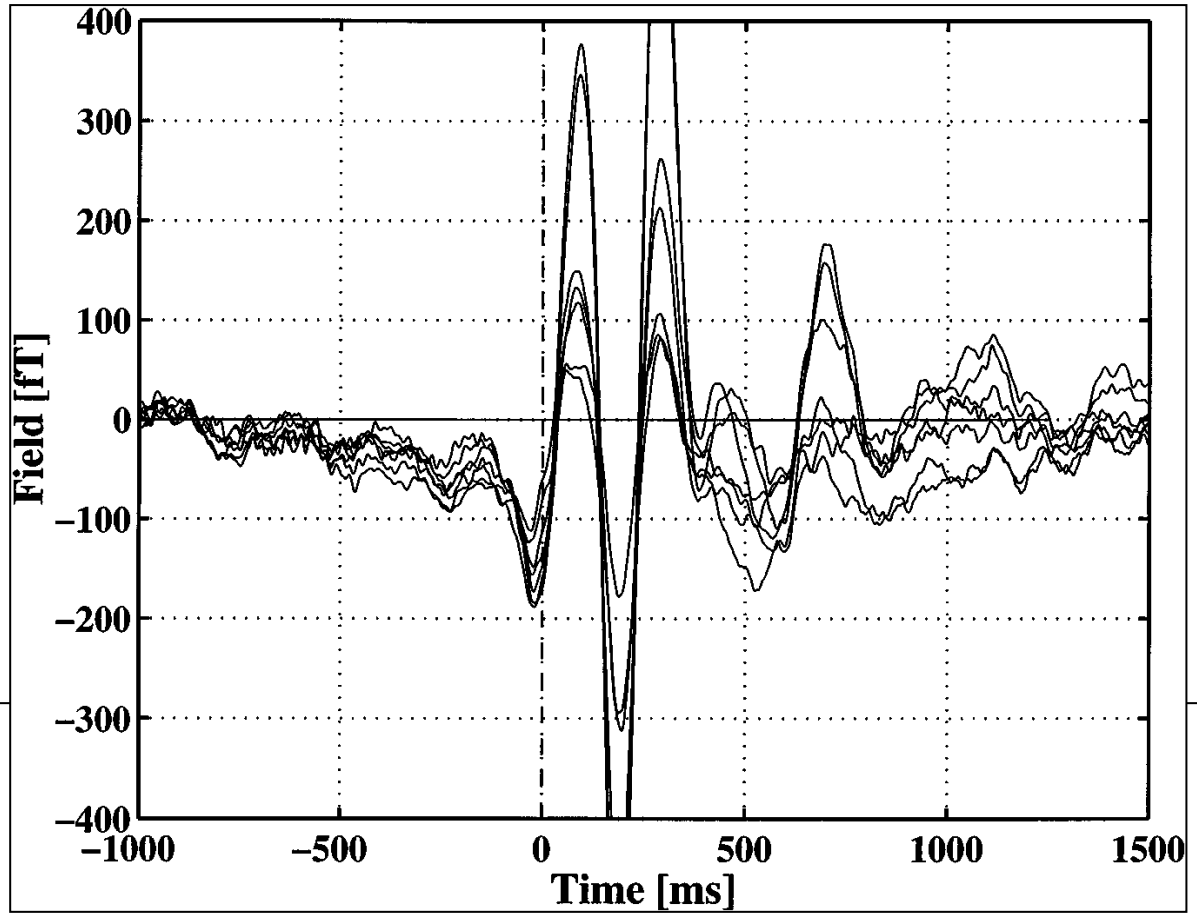
Frontal
-900 to –250 ms



SMA
-300 to 100 ms

Premotor
-100 to 0 ms

Motor
-20 to +100 ms



NEUROIMAGE **8**, 214–220 (1998)
ARTICLE NO. NI980362

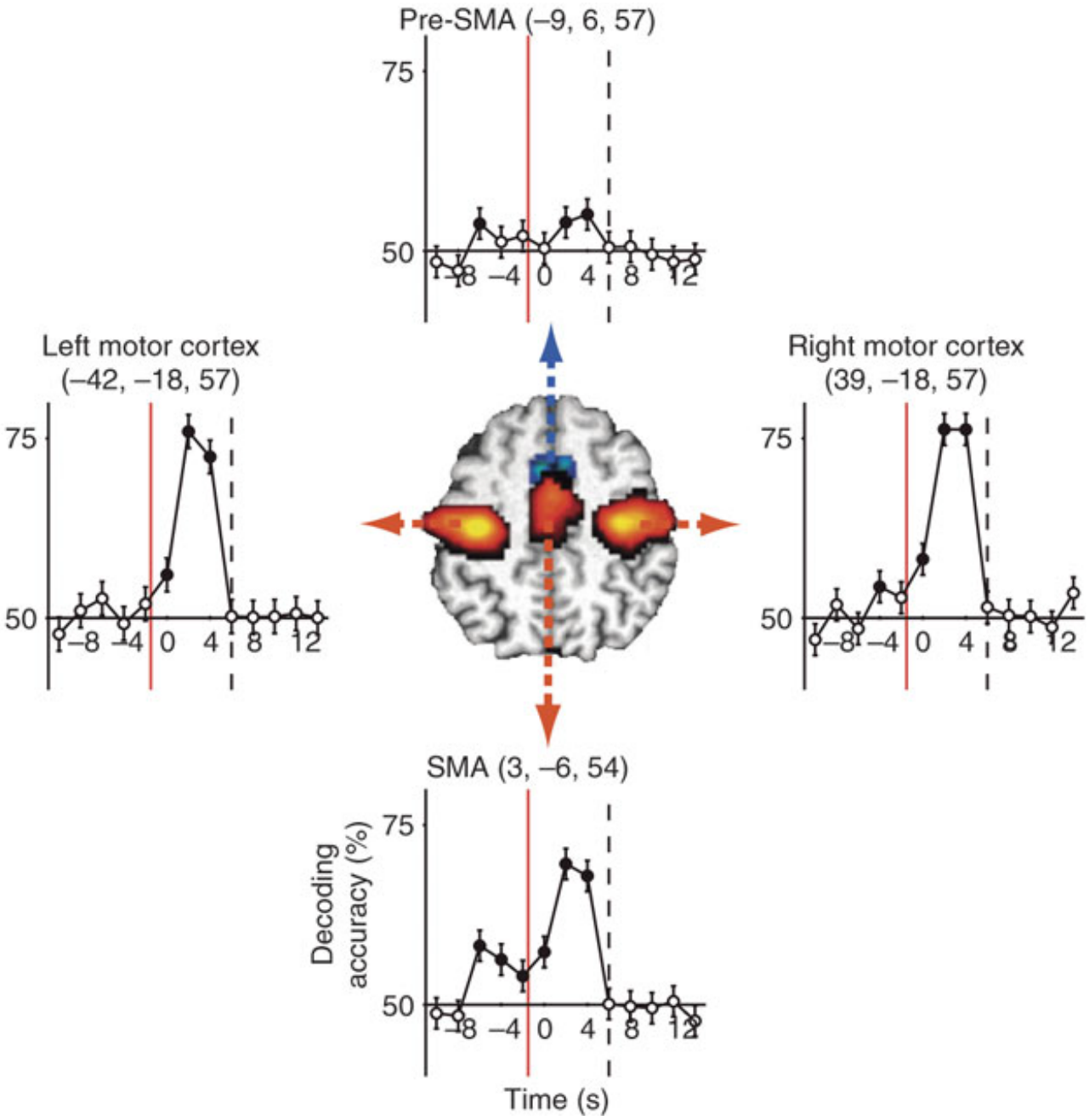
Origin of Human Motor Readiness Field Linked to Left Middle Frontal Gyrus by MEG and PET

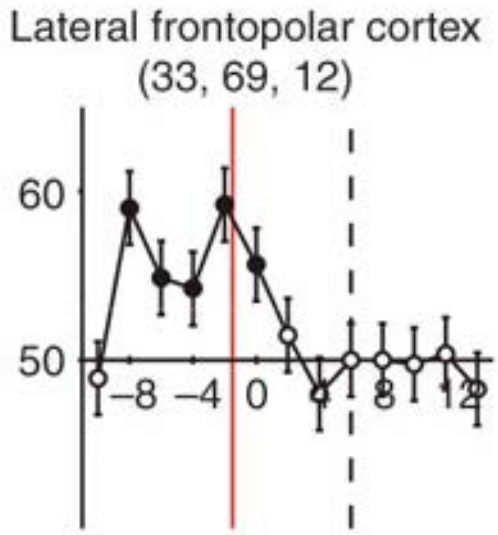
Jane R. Pedersen,* Peter Johannsen,† Christen K. Bak,* Bent Kofoed,* Knud Saermark,* and Albert Gjedde†,[1]

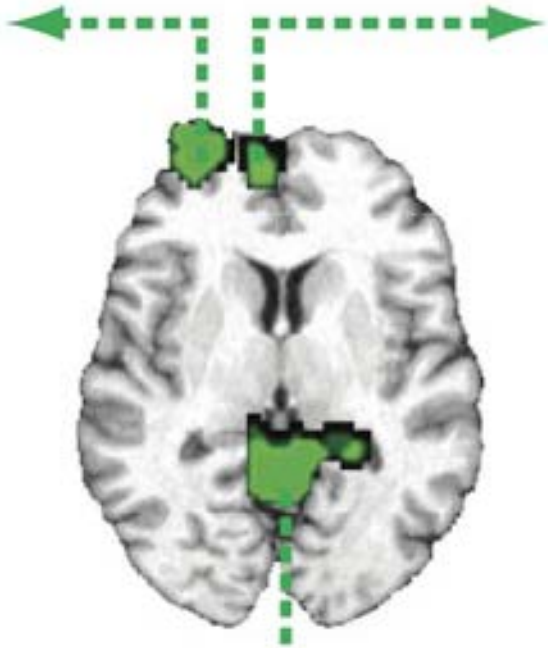
*Department of Physics, Technical University of Denmark, DK-2800 Lyngby, Denmark; and †PET Center, Aarhus University Hospital, DK-8000 Aarhus C, Denmark

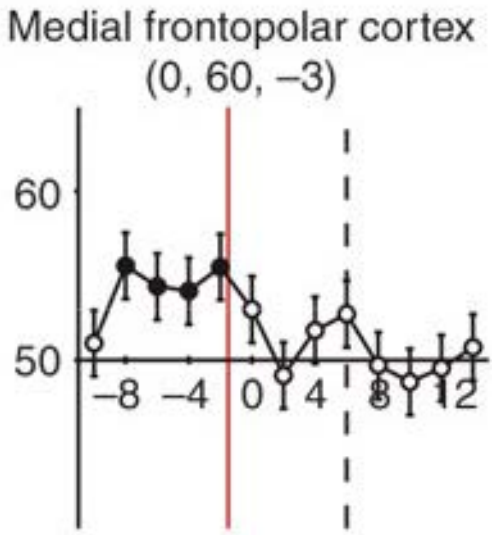
Regions where the specific outcome of a motor decision could be detected **after** the movement (red).

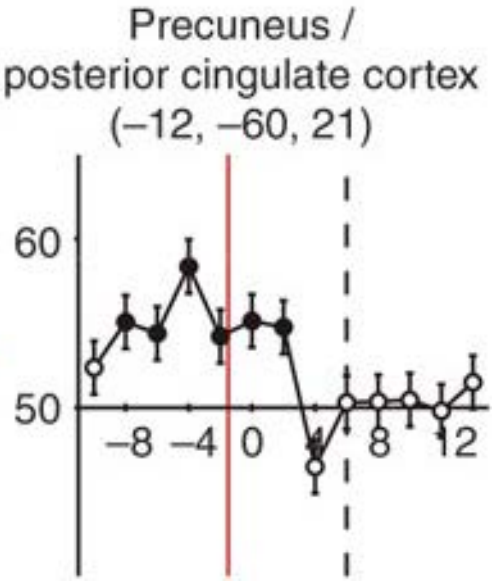
Soon et al. 2008





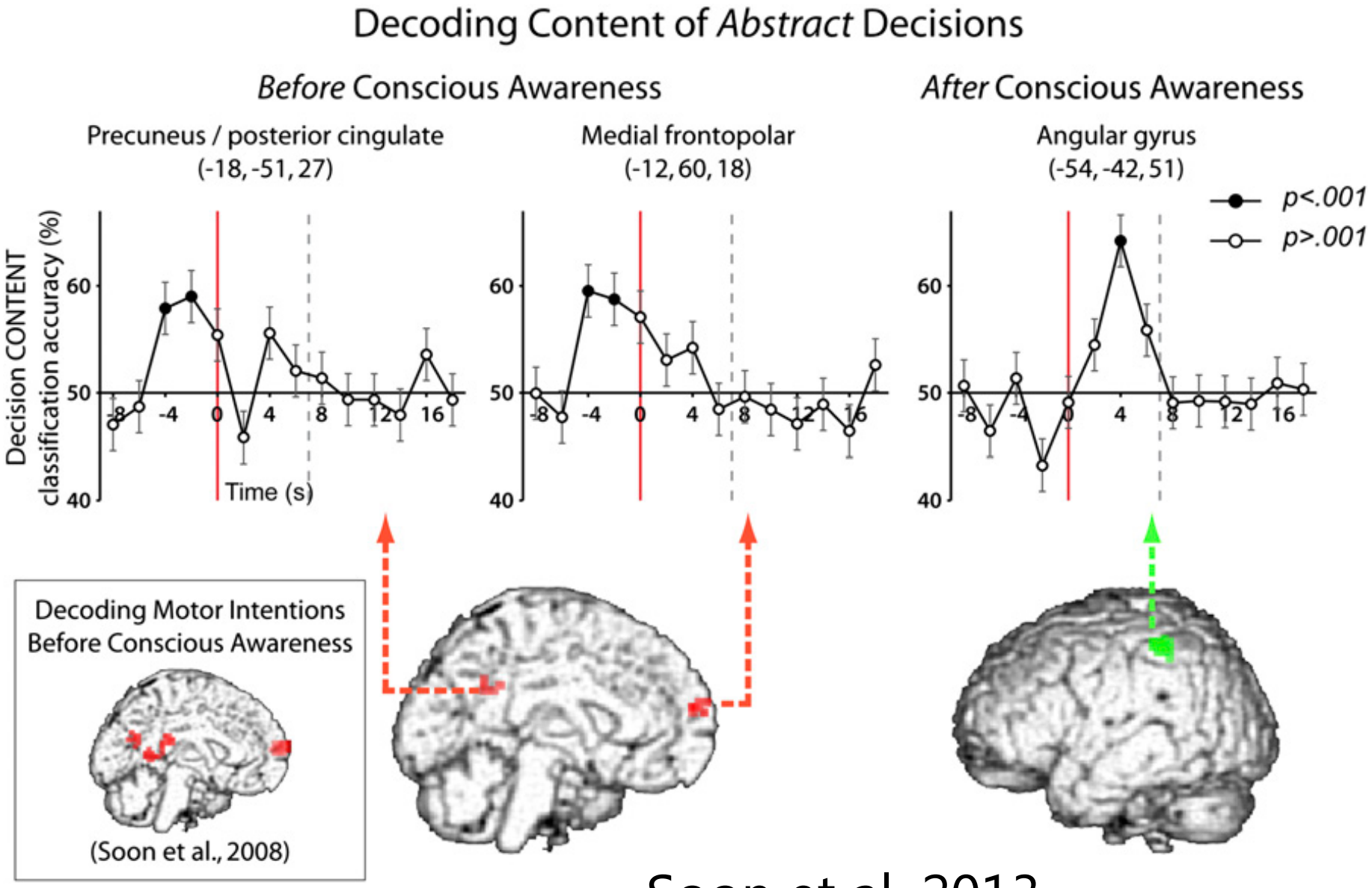






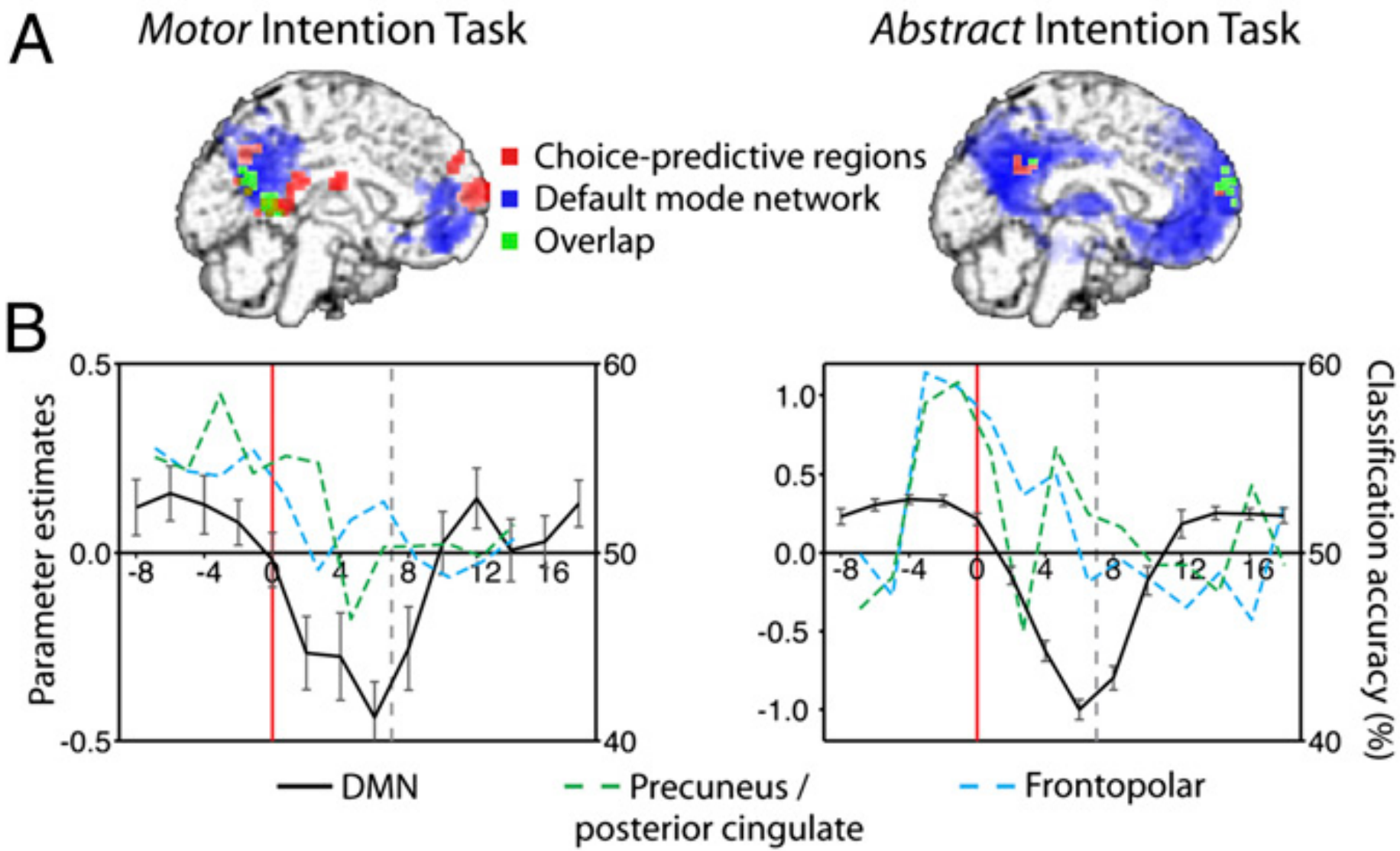
Regions where the specific outcome of a motor decision could be detected **before** the movement (green)

Soon et al. 2008

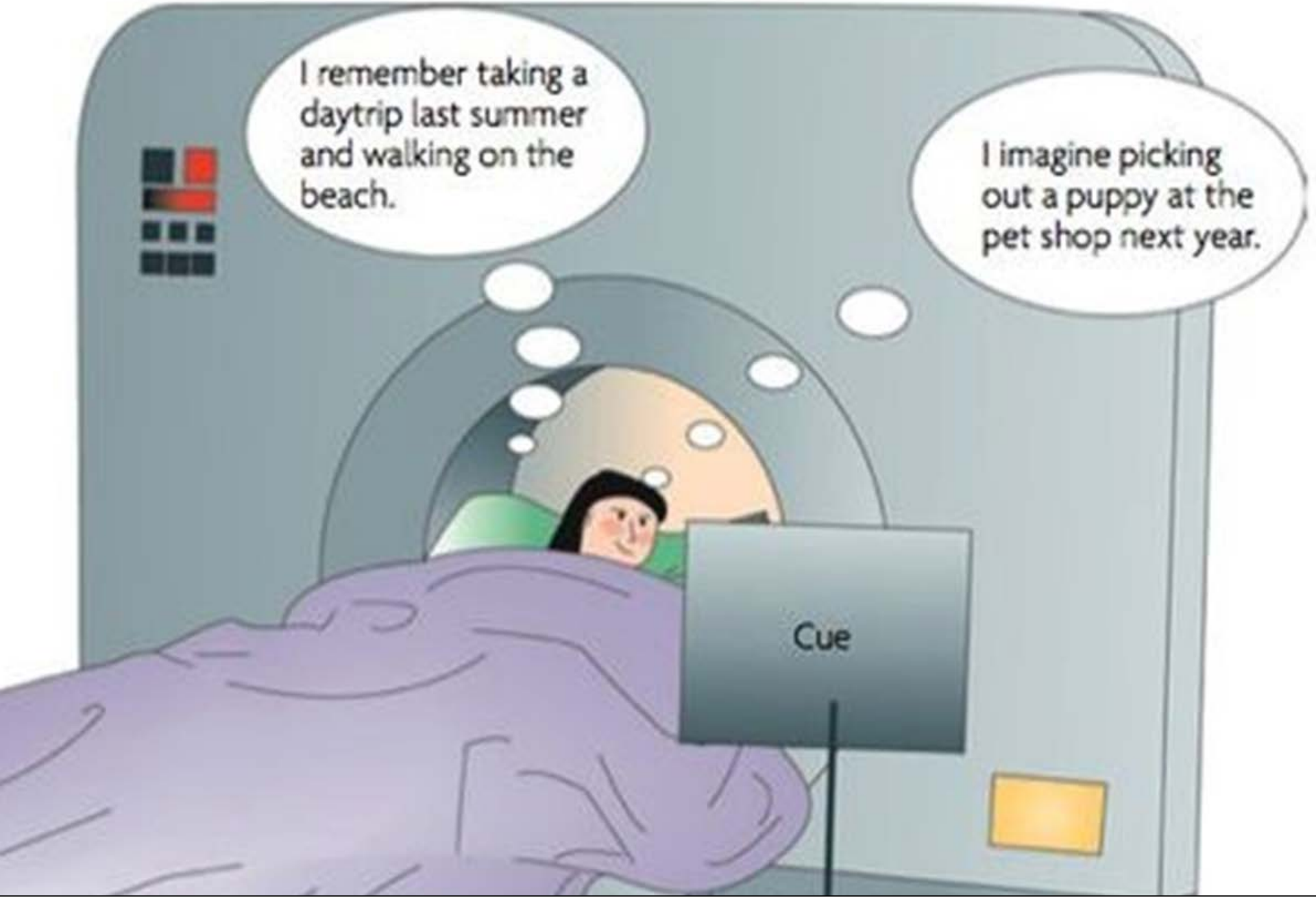


Soon et al. 2013

Default Mode Network Activations



Soon et al. 2013


I remember taking a daytrip last summer and walking on the beach.
I imagine picking out a puppy at the pet shop next year.
Cue

Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration.

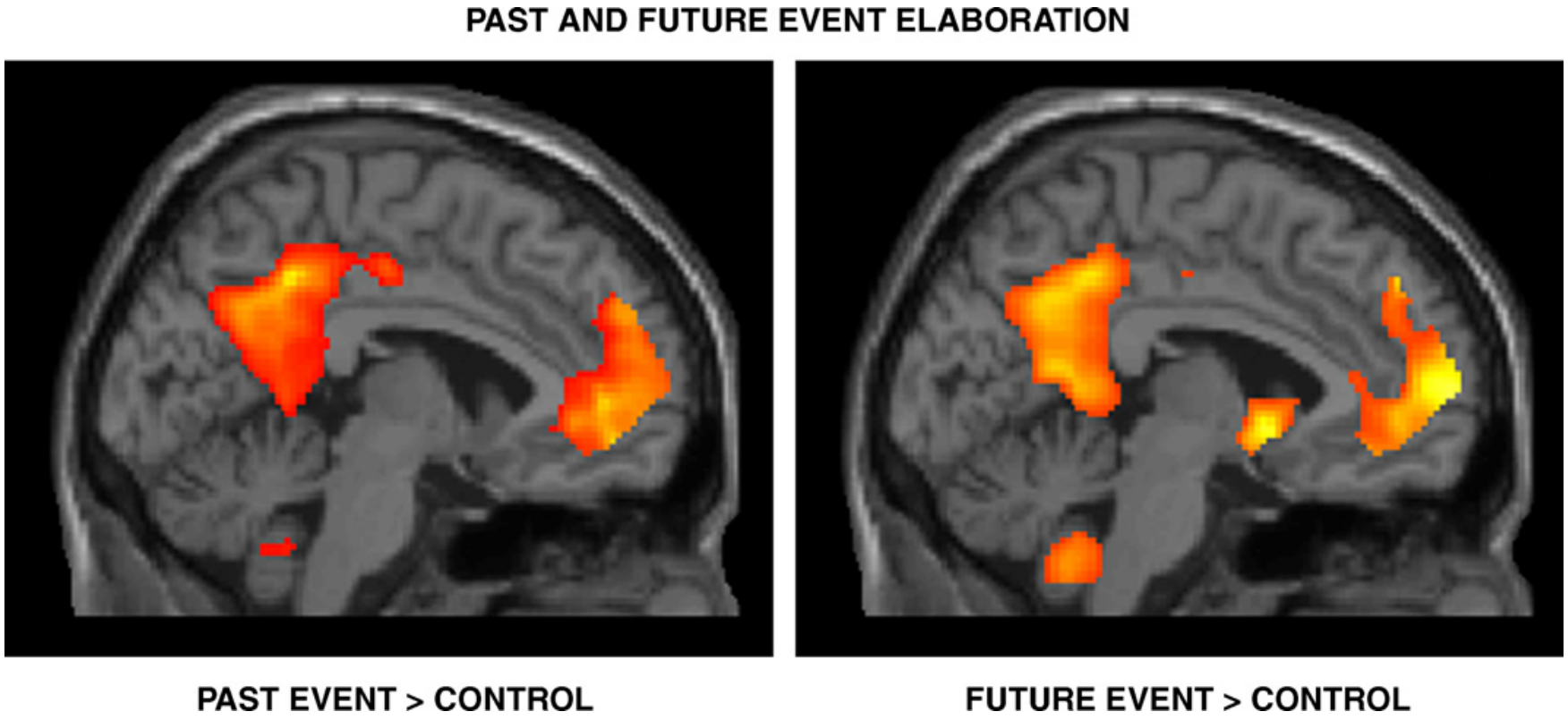
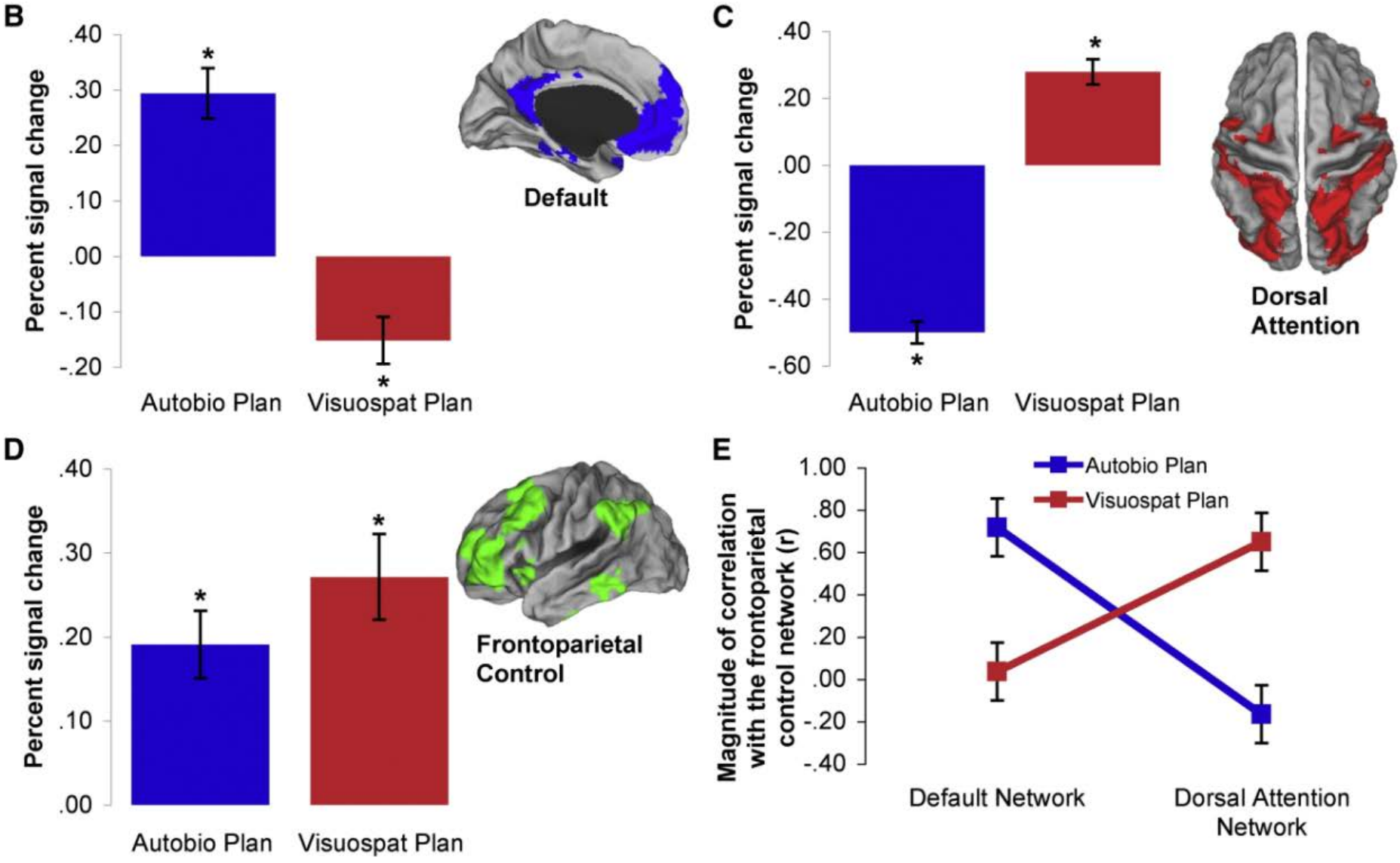


Fig. 2. Sagittal slice (x =−4) illustrating the striking commonalities in medial left prefrontal and parietal activity during the elaboration of (a) past and (b) future events (relative to the control tasks) at a threshold of p < .001, uncorrected (shown at p < .005, uncorrected).

Addis et al. 2007

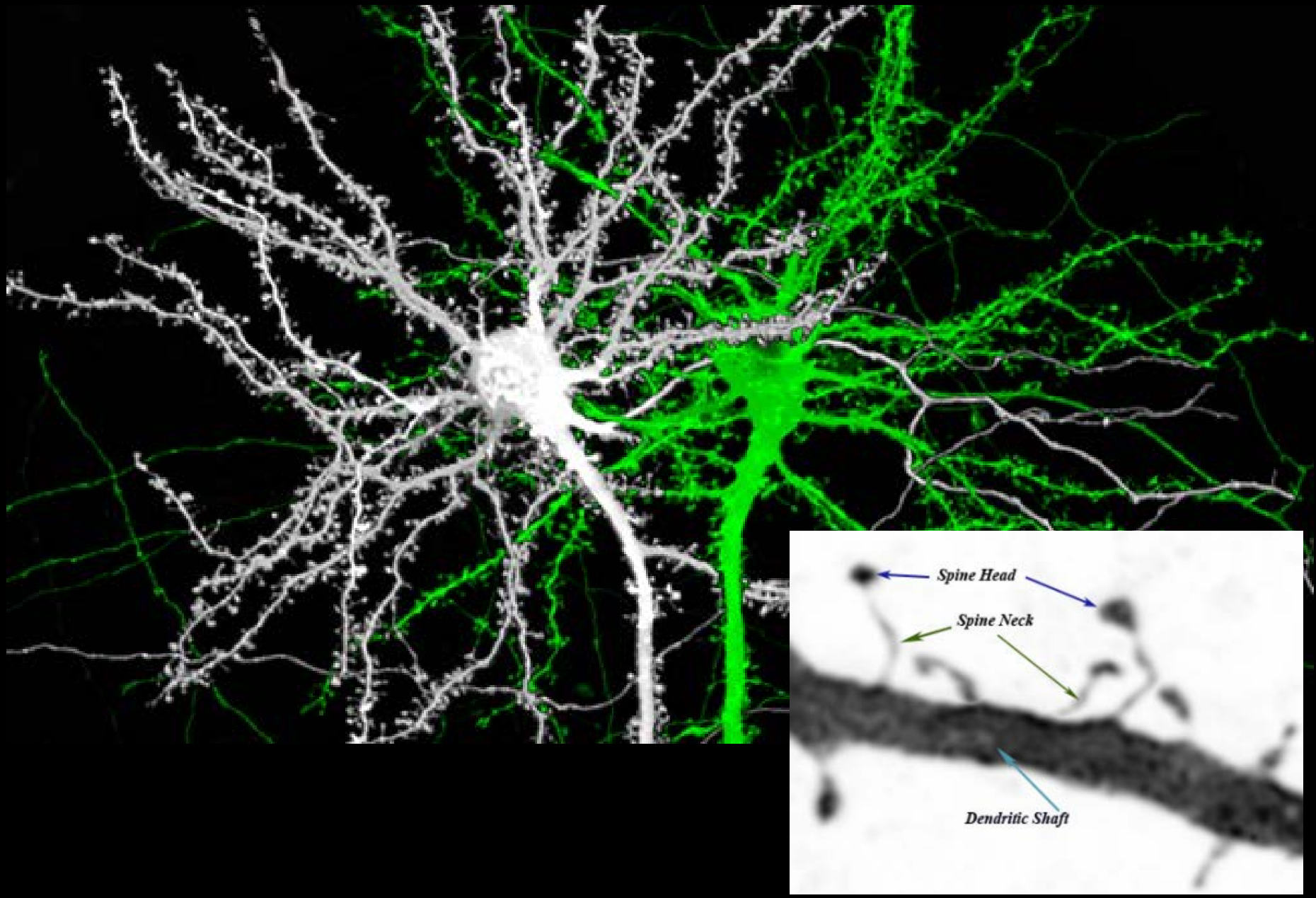


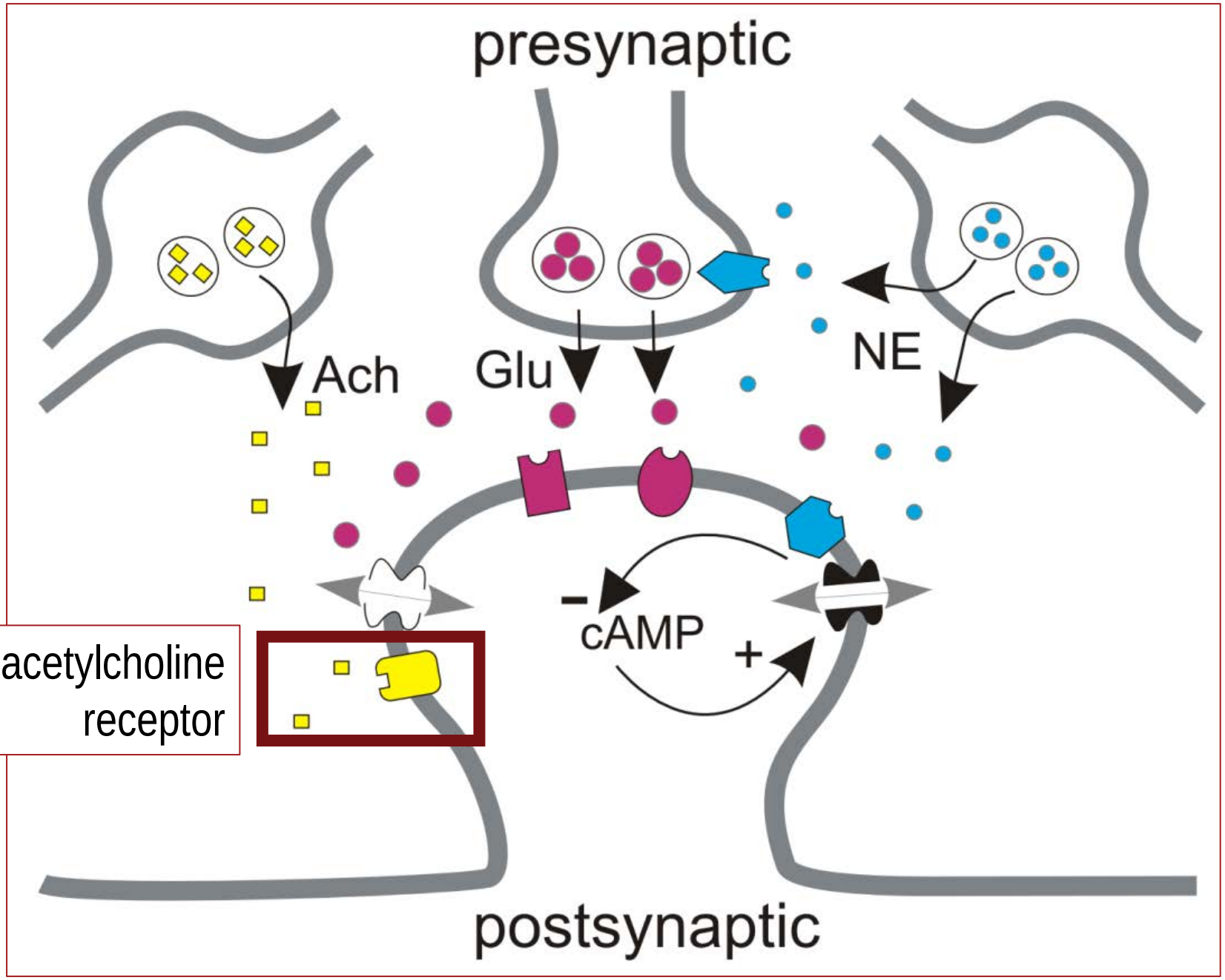
The Future of Memory: Remembering, Imagining, and the Brain (Schacter et al. 2012)

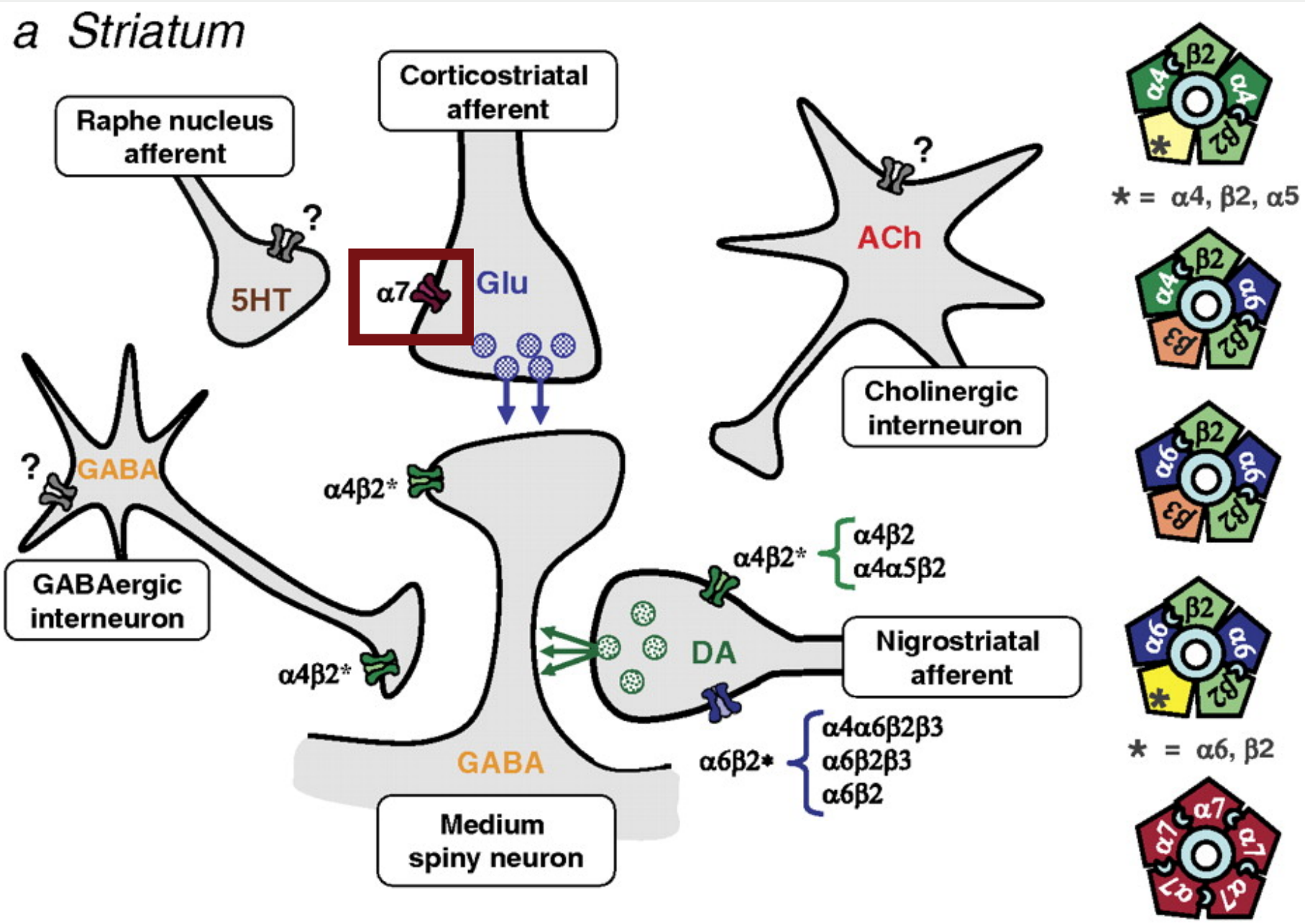
Outline

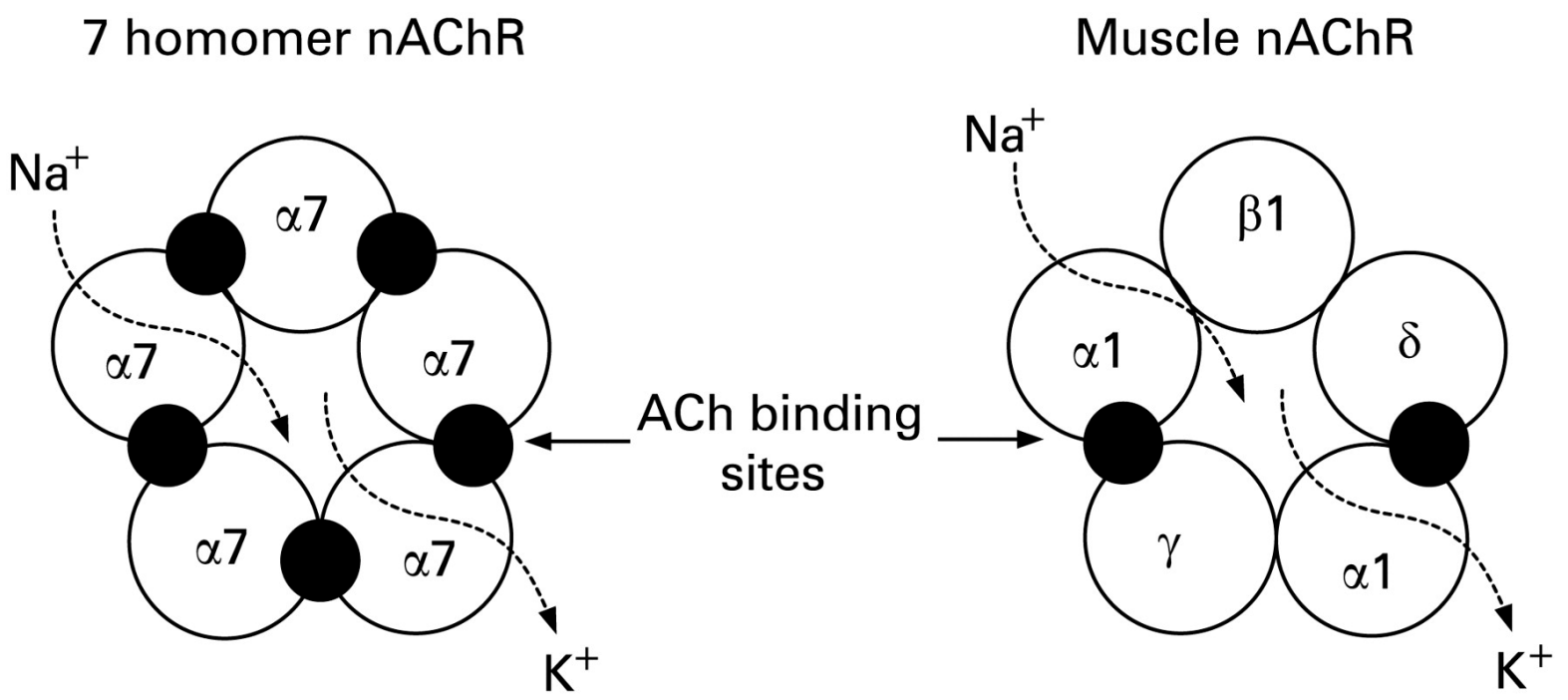
4

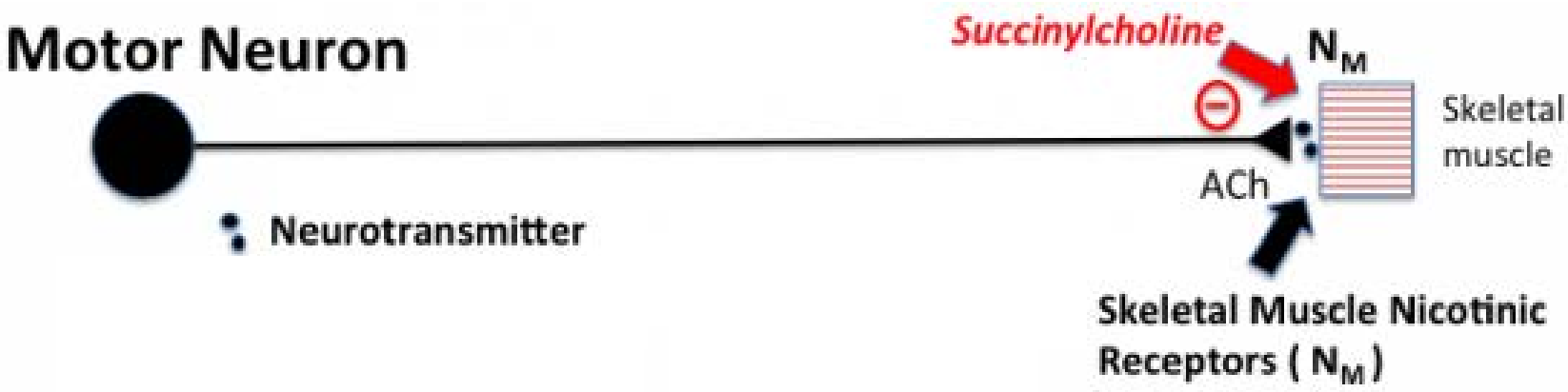
Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia


Spine Head
Spine Neck
Dendritic Shaft


presynaptic
Ach
Glu
NE
cAMP
–
+
acetylcholine receptor
postsynaptic


a Striatum
Corticostriatal afferent
Raphe nucleus afferent
5HT
?
α7
Glu
ACh
?
Cholinergic interneuron
?
GABA
GABAergic interneuron
α4β2*
α4β2*
α4β2
α4α5β2
α4β2*
DA
Nigrostriatal afferent
α6β2*
α4α6β2β3
α6β2β3
α6β2
GABA
Medium spiny neuron
β2
α4
α4
β2
*
* = α4, β2, α5
β2
α4
α6
β2
β3
β2
β2
α6
α6
β2
β3
β2
β2
α6
α6
β2
*
β2
* = α6, β2
α7
α7
α7
α7
α7

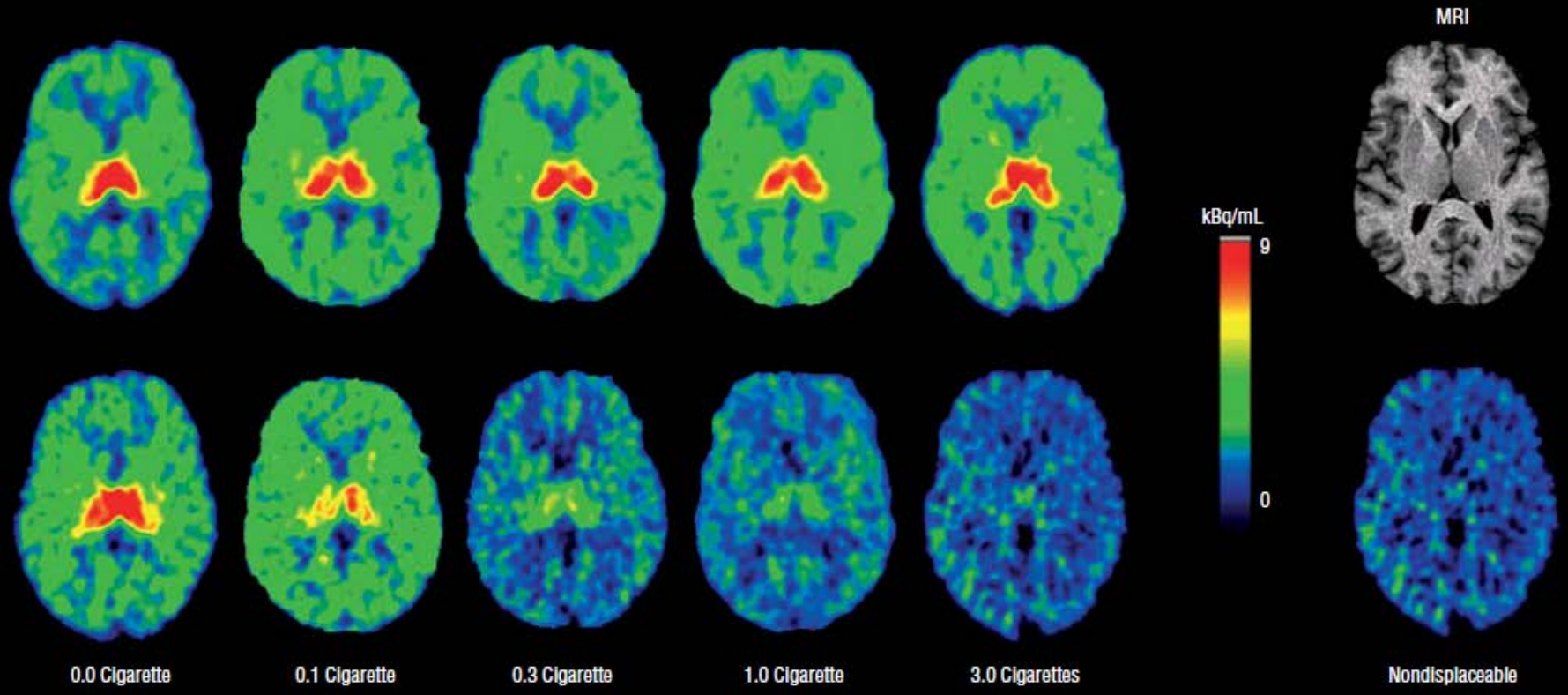

7 homomer nAChR
Muscle nAChR
Na+
α7
α7
α7
α7
α7
ACh binding sites
K+
Na+
β1
α1
δ
γ
α1
K+


Motor Neuron
Succinylcholine
N_M
Skeletal muscle
ACh
Neurotransmitter
Skeletal Muscle Nicotinic Receptors (N_M)

Cigarette Smoking Saturates Brain $\alpha_4\beta_2$ Nicotinic Acetylcholine Receptors

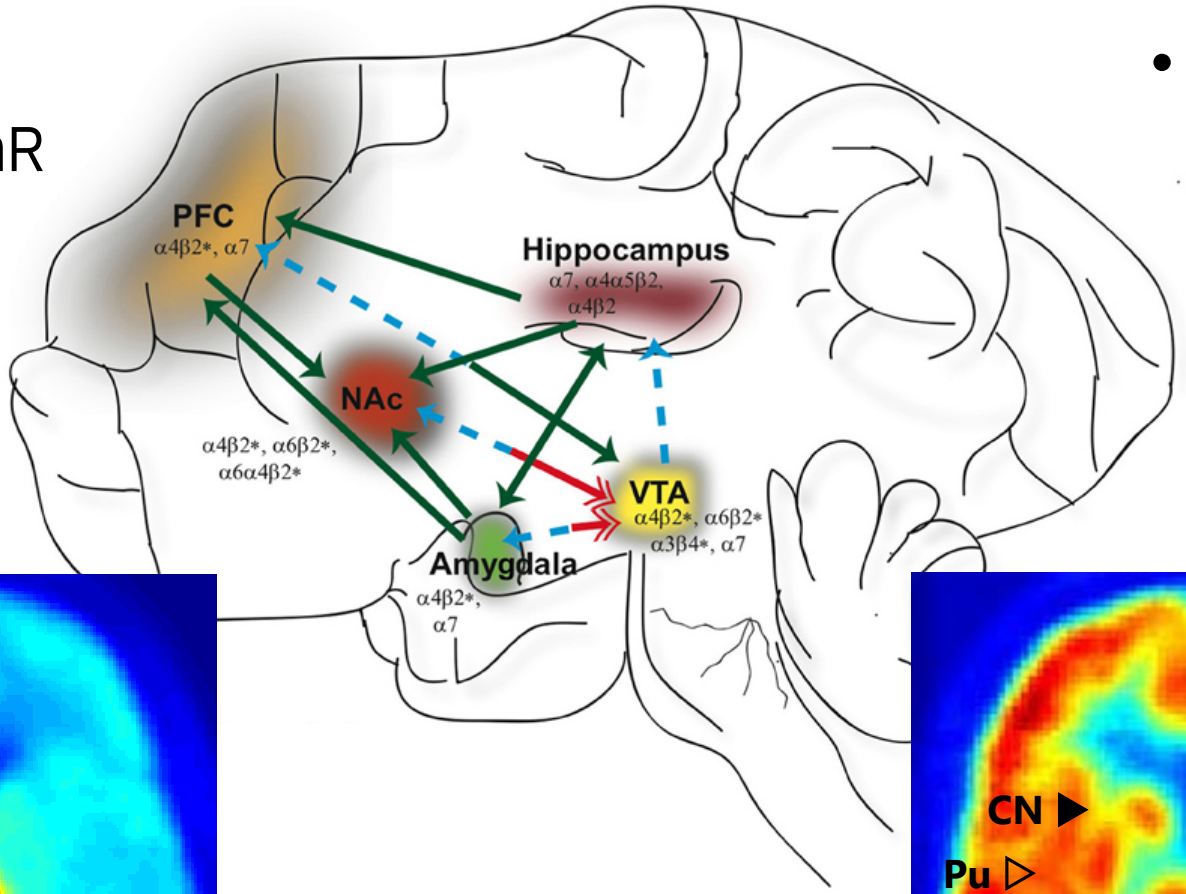
Arch Gen Psychiatry. 2006;63:907-915

Arthur L. Brody, MD; Mark A. Mandelkern, MD, PhD; Edythe D. London, PhD; Richard E. Olmstead, PhD; Judah Farahi, PhD; David Scheibal, BS; Jennifer Jou, BS; Valerie Allen, BS; Emmanuelle Tiongson, BS; Svetlana I. Chefer, PhD; Andrei O. Koren, PhD; Alexey G. Mukhin, MD, PhD

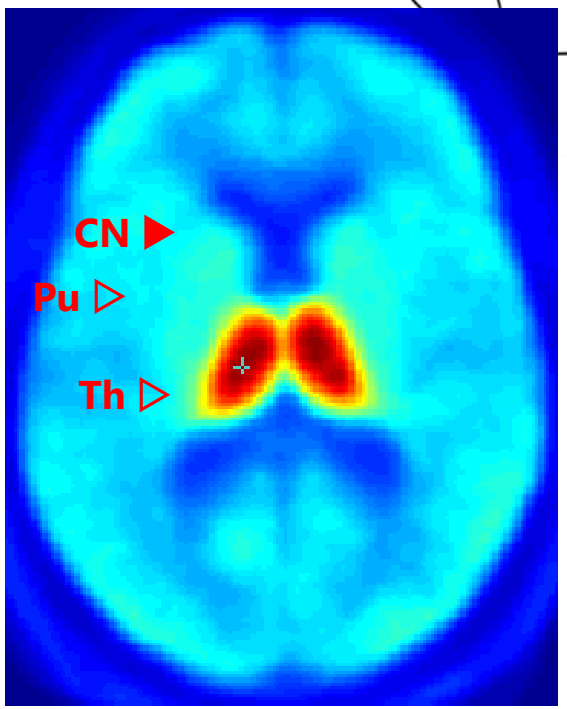


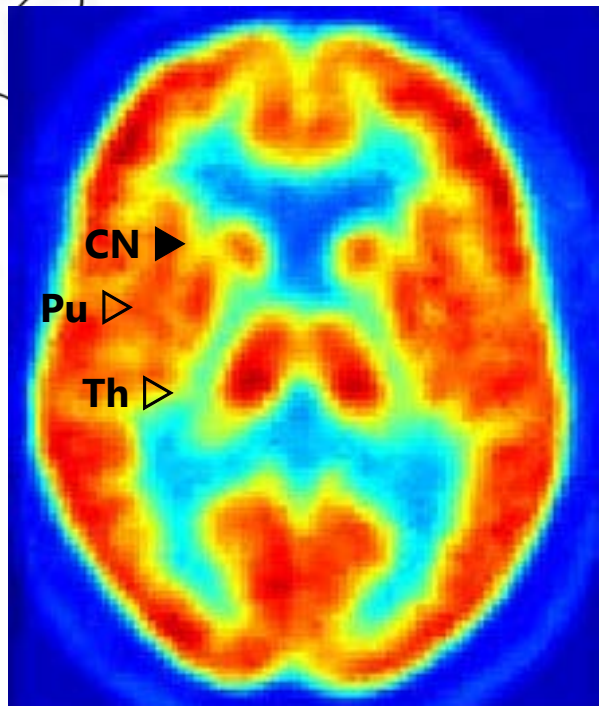
- [^{18}F]AZAN
  α4β2-nAChR

Wong DF et al
Mol Imaging
Biol (5):730-8,
2014



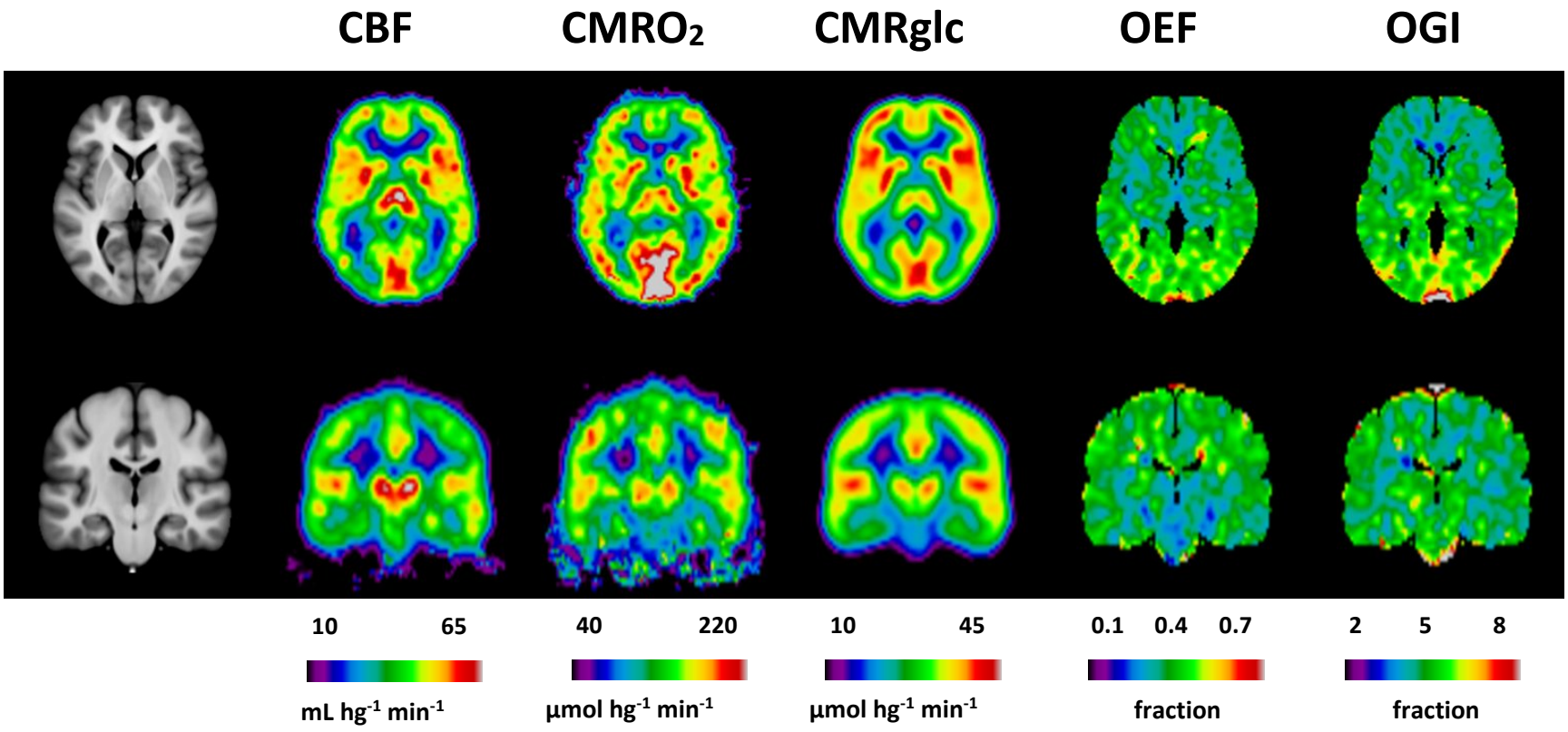
- [^{18}F]ASEM
  α7-nAChR





nAChR
α4β2 og α7

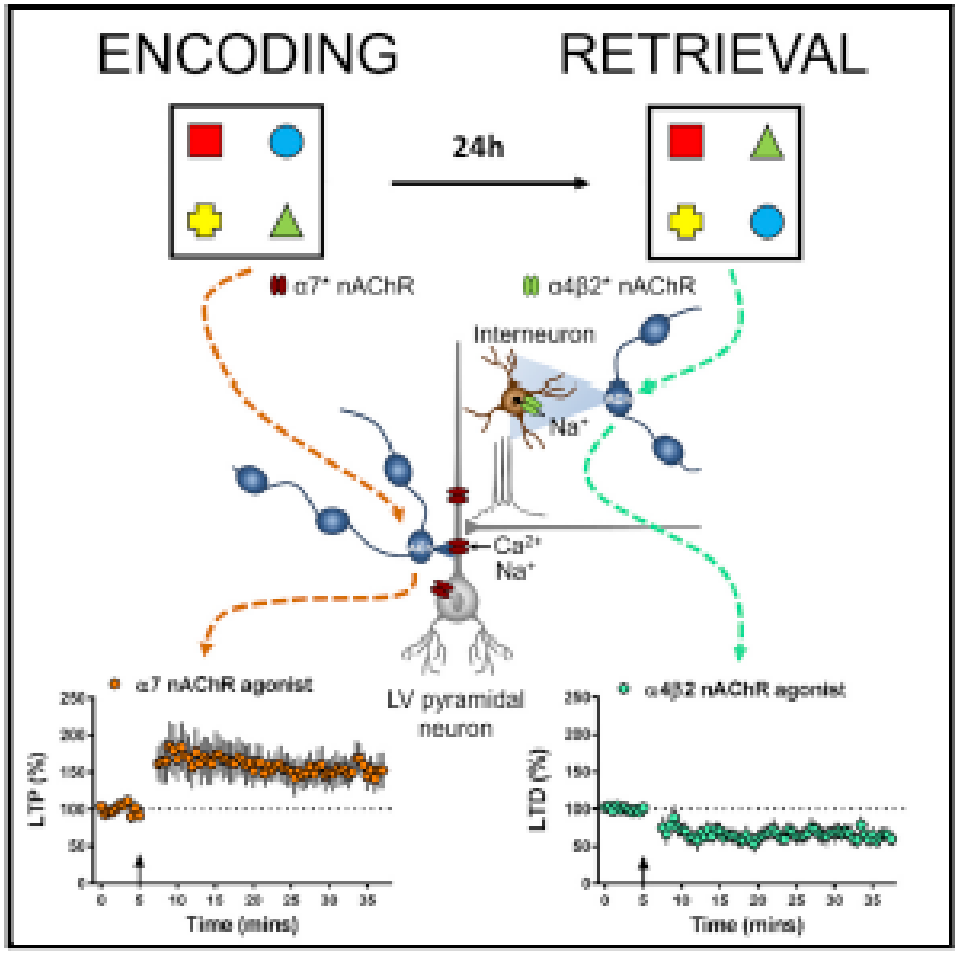
Average Circulatory and Metabolic Variables in Human Brain (n=14)



Hyder et al. 2016

Nicotinic Acetylcholine Receptors Control Encoding and Retrieval of Associative Recognition Memory through Plasticity in the Medial Prefrontal Cortex

Graphical Abstract



Authors

Marie H. Sabec, Susan Wonnacott, E. Clea Warburton, Zafar I. Bashir

Prefrontal a7 nAChRs are critical for encoding of associative recognition memory

Prefrontal a4b2 nAChRs are required for retrieval of associative recognition memory

a7 and a4b2 nAChRs gate bidirectional plasticity at hippocampal-prefrontal synapses

Bidirectional plasticity underlies the role of nAChR in associative recognition

Oxidative stress (stress oxidation), glycation, and telomere shortening

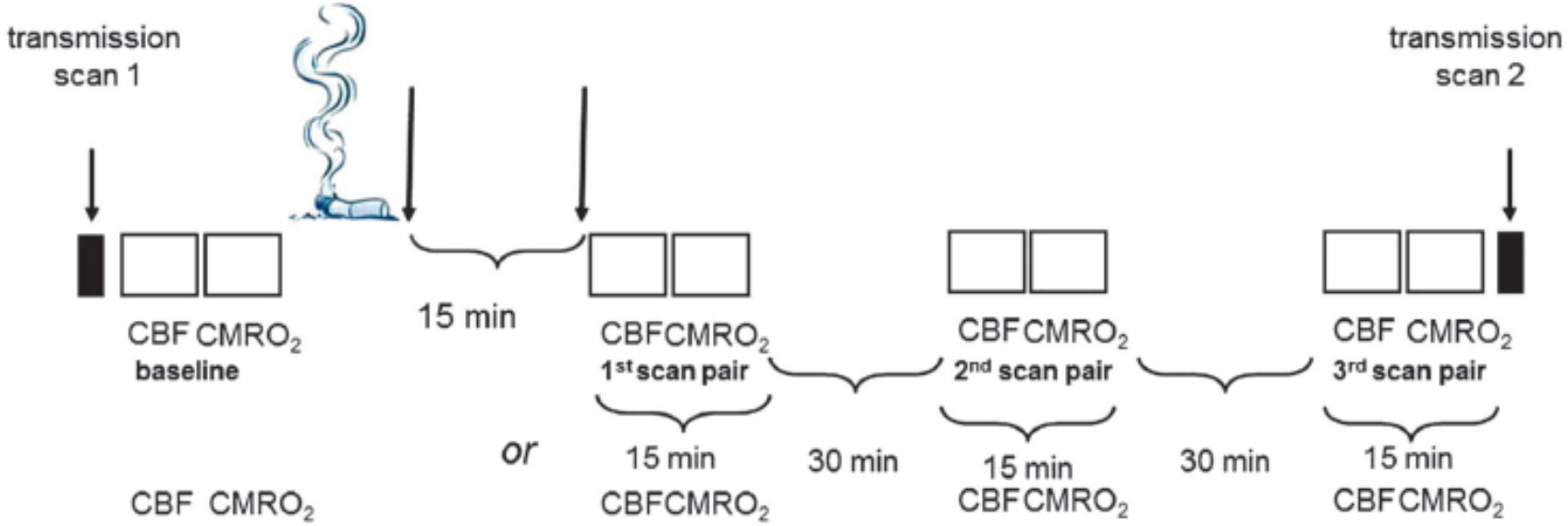
Journal of Cerebral Blood Flow & Metabolism (2015), 1–7

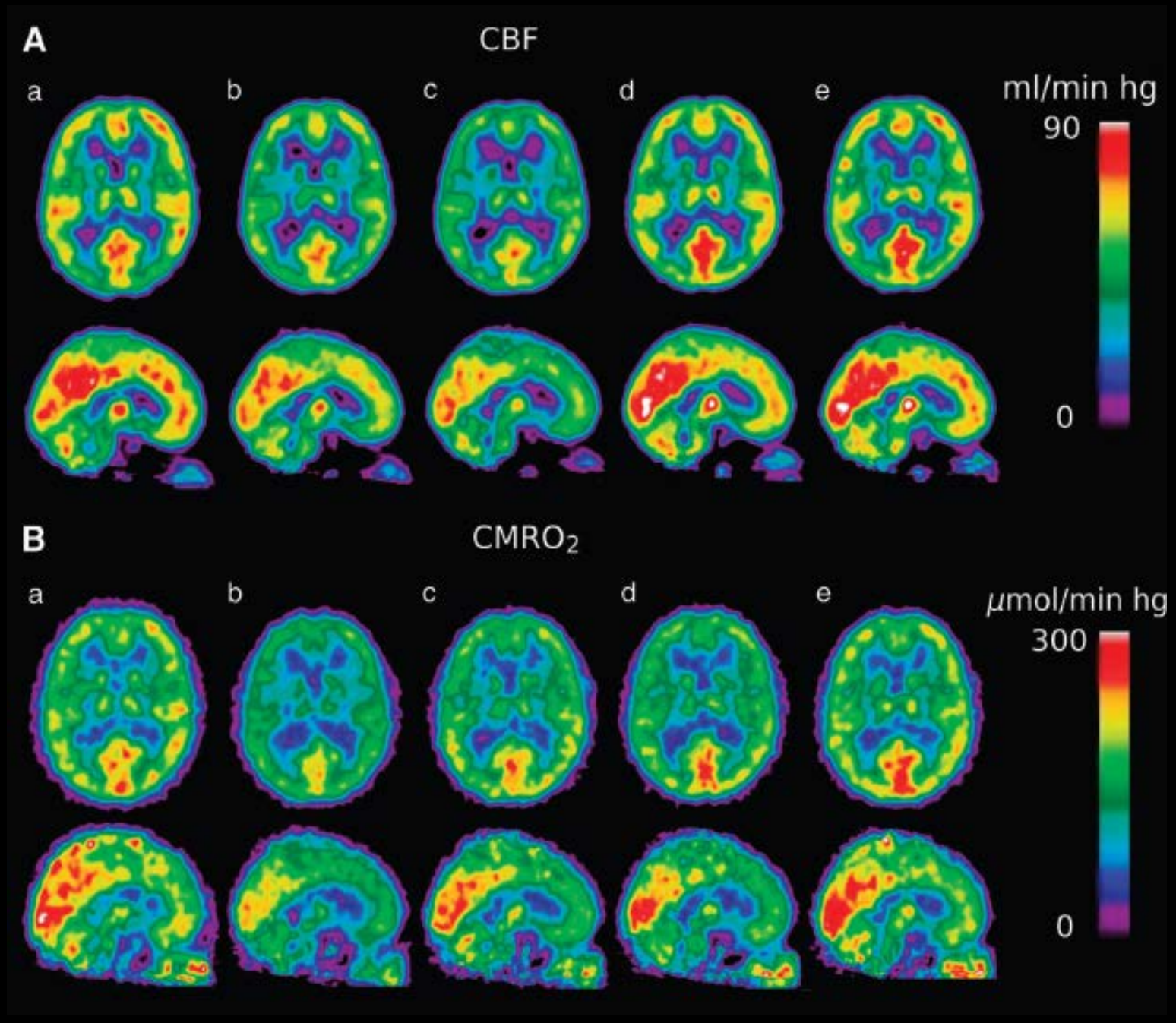
www.jcbfm.com

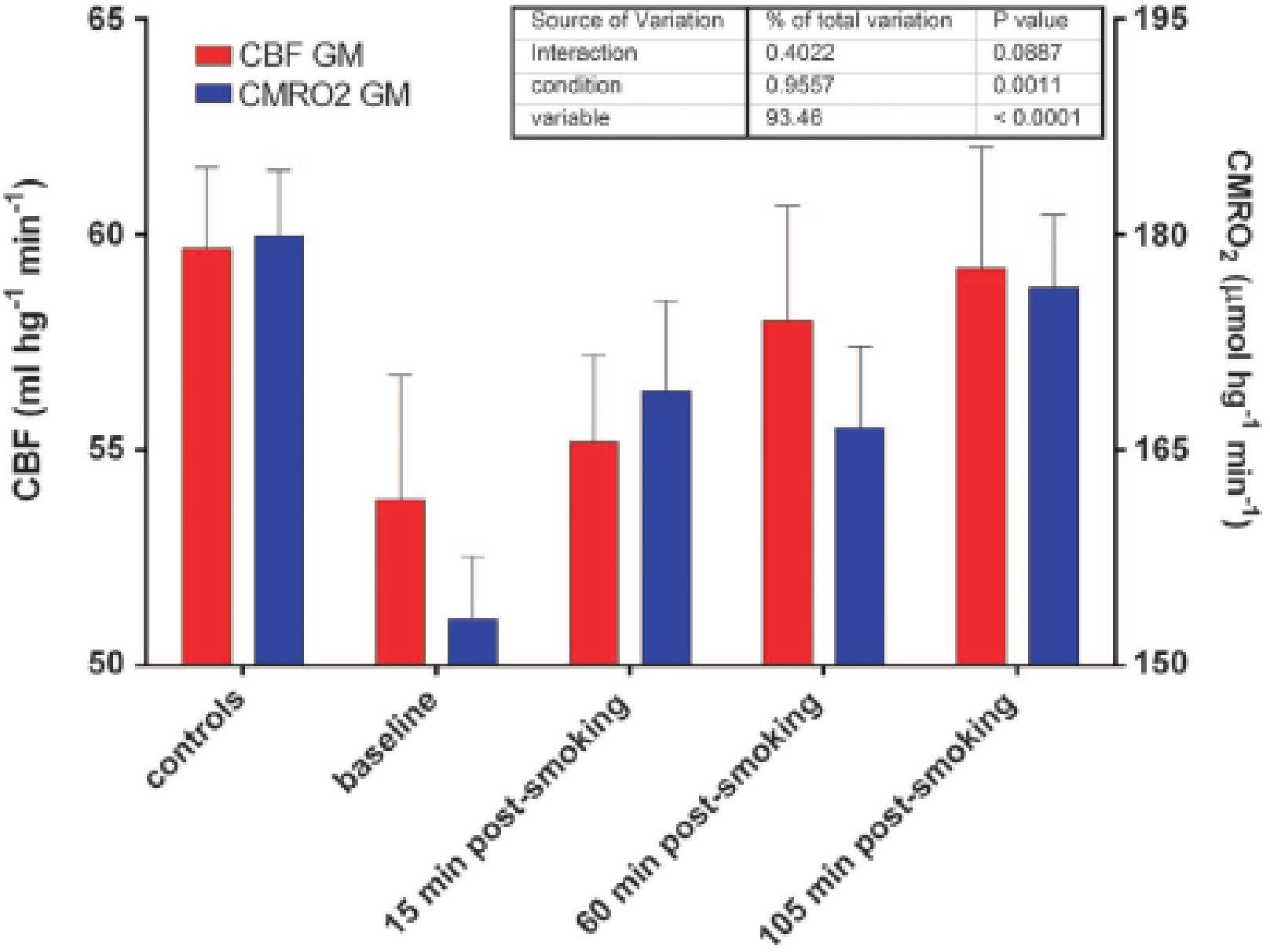
ORIGINAL ARTICLE

Smoking normalizes cerebral blood flow and oxygen consumption after 12-hour abstention

Manouchehr S Vafaee[1], Albert Gjedde[1,2], Nasrin Imamirad[3], Kim Vang[2], Mallar M Chakravarty[4], Jason P Lerch[5] and Paul Cumming[6]




A
CBF
a
b
c
d
e
ml/min hg
90
0
B
CMRO2
a
b
c
d
e
μmol/min hg
300
0

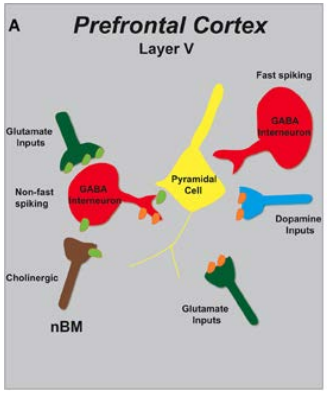


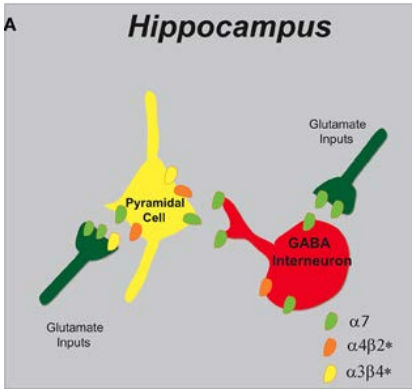
Source of Variation	% of total variation	P value
Interaction	0.4022	0.0887
condition	0.9557	0.0011
variable	93.46	< 0.0001

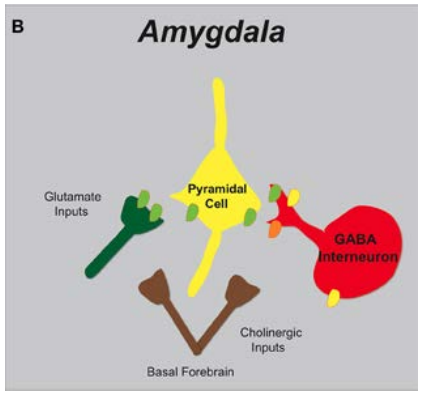
Outline

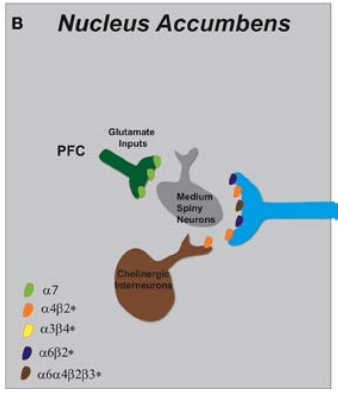
5

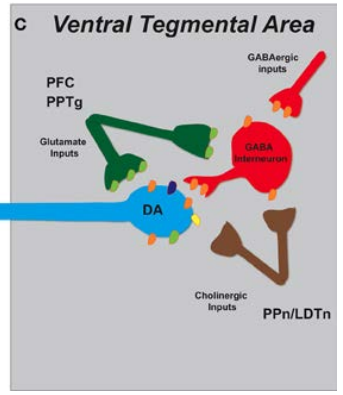
Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia

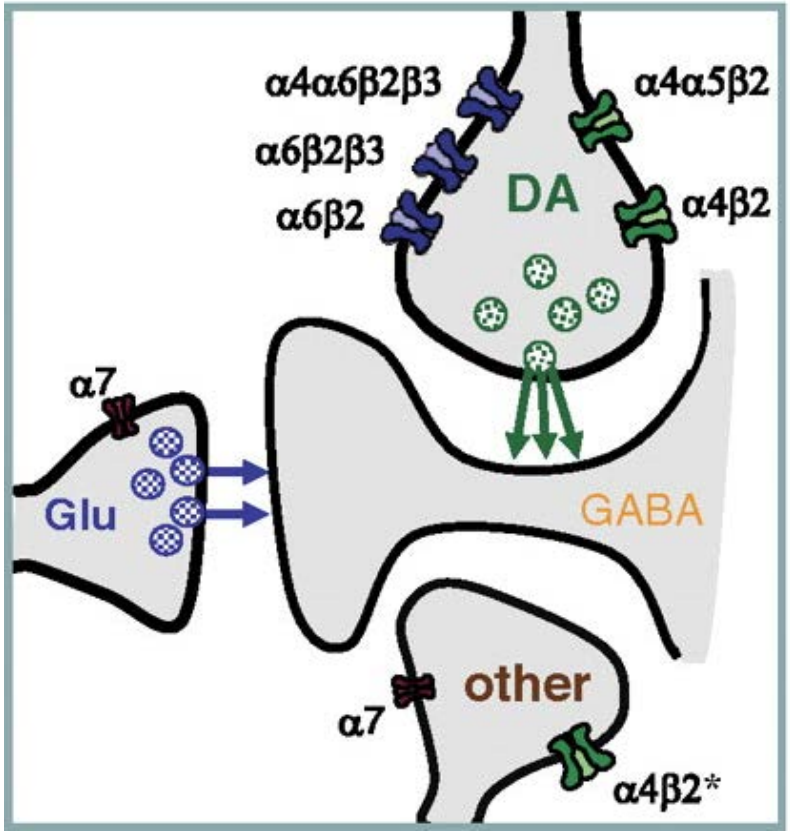

A
Prefrontal Cortex
Layer V
Fast spiking
GABA Interneuron
Glutamate Inputs
Pyramidal Cell
Non-fast spiking
GABA Interneuron
Dopamine Inputs
Cholinergic
nBM
Glutamate Inputs

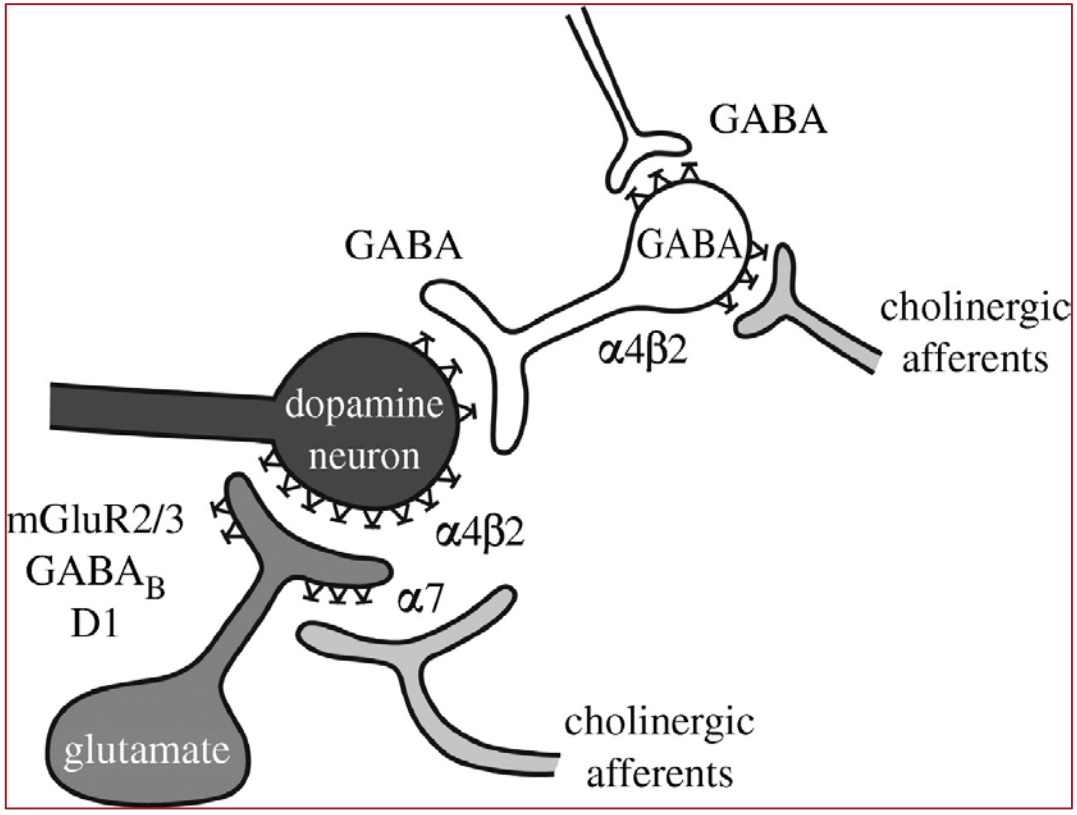

A
Hippocampus
Glutamate Inputs
Pyramidal Cell
GABA Interneuron
Glutamate Inputs
α7
α4β2*
α3β4*

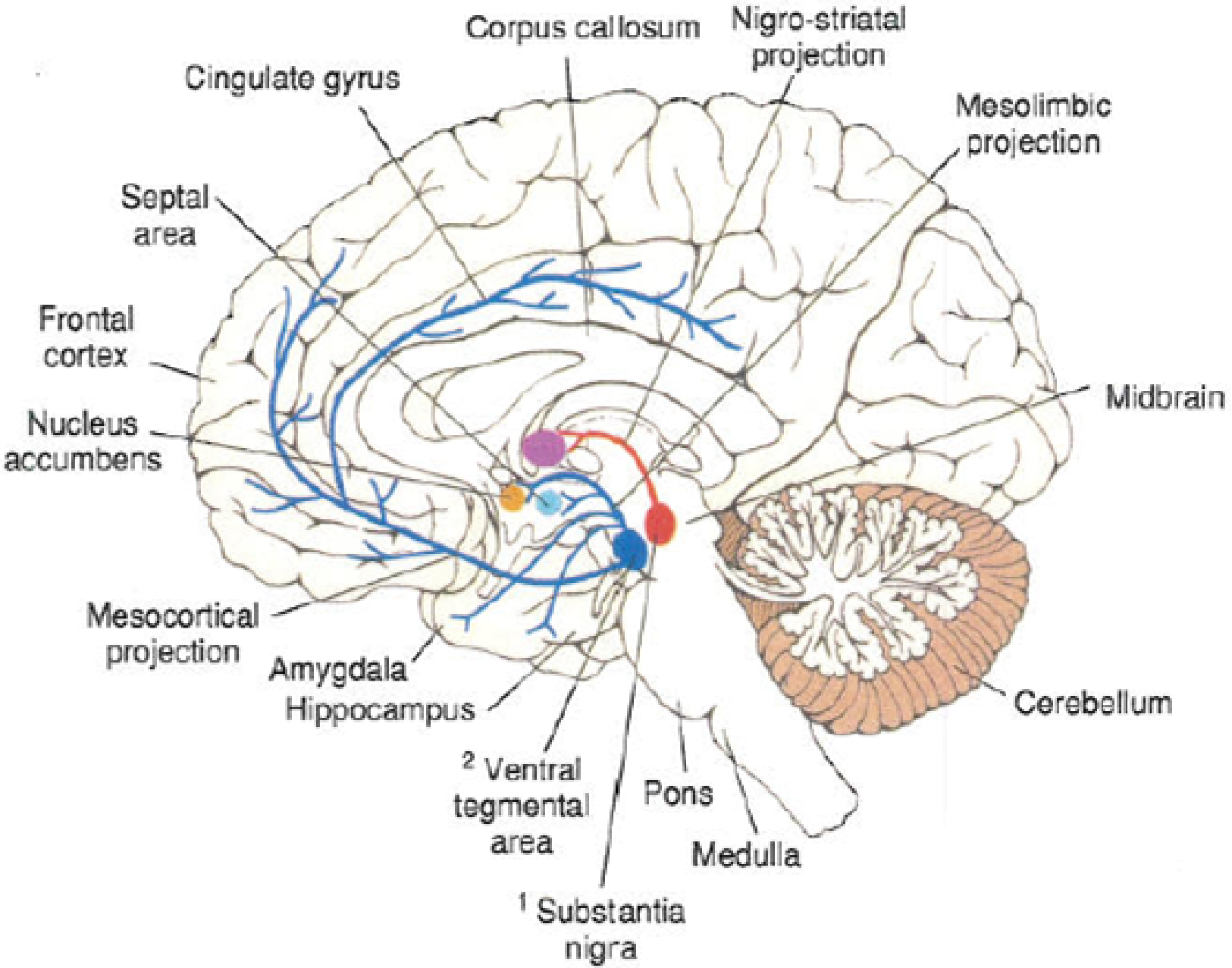

B
Amygdala
Glutamate Inputs
Pyramidal Cell
GABA Interneuron
Cholinergic Inputs
Basal Forebrain

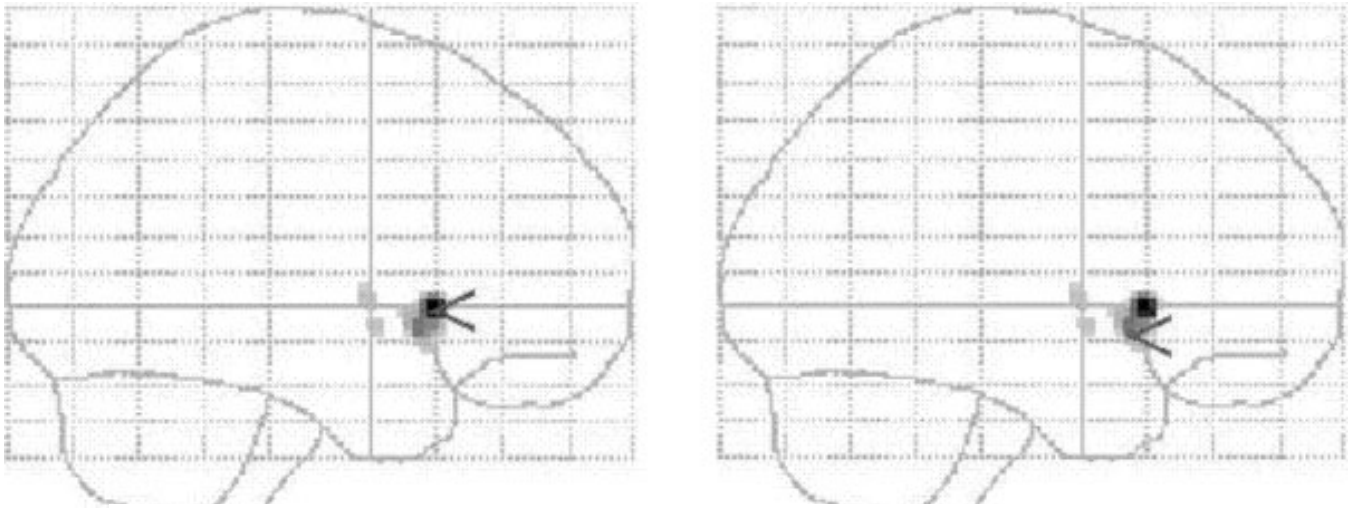

B
Nucleus Accumbens
PFC
Glutamate Inputs
Medium Spiny Neurons
Cholinergic Interneurons
α7
α4β2*
α3β4*
α6β2*
α6α4β2β3*


C
Ventral Tegmental Area
GABAergic inputs
PFC
PPTg
Glutamate Inputs
GABA Interneuron
DA
Cholinergic Inputs
PPn/LDTn

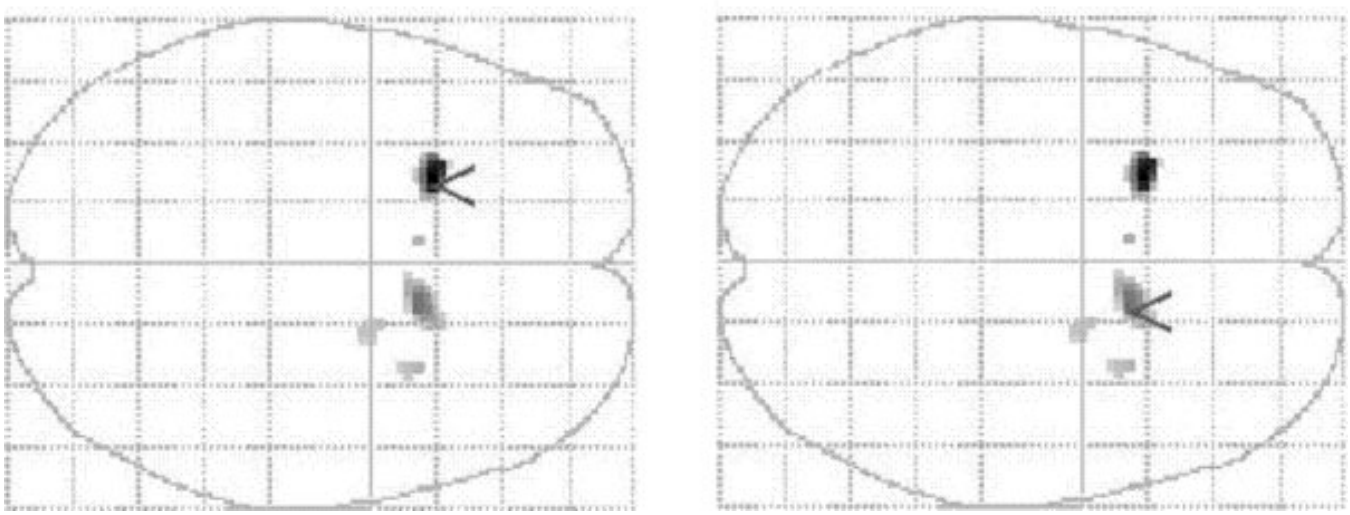

α4α6β2β3
α4α5β2
α6β2β3
DA
α6β2
α4β2
α7
Glu
GABA
α7
other
α4β2*


GABA
GABA
GABA
cholinergic
afferents
α4β2
dopamine
neuron
mGluR2/3
GABA$_B$
D1
α4β2
α7
glutamate
cholinergic
afferents


Corpus callosum
Nigro-striatal projection
Cingulate gyrus
Mesolimbic projection
Septal area
Frontal cortex
Midbrain
Nucleus accumbens
Mesocortical projection
Amygdala
Hippocampus
Cerebellum
2 Ventral tegmental area
Pons
Medulla
1 Substantia nigra



Nicotine invoked dopamine release



The Effect of Nicotine on Striatal Dopamine Release in Man: An [^{11}C]raclopride PET Study

ANDREW J. MONTGOMERY,[1*] ANNE R. LINGFORD-HUGHES,[2] ALICE EGERTON,[1] DAVID J. NUTT,[2] AND PAUL M. GRASBY[1]

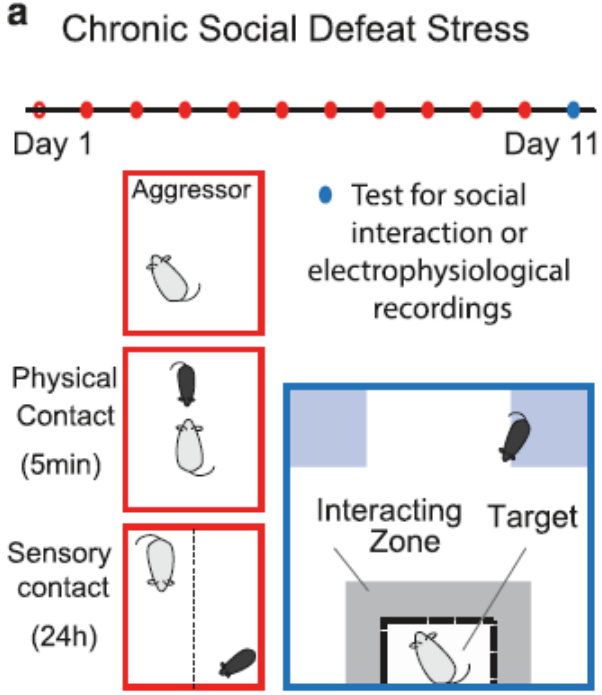
Molecular Psychiatry (2018) 23, 1597–1605
www.nature.com/mp

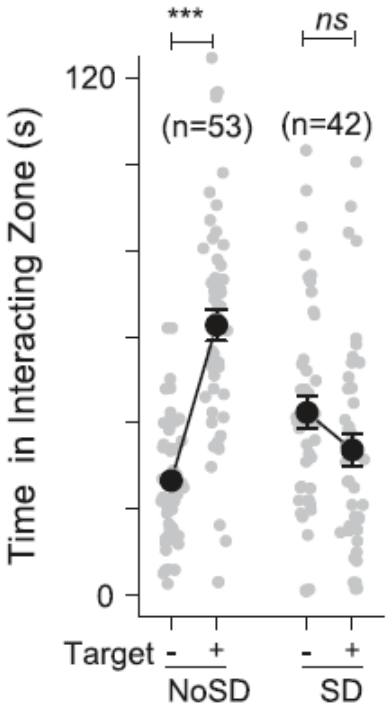
ORIGINAL ARTICLE

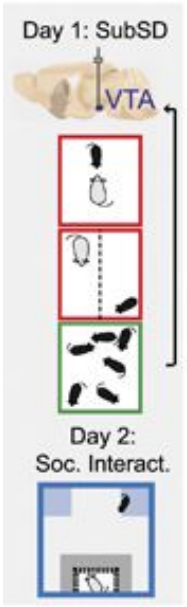
Nicotinic receptors mediate stress-nicotine detrimental interplay via dopamine cells' activity

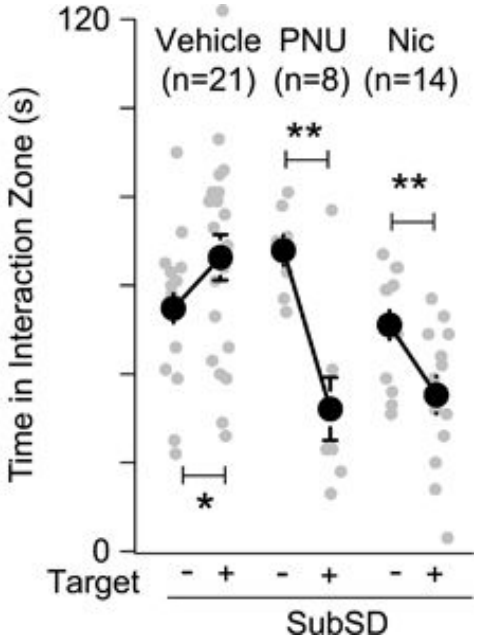
C Morel[1,2,3,4,12], SP Fernandez[5,6,12], F Pantouli[7], FJ Meye[2,8], F Marti[1,2], S Tolu[1,2], S Parnaudeau[2,9], H Marie[5,6], F Tronche[2,9], U Maskos[10], M Moretti[11], C Gotti[11], M-H Han[3,4], A Bailey[7], M Mameli[2,8], J Barik[5,6,12] and P Faure[1,2,12]

"Social Defeat"









Outline

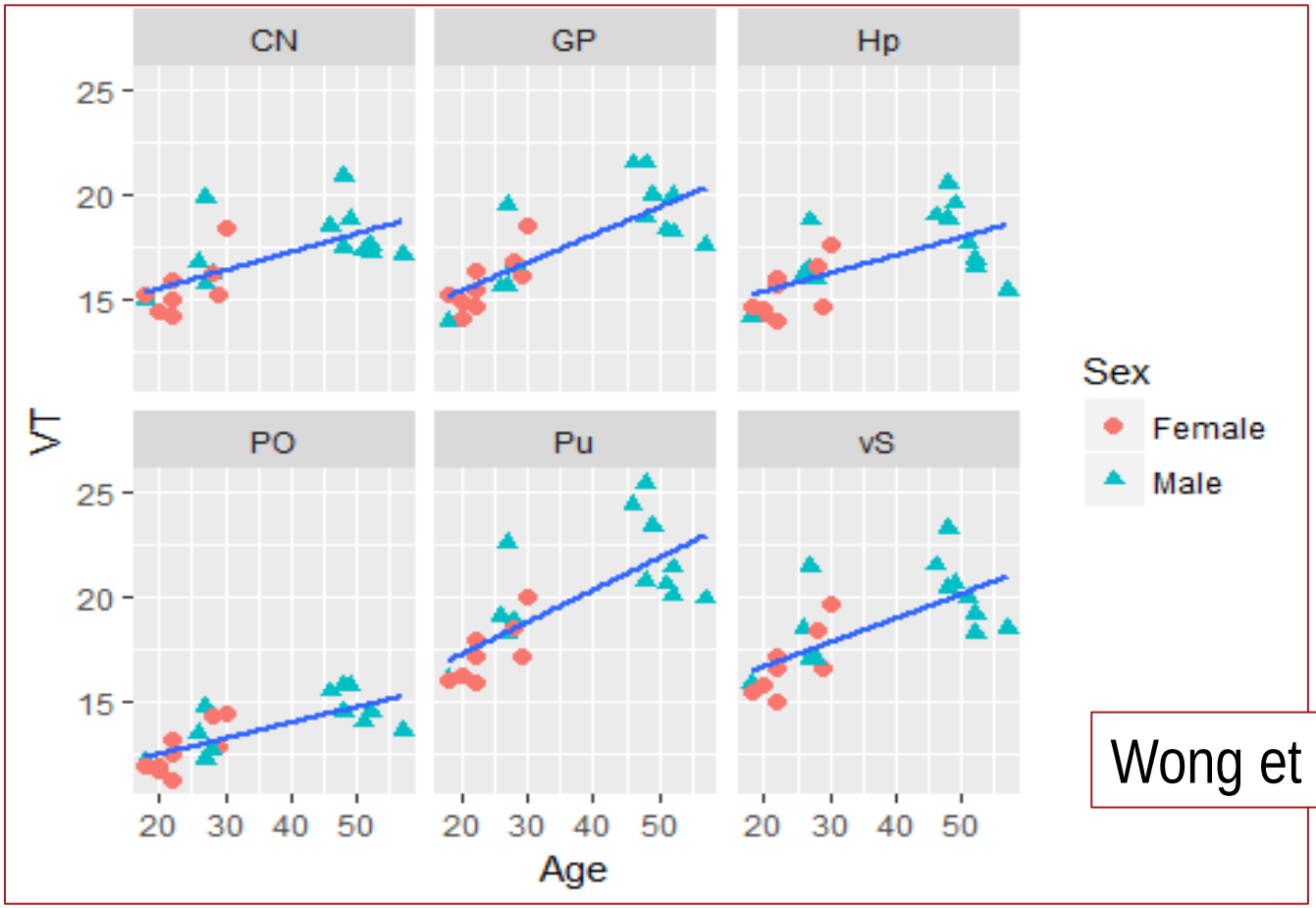
6

Definitions of stress
Brain and motion
Consciousness
Cholinergic neurotransmission
Dopaminergic neurotransmission
From stress to dementia

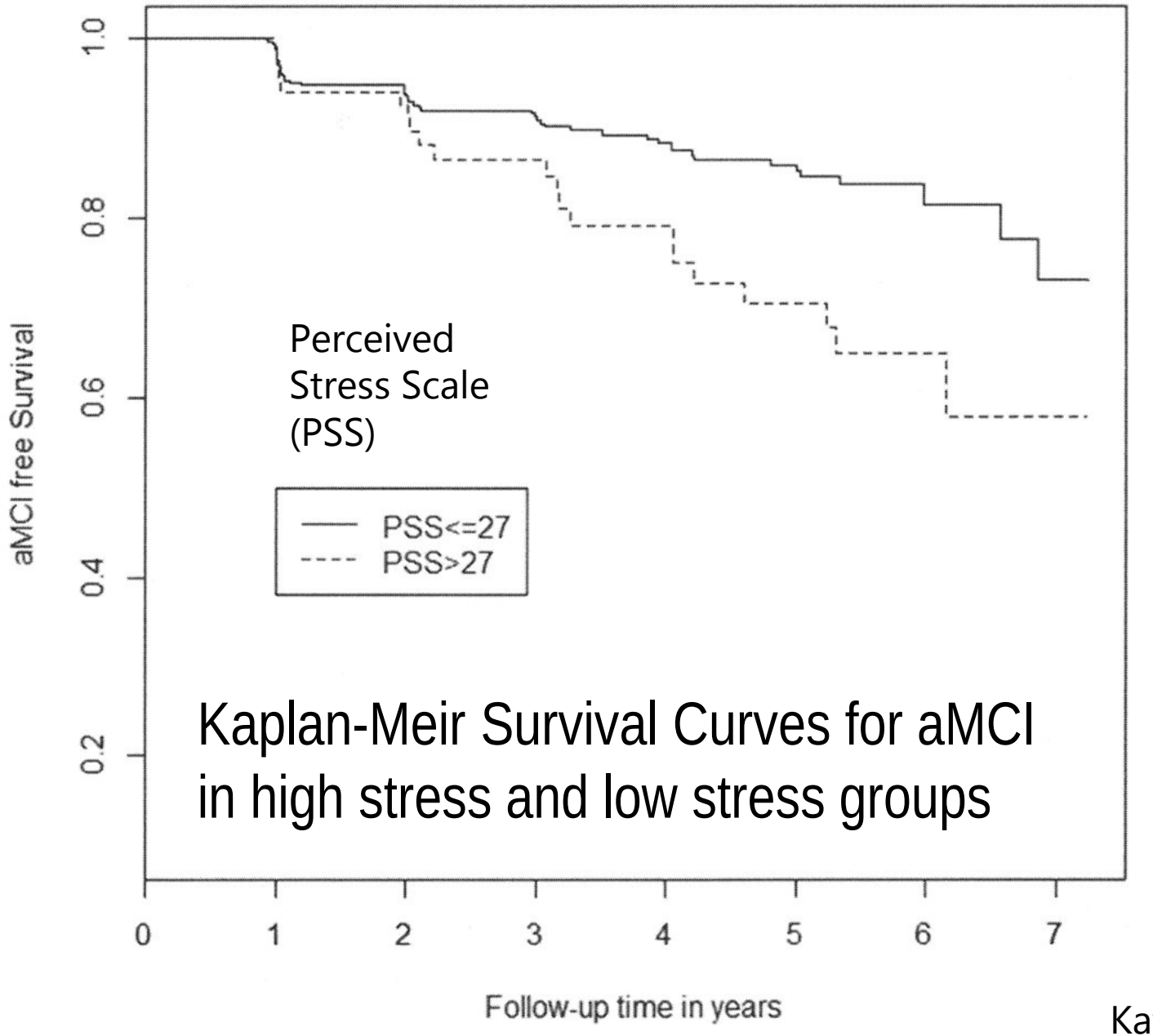
J Neurobiol. 2002 Dec;53(4):641-55.

Nicotinic receptors in aging and dementia. Picciotto MR[1], Zoli M.

Activation of neuronal nicotinic acetylcholine receptors (nAChRs) has been shown to maintain cognitive function following aging or the development of dementia. Nicotine and nicotinic agonists have been shown to improve cognitive function in aged or impaired subjects. Smoking has also been shown in some epidemiological studies to be protective against the development of neurodegenerative diseases.

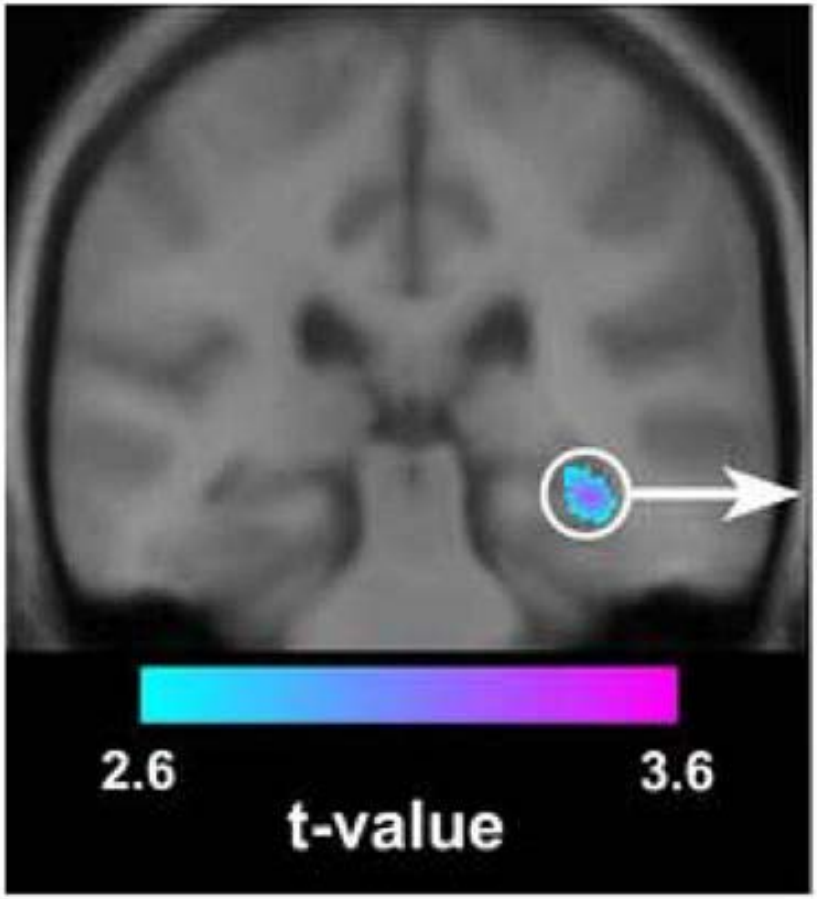


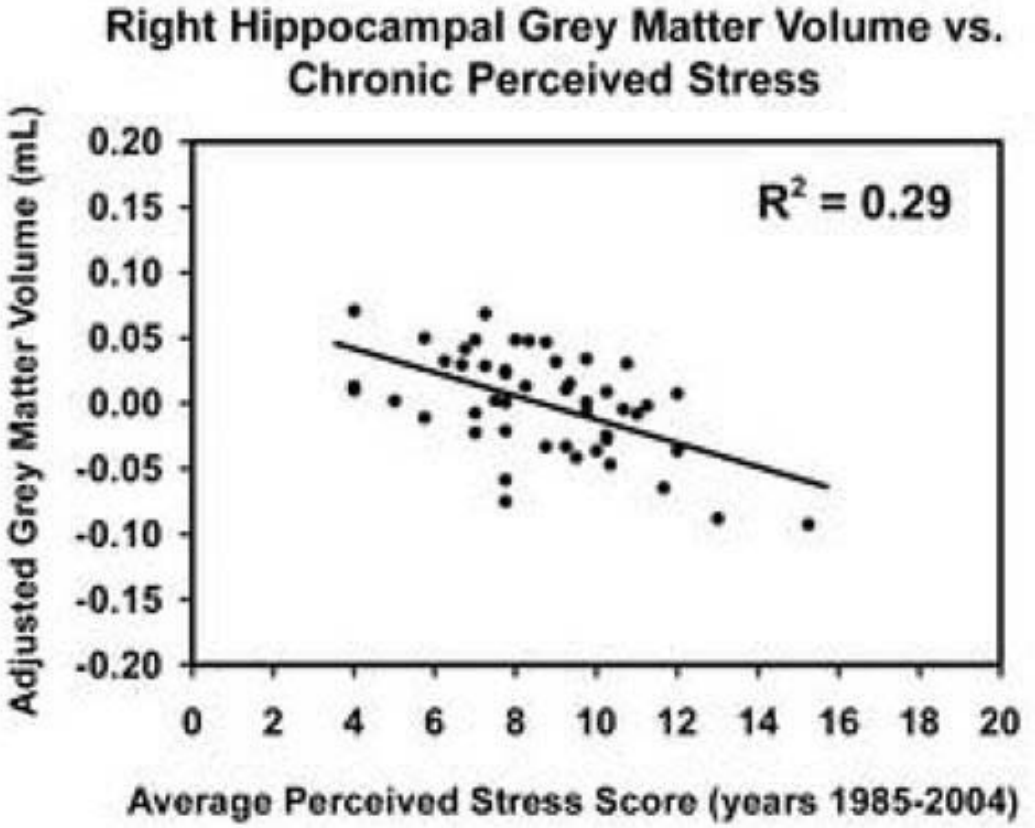
Wong et al. 2018



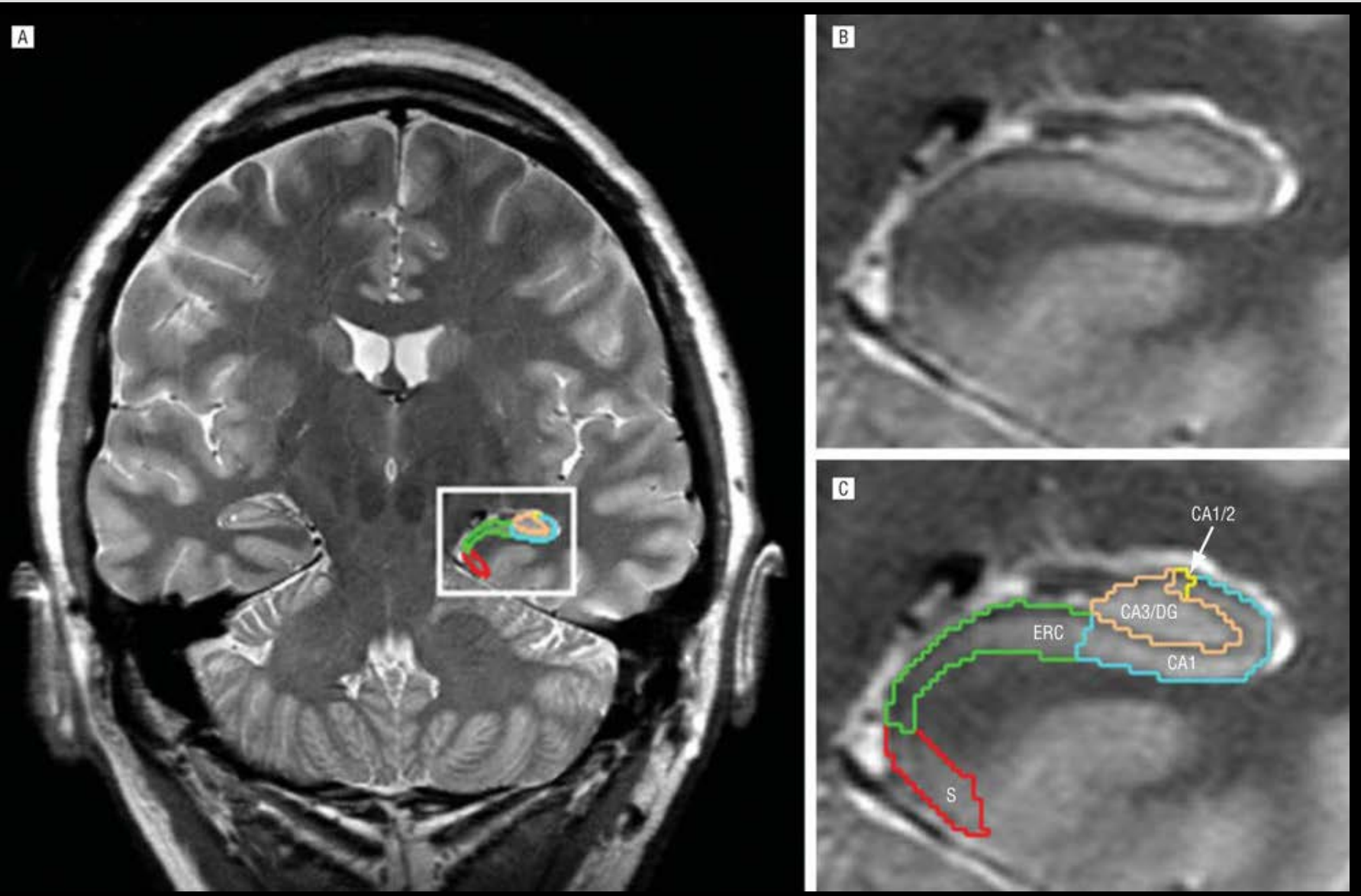
Kaplan-Meir Survival Curves for aMCI in high stress and low stress groups

Katz et al. 2016

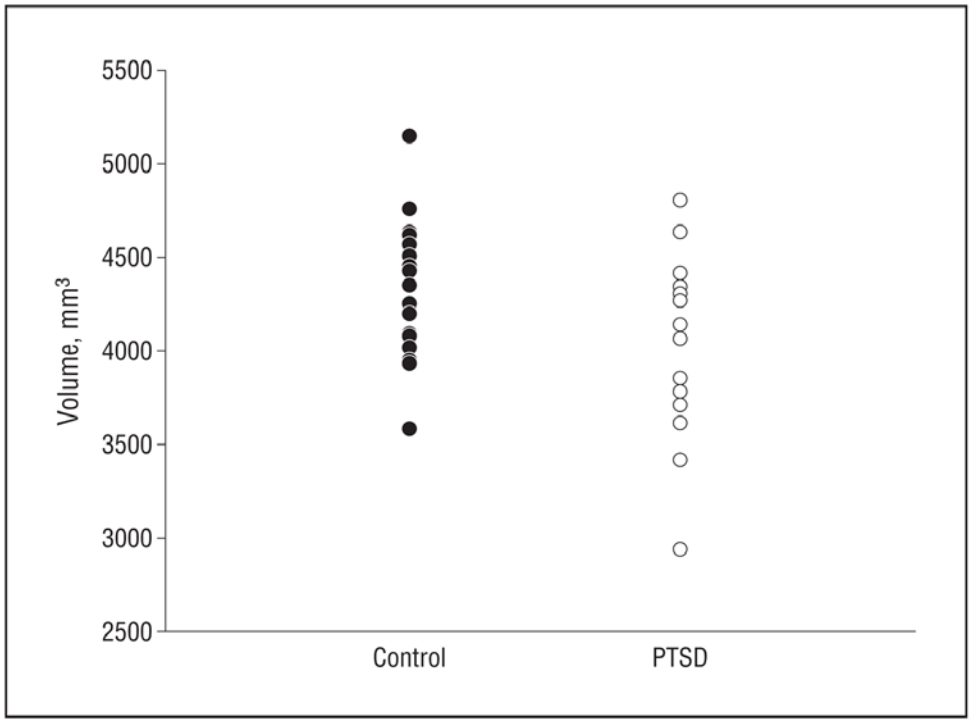


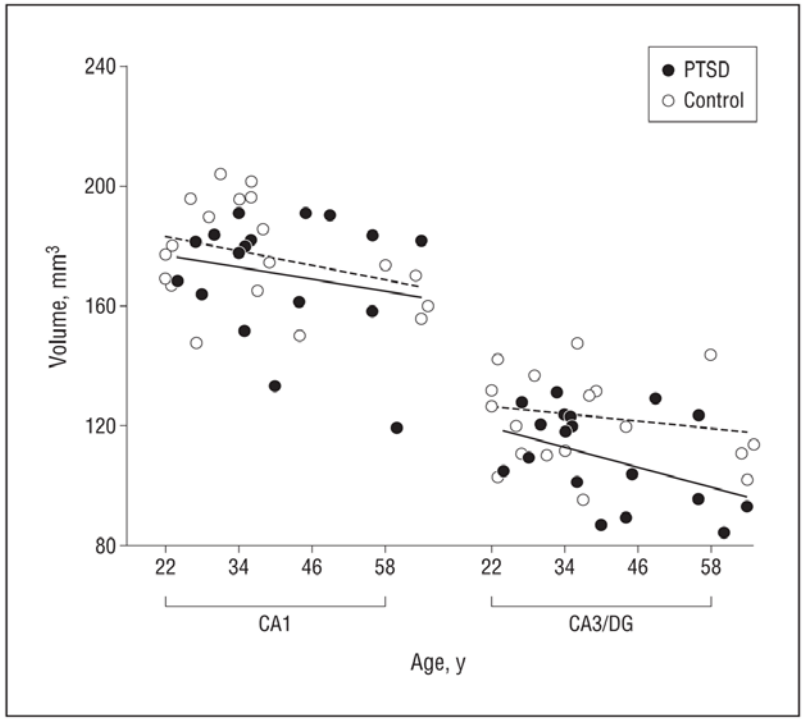


Higher chronic perceived stress among 48 healthy postmenopausal women predicted decreased grey matter volume in the right hippocampus. Left panel: Profiled with color-scaled t-values (legend beneath the coronal image) is a cluster of right hippocampal voxels where chronic perceived stress predicted decreased grey matter volume after controlling for age and total grey matter volume in a region-of-interest analysis. Right panel: Plotted along the y-axis is the grey matter volume from the cluster of hippocampal voxels profiled at left; these volume estimates are adjusted for age and total grey matter volume. Plotted along the x-axis is the average Perceived Stress Scale score from 1985–2004, which was used to define chronic stress (Gianaros et al. 2007).

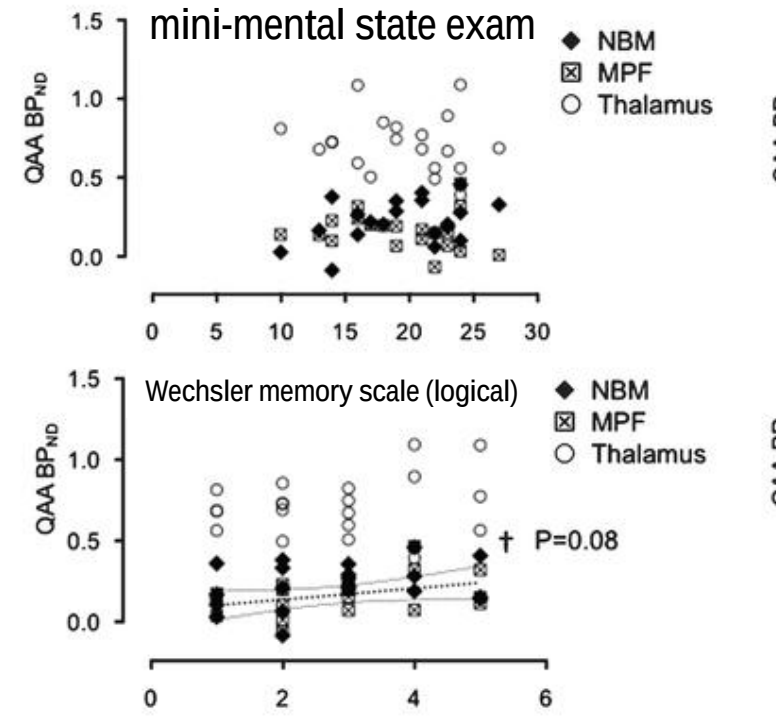


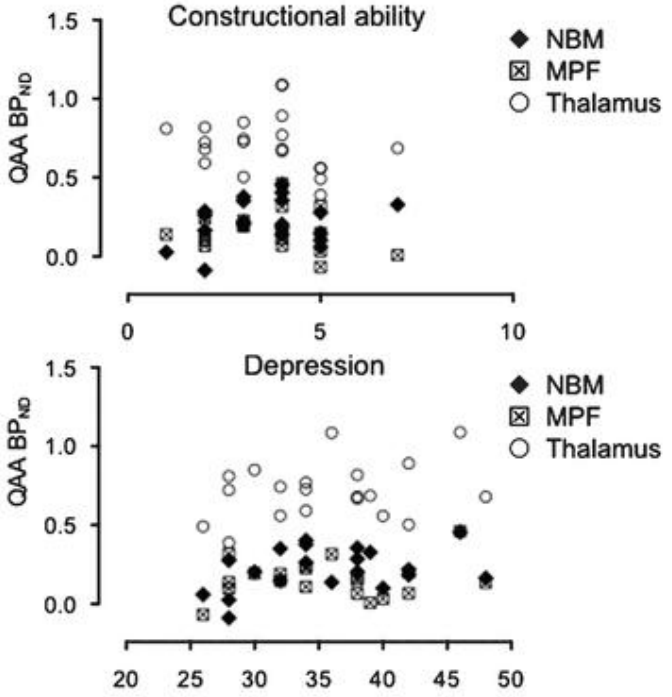
High-resolution magnetic resonance images of the hippocampus. A, A high-resolution (0.4 × 0.5–mm inplane), T2-weighted magnetic resonance image of the brain shows a coronal section through the hippocampus. The zoomed-in image shows a view of the subfields (B) with the tracings in color superimposed (C). CA indicates cornu ammonis; DG, dentate gyrus; ERC, entorhinal cortex; and S, subiculum (Wang et al. 2010).

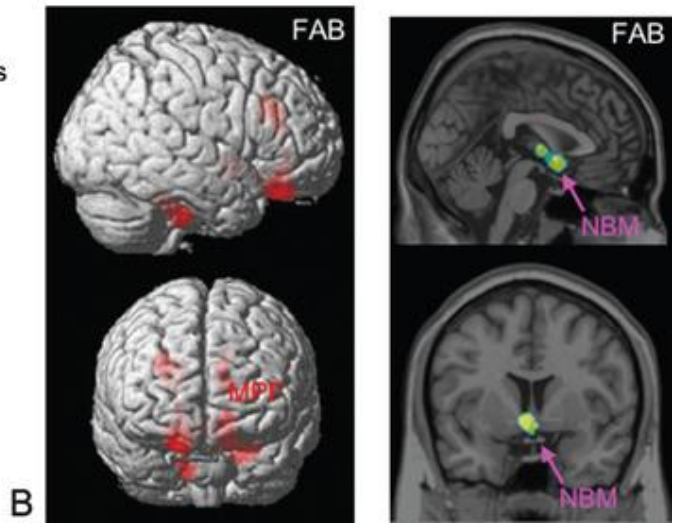




Dissociation between the effects of posttraumatic stress disorder (PTSD) and aging on subfields, separately for cornu ammonis 1 (CA1) and CA3 and the dentate gyrus (CA3/DG). The solid and dashed lines represent regressions of subfield volumes against age by group. This shows a PTSD effect on CA3/DG but not on CA1 after accounting for age.



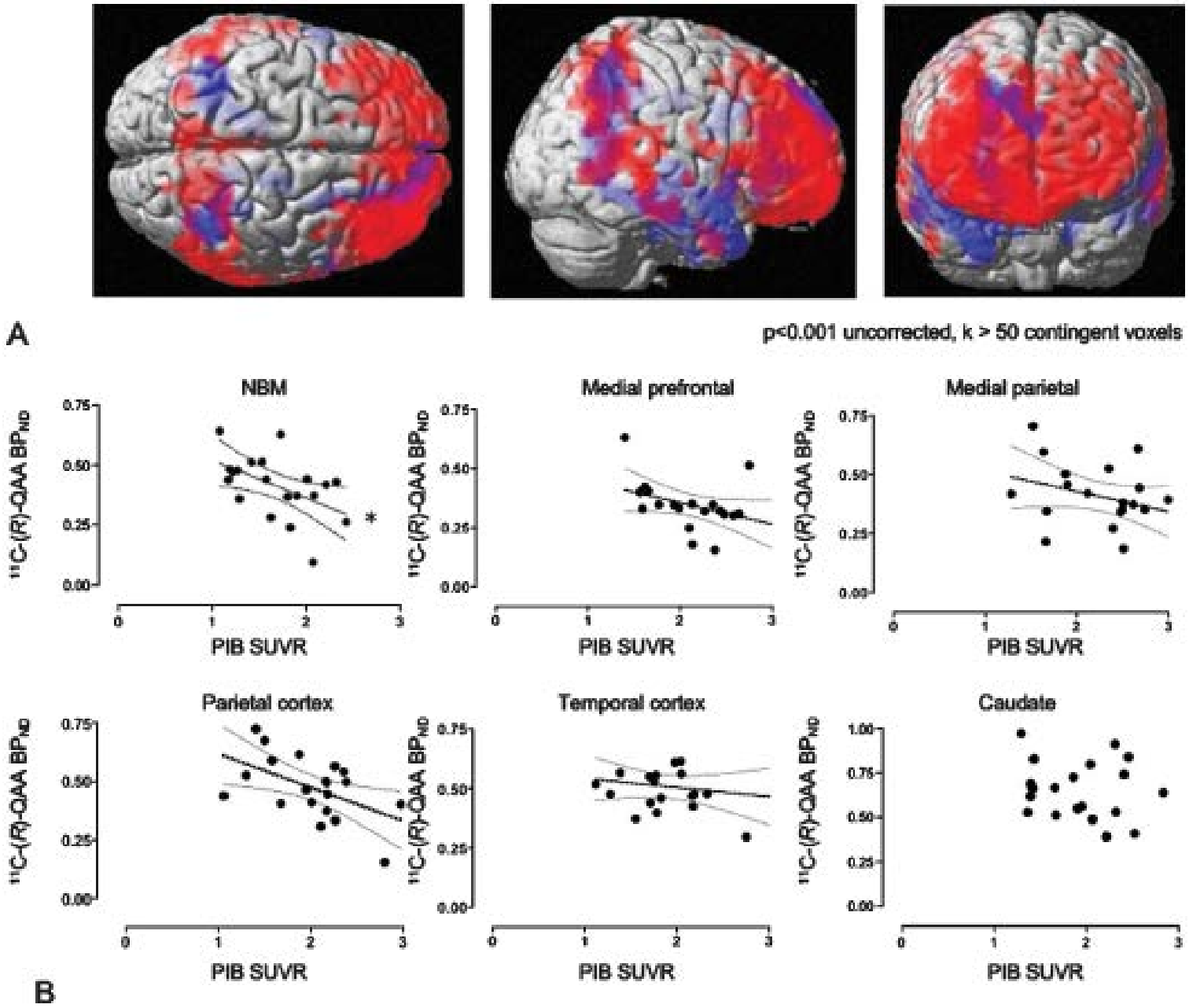




In vivo Depiction of α7 Nicotinic Receptor Loss for Cognitive Decline in Alzheimer's Disease

Nakaizumi, Kyoko
Ouchi, Yasuomi
Terada, Tatsuhiro
Yoshikawa, Etsuji
Kakimoto, Akihiro
Isobe, Takashi
Bunai, Tomoyasu
Yokokura, Masamichi
Suzuki, Katsuaki
Magata, Yasuhiro

Journal of Alzheimer's Disease
vol. 61, no. 4, pp. 1355-1365, 2018

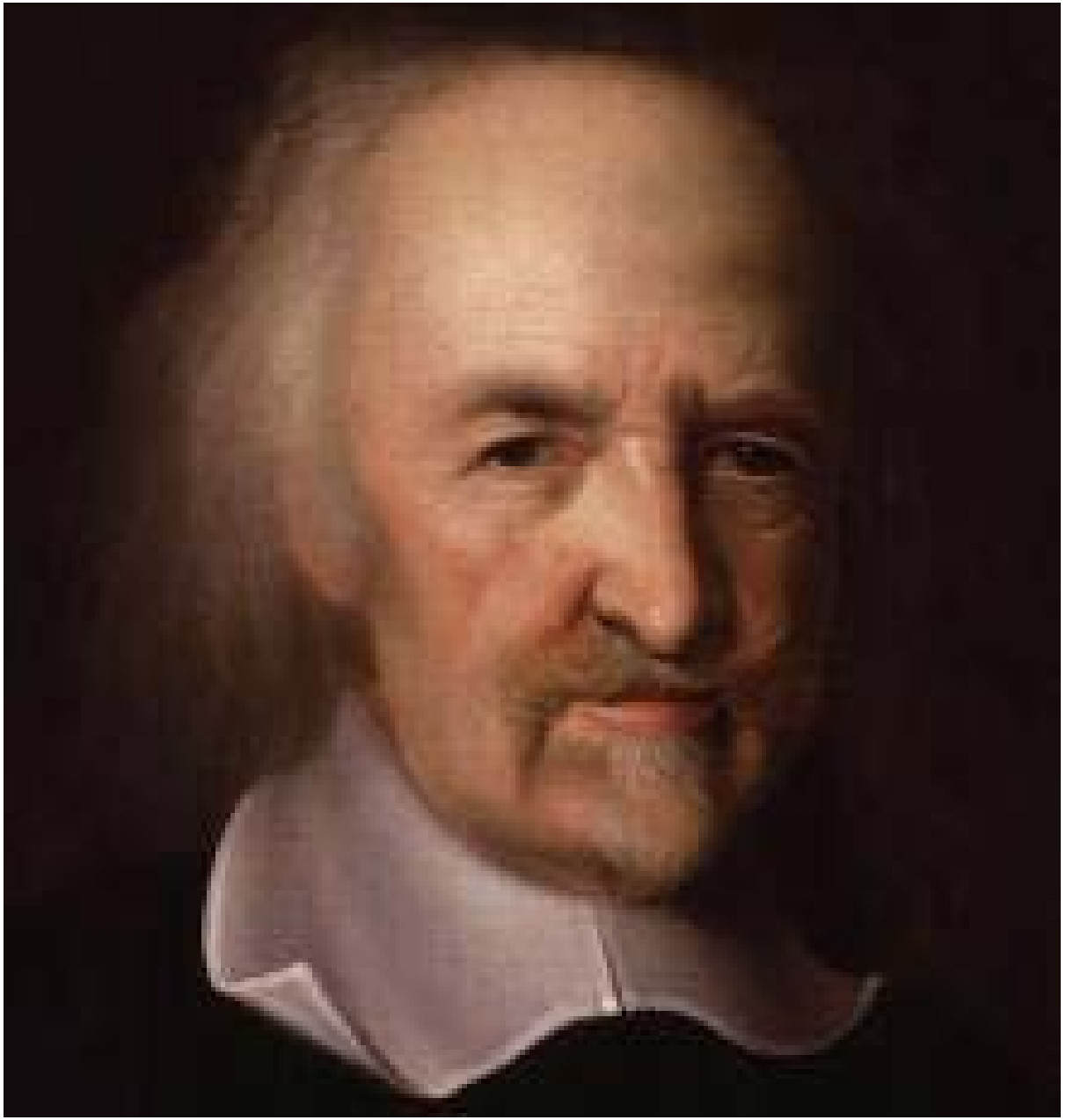

A
p<0.001 uncorrected, k > 50 contingent voxels
NBM
Medial prefrontal
Medial parietal
Parietal cortex
Temporal cortex
Caudate
^{11}C-(R)-QAA BP$_{ND}$
PIB SUVR
B

Conclusions

- Stress is the response of the predictive brain to the need to move the individual into the future.
- The brain prepares multiple possible moves for the individual to choose from.
- Consciousness signifies the cognitive space where memories are recycled for the presentation of future choices to the individual.
- Nicotine influences brain metabolism throughout cerebral cortex, with foci in medial prefrontal cortex, nucleus accumbens, hippocampus, amygdala, and VTA in support of consciousness.
- Nicotinic cholinergic neurotransmission controls encoding and retrieval of memories in medial prefrontal cortex by means of dopaminergic neurotransmission.
- Stress interferes with the preparatory functions of the nicotine-dopamine axis of memory encoding and retrieval during aging.

The Present only has a being in Nature; things Past have a being in the Memory only, but things to come have no being at all; the Future is but a fiction of the mind.

THOMAS HOBBES, Leviathan 1651



Thanks to the co-authors of the selected references:

Wong DF, Kuwabara H, Horti AG, Roberts JM, Nandi A, Cascella N, Brasic J, Weerts EM, Kitzmiller K, Phan JA, Gapasin L, Sawa A, Valentine H, Wand G, Mishra C, George N, McDonald M, Lesniak W, Holt DP, Azad BB, Dannals RF, Kem W, Freedman R, Gjedde A. Brain PET Imaging of α7-nAChR with [18F]ASEM: Reproducibility, Occupancy, Receptor Density, and Changes in Schizophrenia.
Int J Neuropsycho-pharmacol. **2018** Jul 1;21(7):656-667.

Hyder F, Herman P, Bailey CJ, Møller A, Globinsky R, Fulbright RK, Rothman DL, Gjedde A. Uniform distributions of glucose oxidation and oxygen extraction in gray matter of normal human brain: No evidence of regional differences of aerobic glycolysis.
J Cereb Blood Flow Metab. **2016** May;36(5):903-16.

Vafaee MS, Gjedde A, Imamirad N, Vang K, Chakravarty MM, Lerch JP, Cumming P. Smoking normalizes cerebral blood flow and oxygen consumption after 12-hour abstention.
J Cereb Blood Flow Metab. **2015** Mar 31;35(4):699-705.

Vafaee MS, Vang K, Bergersen LH, Gjedde A. Oxygen consumption and blood flow coupling in human motor cortex during intense finger tapping: implication for a role of lactate.
J Cereb Blood Flow Metab. **2012** Oct;32(10):1859-68.

Pedersen JR, Johannsen P, Bak CK, Kofoed B, Saermark K, Gjedde A. Origin of human motor readiness field linked to left middle frontal gyrus by MEG and PET.
Neuroimage. **1998** Aug;8(2):214-20.