

A grayscale image of a human brain, viewed from a slightly elevated perspective, with a red highlight on the left side. The brain is centered in the background of the slide.

# Elements of the BPSE Model: Brain Network Dysfunction

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# Disclosures

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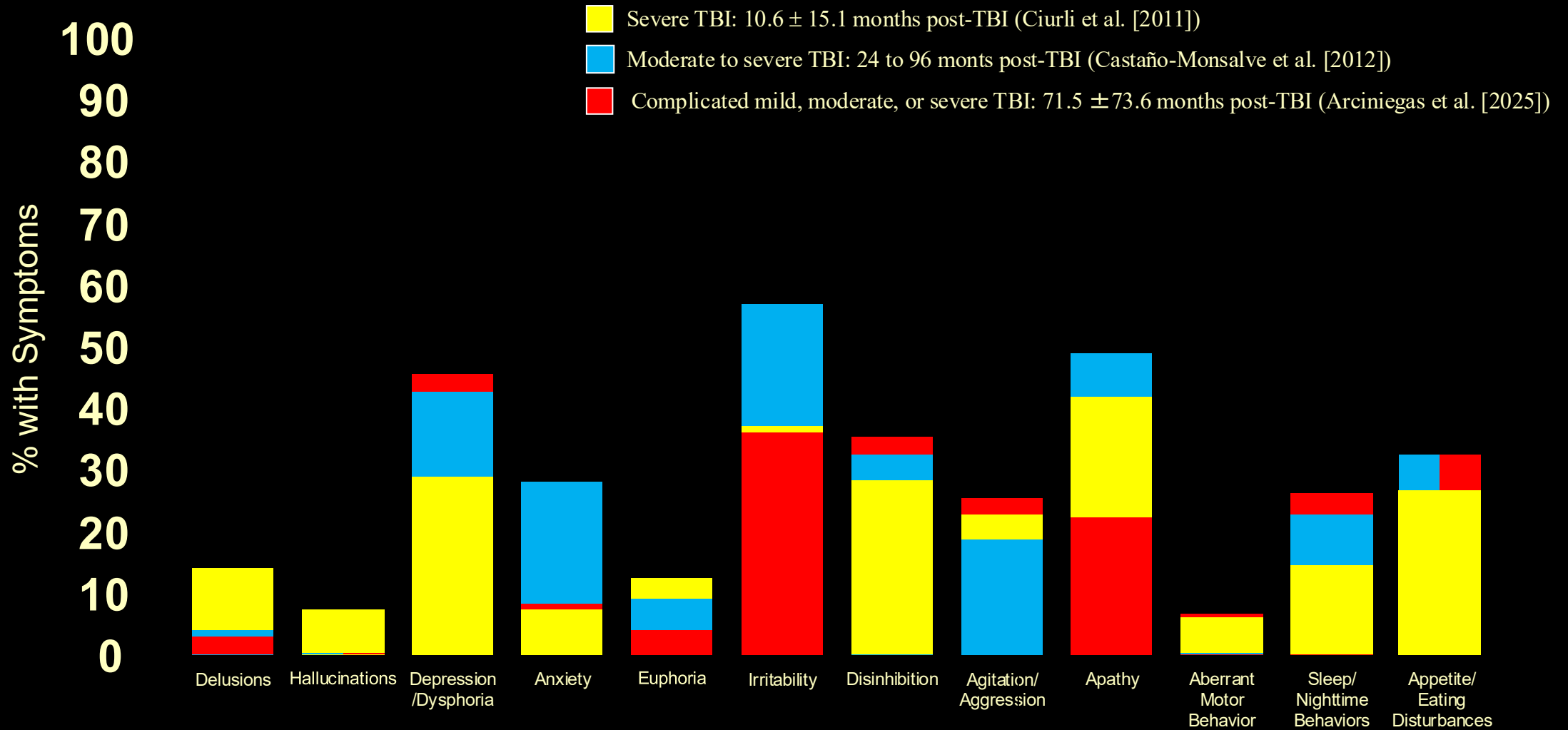
# Disturbances of Emotion and Behavior after TBI

	<b>Acute/Subacute</b>	<b>Chronic</b>
Major depressive episode/disorder	6-50%	26-64%
Anxiety disorders (i.e., GAD, PD, Anxiety disorder NOS)	10-35%	17-27%
Traumatic stress disorders (i.e., ASD vs. PTSD)	up to 14%	17-36%*
Secondary mania (not bipolar disorder)	1-8%	<<1%
Pathological laughing and crying	5-11%	up to 11%
Affective lability (aka “pseudobulbar affect”)	33-46%	14-62%
Irritability	35-71%	35-61%
Disinhibition	up to 48%	12-34%
Aggression	30-80%	15-51% (avg. 20%)

(Reviewed in Jorge RE, Arciniegas DB. Mood disorders after traumatic brain injury. *Psychiatric Clinics of North America* 37(1):13-29, 2014; Arciniegas DB, Wortzel HS. Emotional and behavioral dyscontrol after traumatic brain injury. *Psychiatric Clinics of North America* 37(1):31-53, 2014; Arciniegas DB, Wortzel HS. Emotional Dyscontrol. In Silver JM, McAllister TW, Arciniegas DB. *Textbook of Traumatic Brain Injury, Third Edition*. Washington DC, American Psychiatric Association Publishing, Inc., 2019, pp. 347-360; Wortzel HS, Silver JM. Behavioral Dyscontrol. In Silver JM, McAllister TW, Arciniegas DB. *Textbook of Traumatic Brain Injury, Third Edition*. Washington DC, American Psychiatric Association Publishing, Inc., 2019, pp. 395-411. \*Reported frequencies of PTSD in military and veteran populations are often higher than in civilian populations, approaching 50%.)



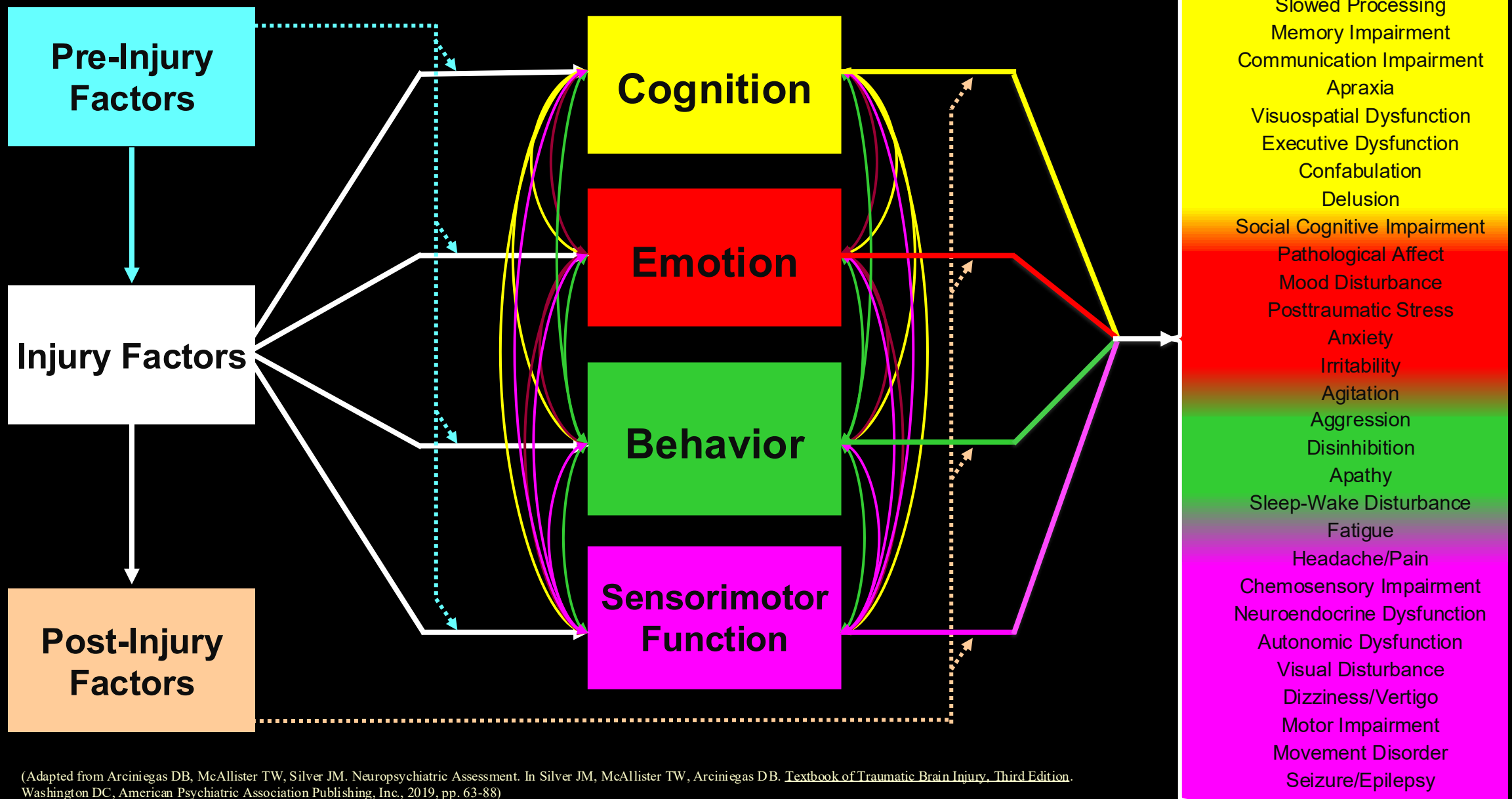
# Neuropsychiatric Symptoms in TBI



(Castano Monsalve B, Bernabeu Guitart M, Lopez R, Bulbena Vilassar A, Ignacio Quemada J. Psychopathological evaluation of traumatic brain injury patients with the Neuropsychiatric Inventory. Rev Psiquiatr Salud Ment. 2012;5(3):160-166; Ciurli P, Formisano R, Bivona U, Cantagallo A, Angelelli P. Neuropsychiatric disorders in persons with severe traumatic brain injury: prevalence, phenomenology, and relationship with demographic, clinical, and functional features. J Head Trauma Rehabil. 2011 Mar-Apr;26(2):116-26; Arciniegas DB, Almeida EJ, Sander AM, Bogaards JA, Giacino GT, Hammond FM, Harrison-Felix CL, Hart T, Ketchum JM, Mellick DC, Sherer M, Whyte J, Zafonte RD. Multicenter Evaluation of Memory Remediation in Traumatic Brain Injury with Donepezil: A Randomized Controlled Trial. Journal of Neuropsychiatry and Clinical Neurosciences 2025;37(2):102-114)



# Factors Influencing Neuropsychiatric Outcome after Traumatic Brain Injury (NBPSE Framework)



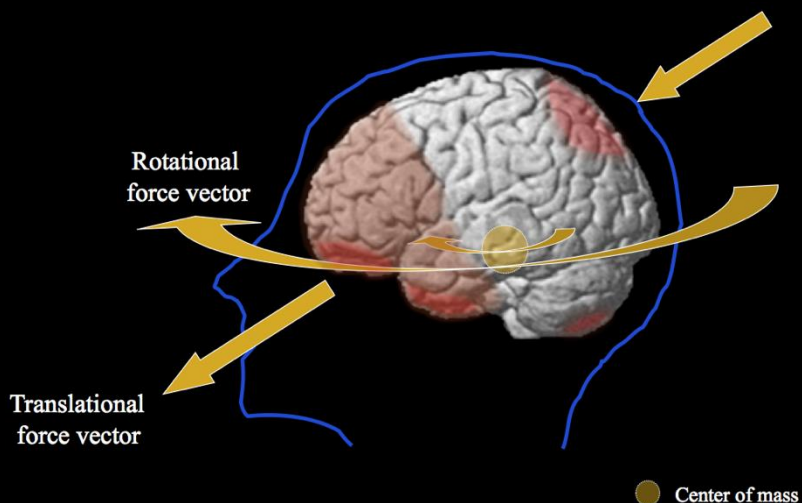
(Adapted from Arciniegas DB, McAllister TW, Silver JM. Neuropsychiatric Assessment. In Silver JM, McAllister TW, Arciniegas DB. *Textbook of Traumatic Brain Injury*. Third Edition. Washington DC, American Psychiatric Association Publishing, Inc., 2019, pp. 63-88)



# Structural and Functional Neuroanatomy of Traumatic Brain Injury

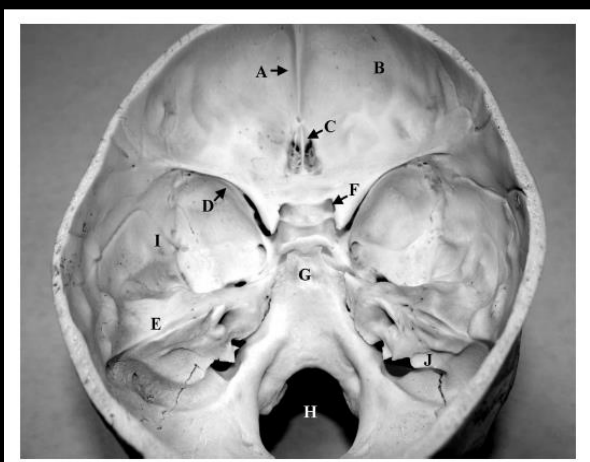
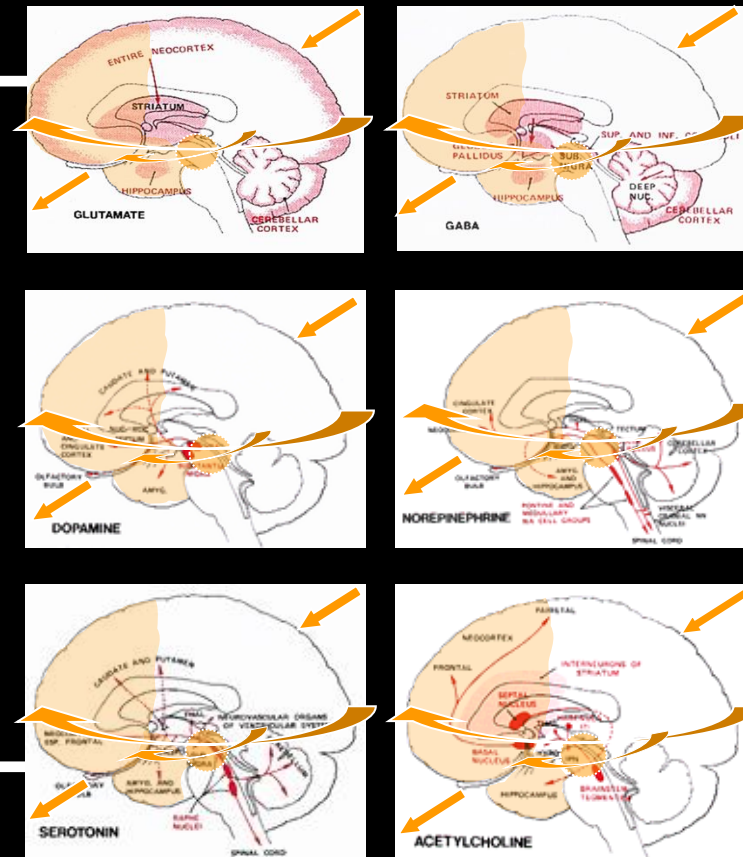
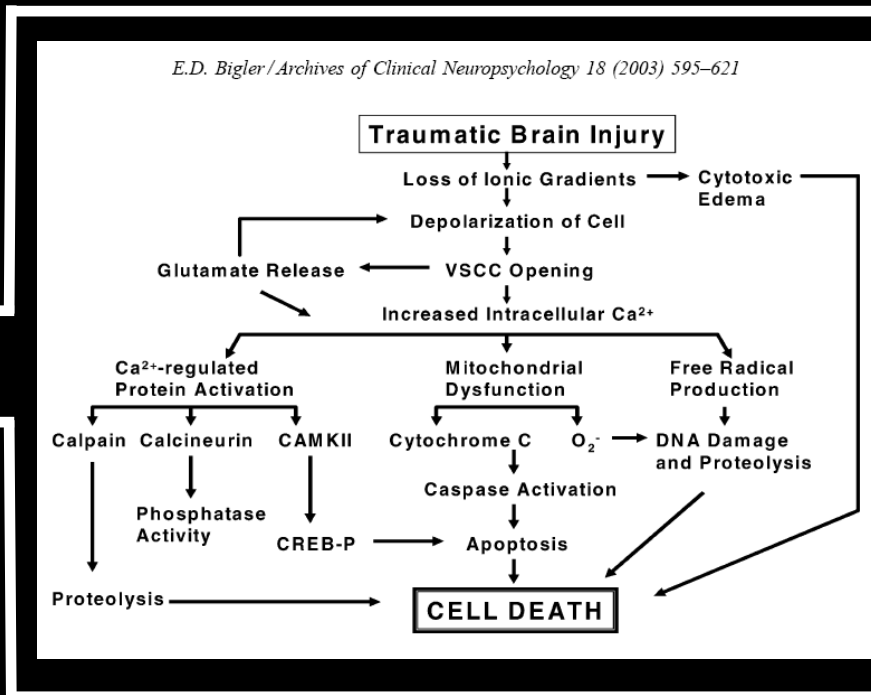


## Inertial Forces: Translation, Rotation, and Angular Acceleration Forces



(Adapted from Arciniegas DB, Beresford TP: Neuropsychiatry: An Introductory Approach. Cambridge University Press, Cambridge 2001)

## Cytotoxic Cascade

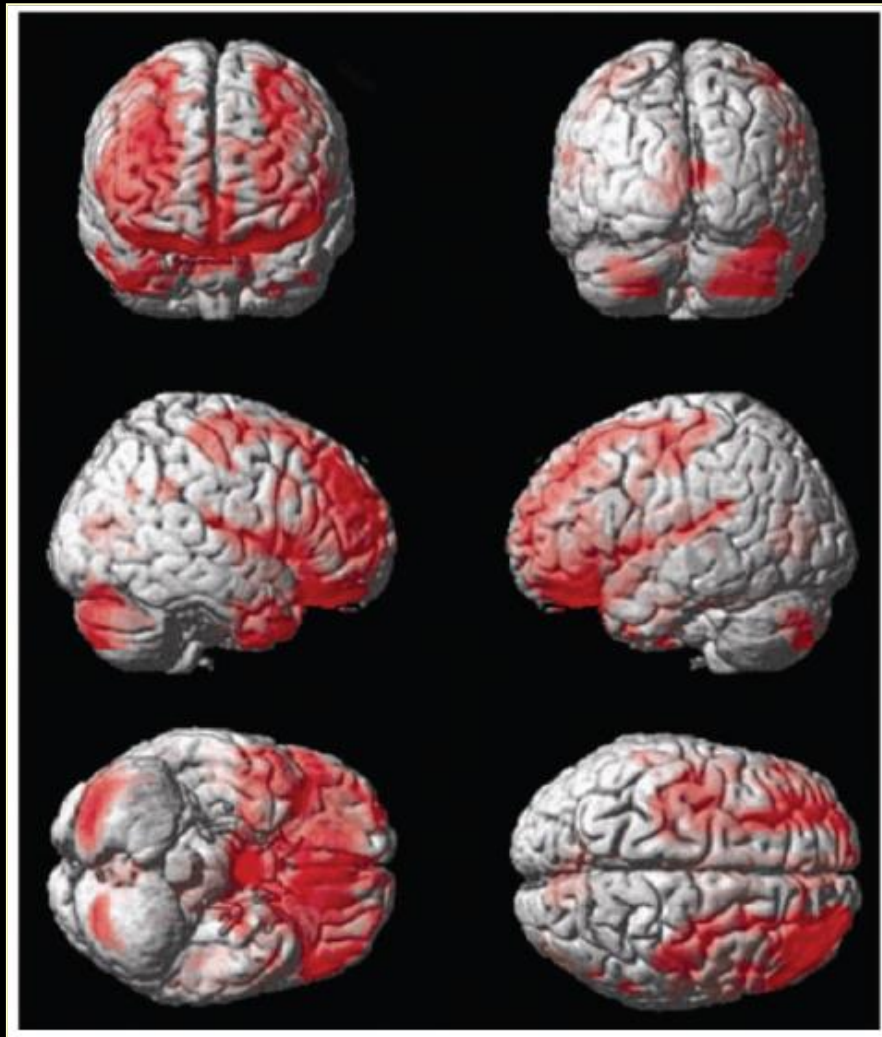


*E.D. Bigler / Archives of Clinical Neuropsychology 18 (2003) 595-621*

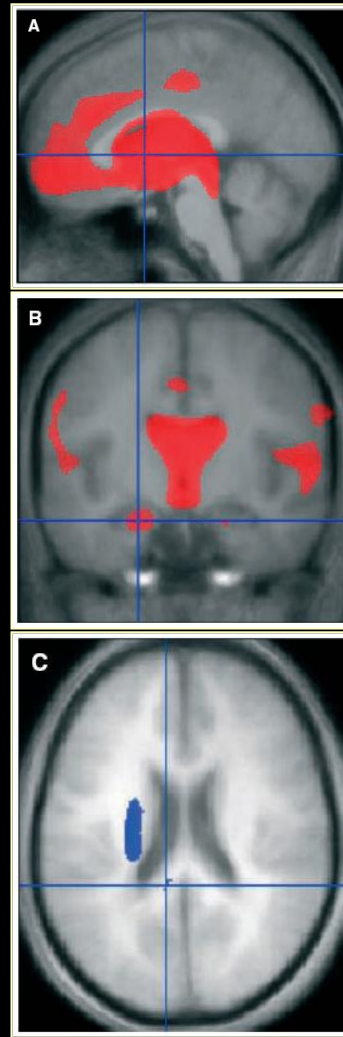
## Contact Forces

Adapted from Gilman S, Newman SW: Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology. FA Davis Co., Philadelphia, 1987.  
Biomechanical force illustrations adapted from Arciniegas DB, Beresford TP: Neuropsychiatry: An Introductory Approach. Cambridge University Press, Cambridge, 2001.  
Markianos et al. 1996; McIntosh et al. 1999; Kerr et al. 2003; reviewed in Arciniegas and McAllister 2008

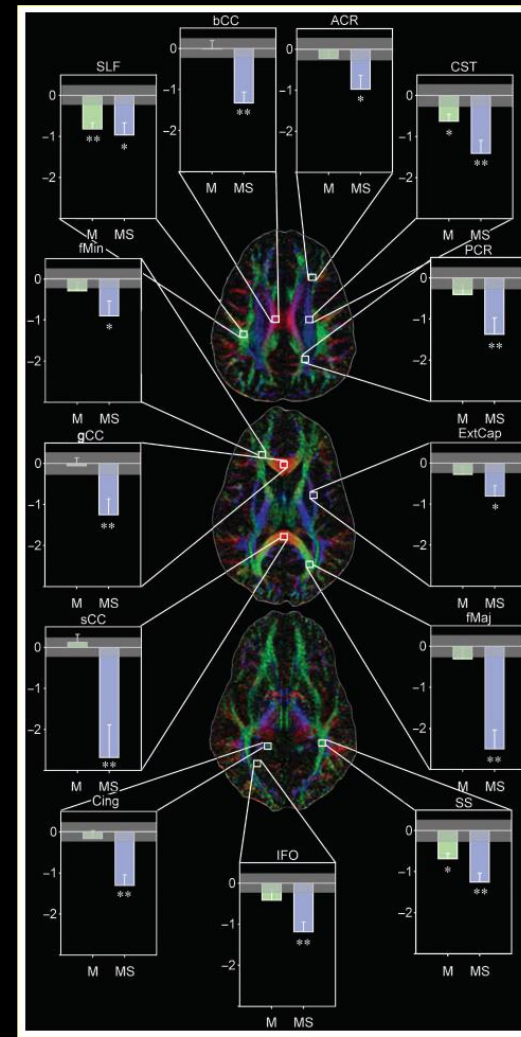
# Regional Vulnerability to TBI



Yeates et al.: Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. *Psychol Bull.* 2007 May;133(3):535-56.



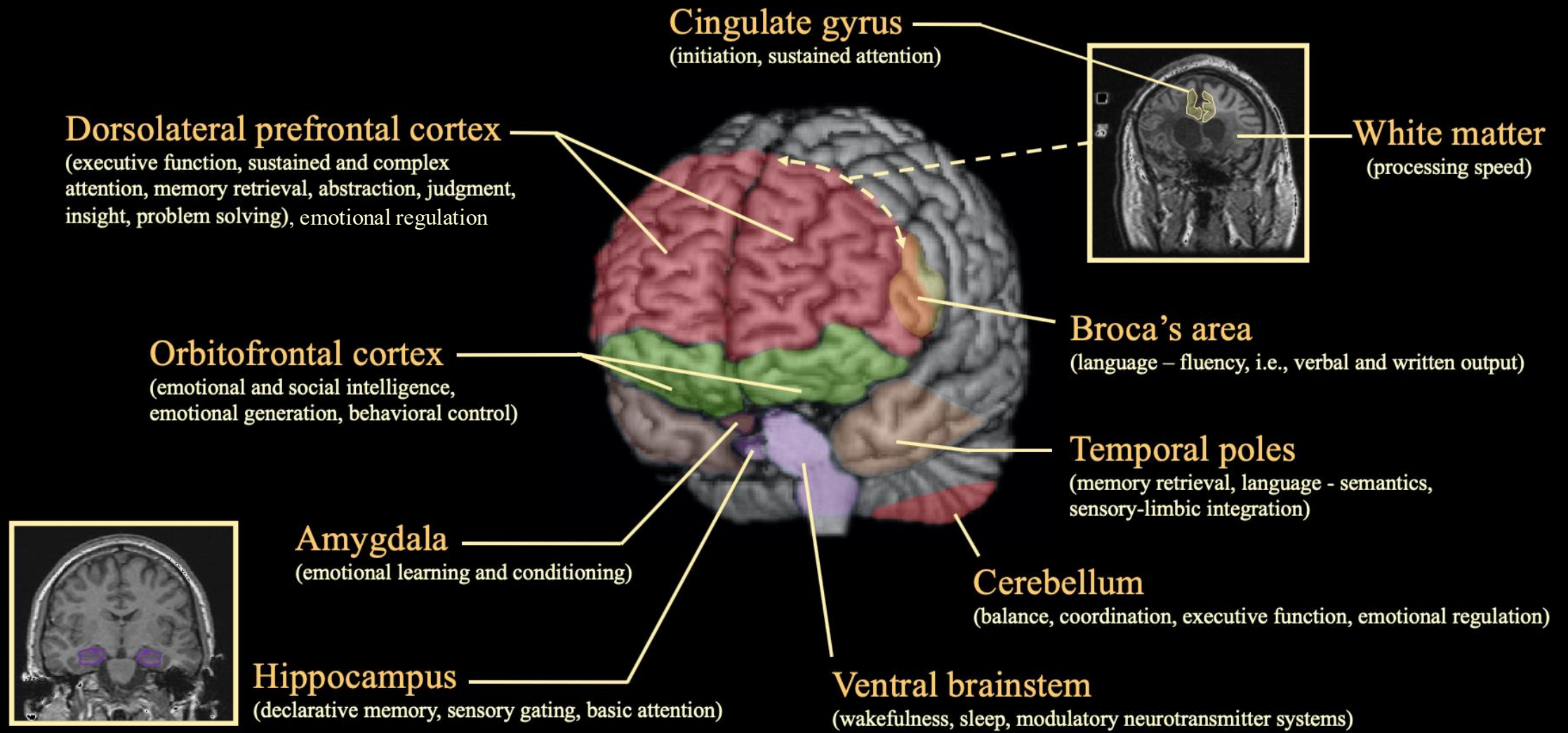
Salmond et al.: Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. *Brain.* 2005 Jan;128(Pt 1):189-200.



Kraus et al.: White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain.* 2007 Oct;130(Pt 10):2508-19.

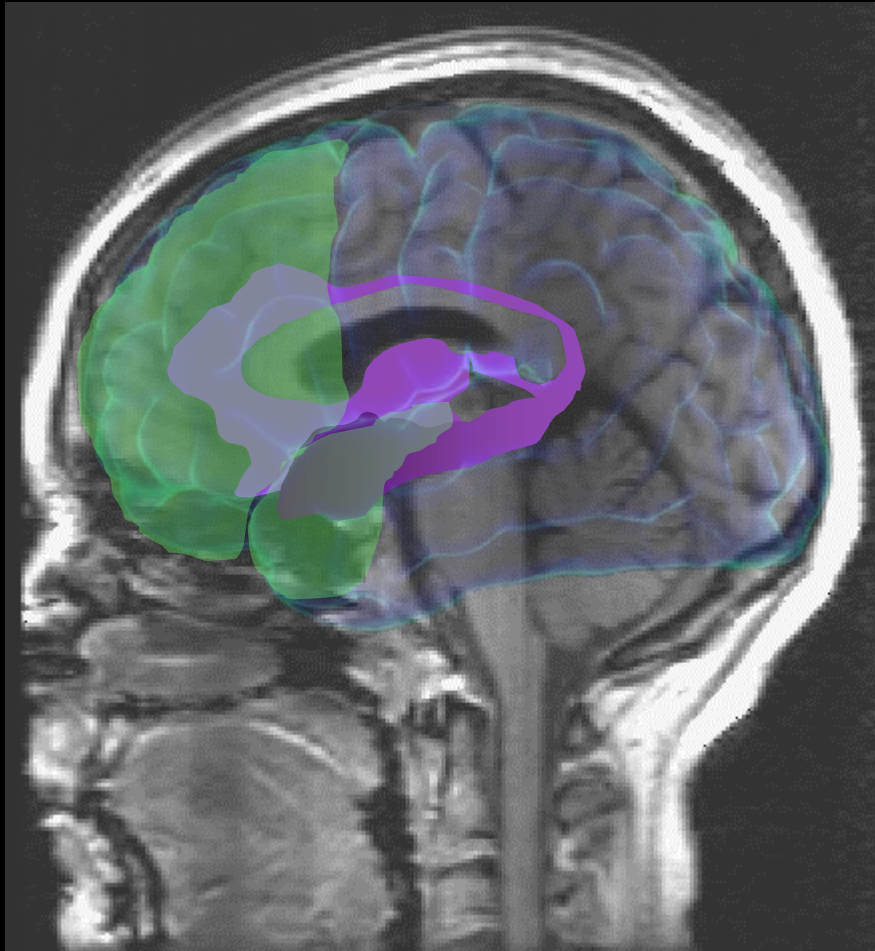


# Regional Vulnerability to TBI: Brain-Behavior Relationships





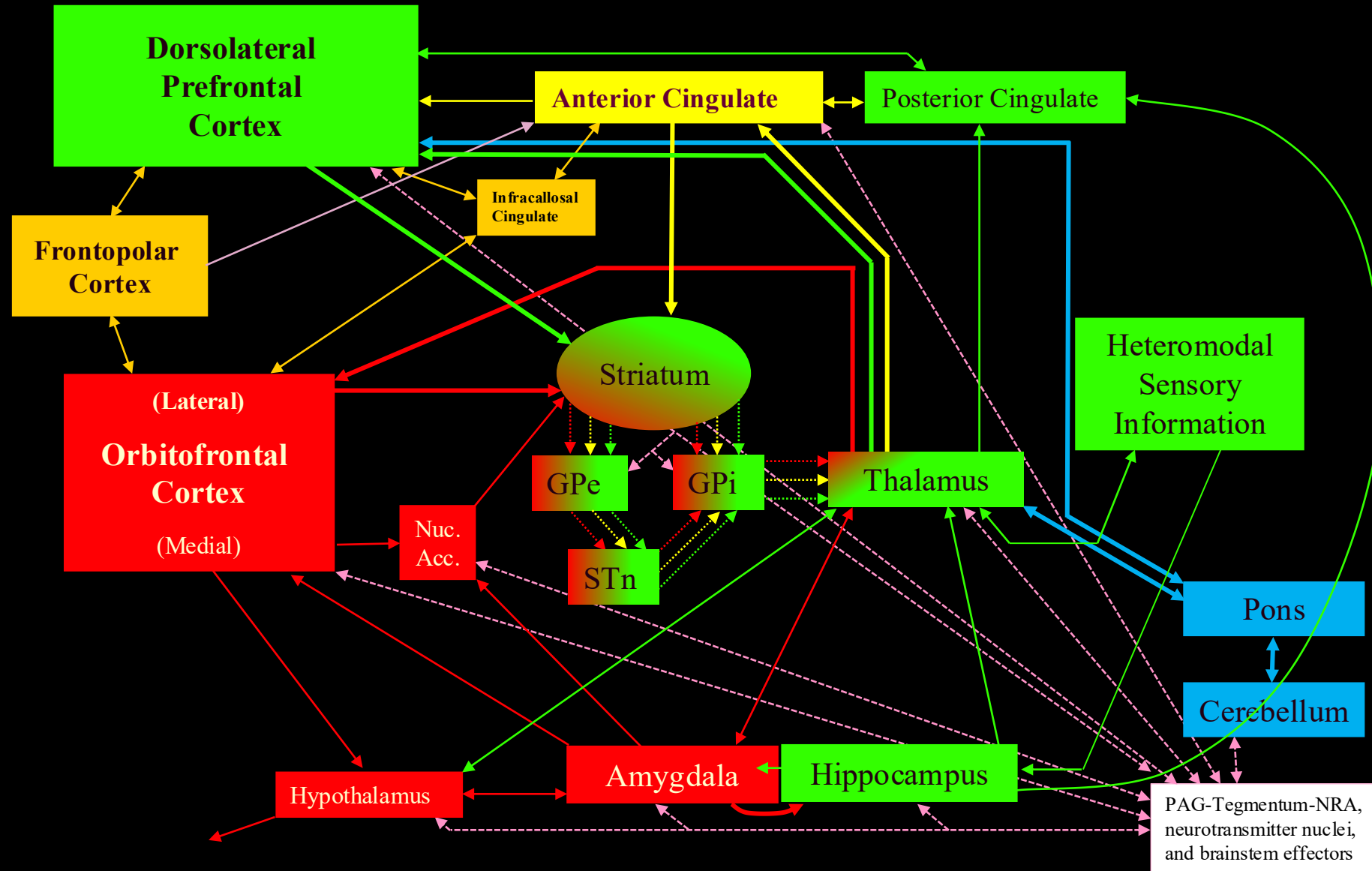
# Structural and Functional Neuroanatomy of Emotion and Emotion-Related Behaviors



- At its core, the core of the limbic system is a ring (fr. Latin, ‘limbus’) of structures on the medial aspect of each hemisphere
- Although sometimes referred to as a ‘lobe’ of the brain, the limbic system is more correctly understood as a network of structures comprised by neocortical areas, diencephalic structures, and midbrain elements
  - amygdala
  - entorhinal-hippocampal complex
  - other medial temporal gyri
  - nucleus accumbens
  - ventral striatum
  - infracallosal and anterior cingulate cortex
  - thalamus (dorsal and anteromedial)
  - hypothalamus
  - limbic midbrain area
- Dorsal, especially prefrontal systems, regulate these systems



# Networks Subserving Emotional Generation, Expression, Experience, and Regulation





# Emotion, Behavior, and TBI: Overlapping Neuroanatomies

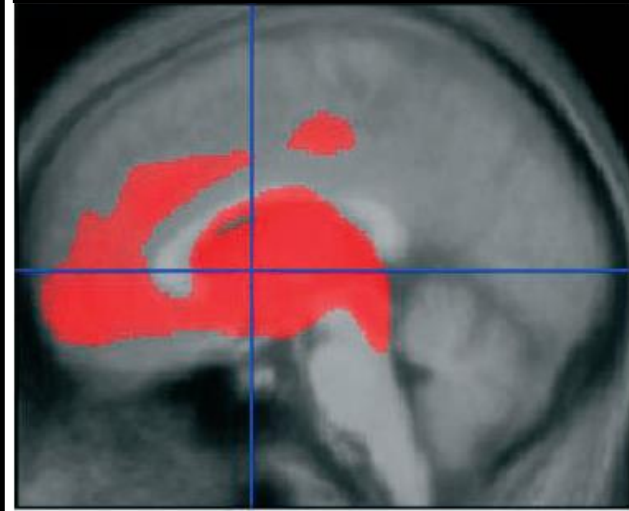
Limbic and paralimbic areas involved in the generation and expression of emotion and behavior

(Purves et al. 2001)



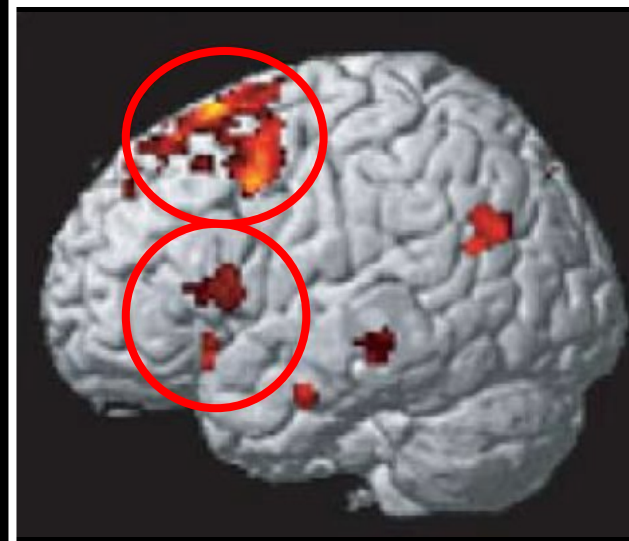
Limbic and paralimbic areas with gray matter volume reductions after moderate-to-severe TBI

(Salmond et al. 2005)



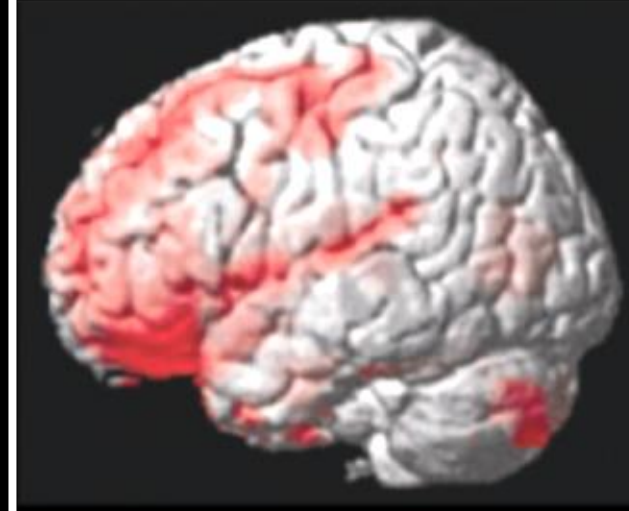
Dorsolateral and inferolateral prefrontal cortices involved in the regulation of emotion and behavior

(Ochsner and Gross 2005)



Dorsolateral, inferolateral, and anterior prefrontal cortices, anterior temporal, and cerebellar areas with gray matter volume reductions after TBI

(Yeates et al. 2007)

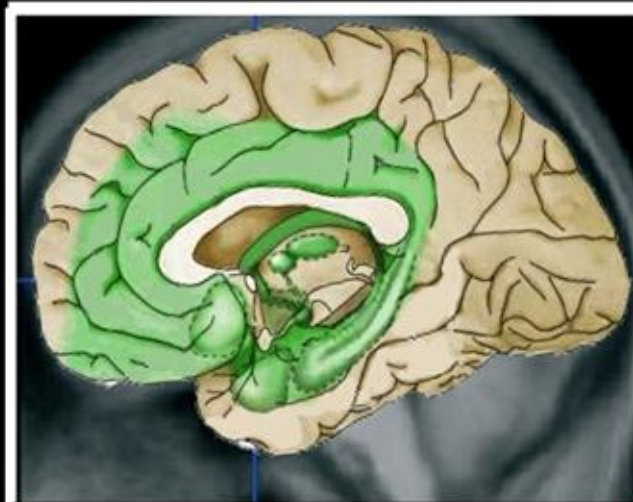




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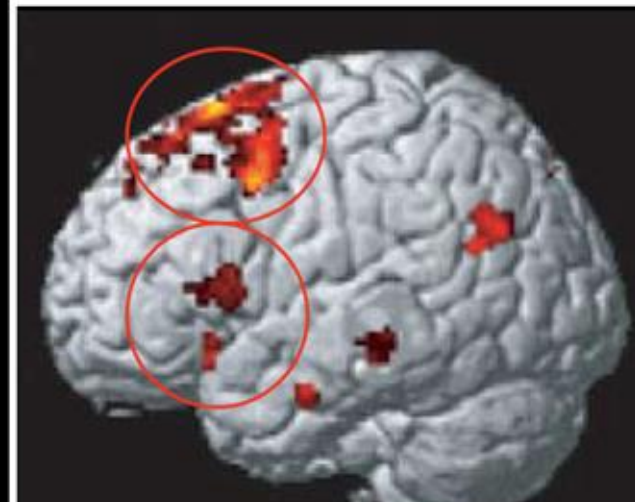
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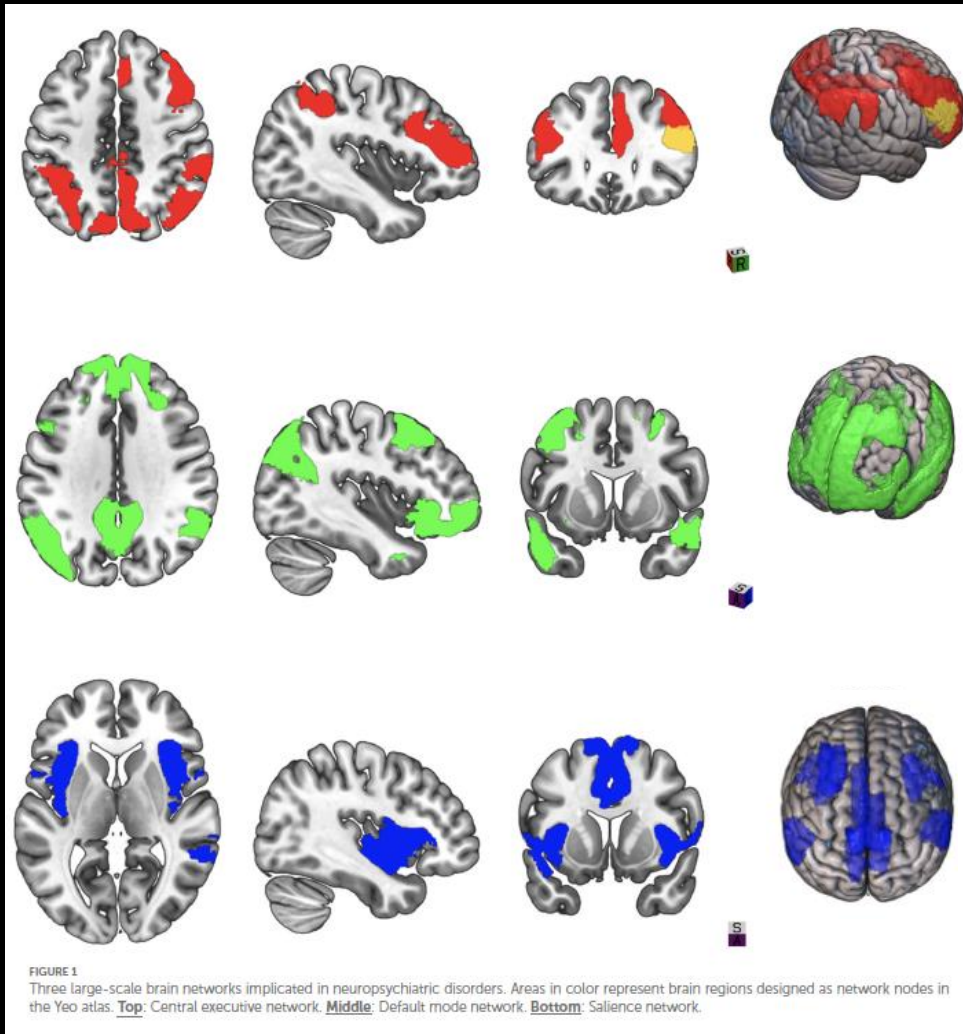




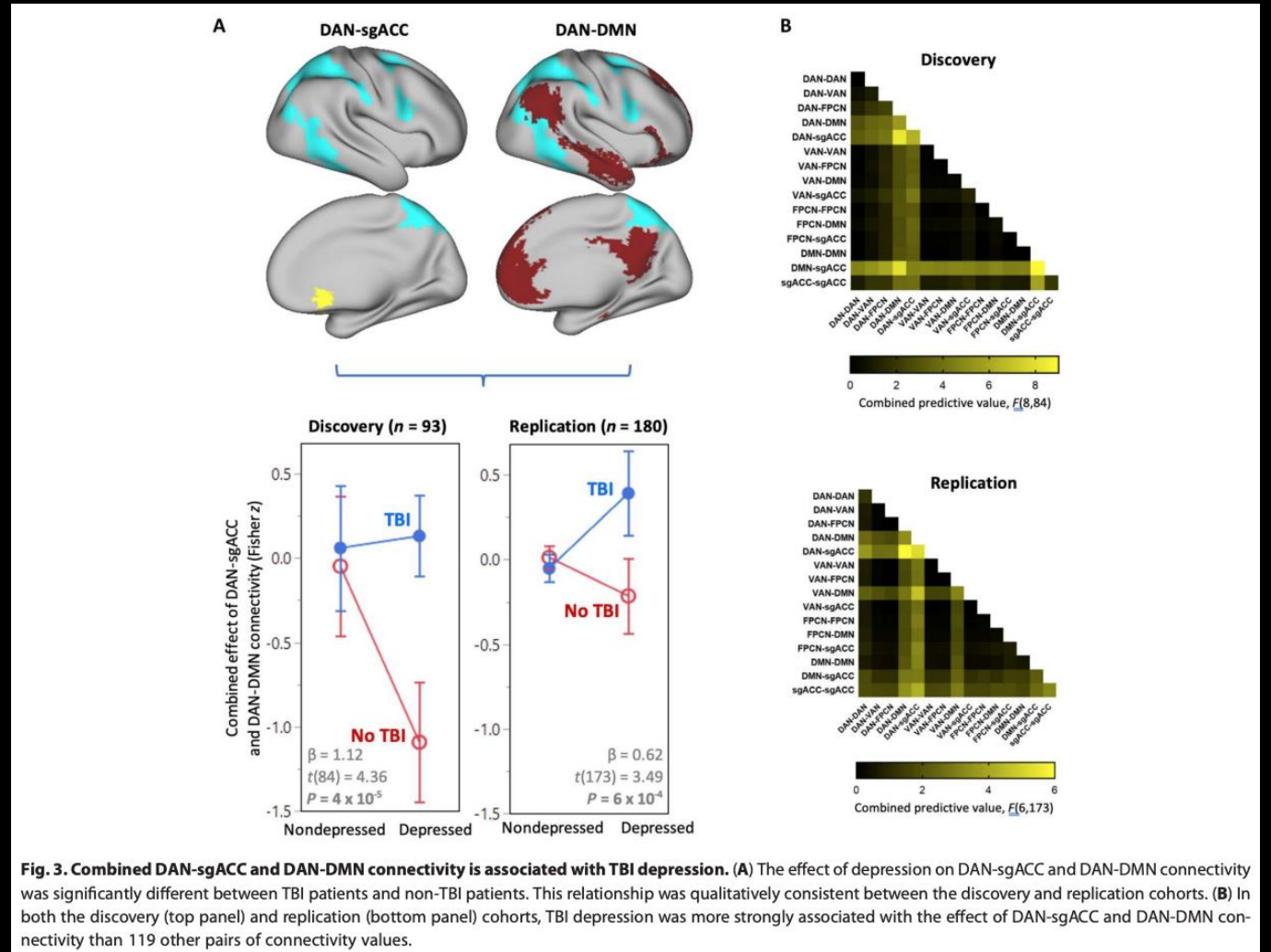
# Network Alterations in Neuropsychiatric Conditions after TBI

	Structural and Functional Neuroanatomic Correlates
Major depressive episode/disorder	<ul style="list-style-type: none"> <li>• Proximity to left frontal pole is directly proportional to the severity of depression</li> <li>• Left lateralized injuries, especially left dorsolateral prefrontal and left ventrolateral prefrontal cortex and left basal ganglia</li> <li>• Altered connectivity between anterior (subgenual) cingulate and default mode network and dorsal attention network</li> <li>• Injury-induced serotonergic dysfunction, especially after left lateralized injuries</li> </ul>
Anxiety disorders	<ul style="list-style-type: none"> <li>• Limbic system dysfunction due to direct structural damage to the limbic system (especially amygdala (L &gt; R), hippocampus, and cingulate gyrus)</li> <li>• Post-injury alterations of noradrenergic function</li> <li>• Reduced top-down modulation of limbic system function by anterior/dorsal prefrontal cortex</li> <li>• Altered functional connectivity within the default mode network</li> </ul>
Traumatic stress disorders	<ul style="list-style-type: none"> <li>• Reduced hippocampal volume and function</li> <li>• Decreased volume and connectivity between areas dependent on internal capsule and uncinate fasciculus</li> <li>• Reduced activity in medial prefrontal cortex and anterior cingulate cortex, which reduces top-down modulation of emotional regulation and appears to release (i.e., permit increased) amygdalar activity</li> </ul>
Secondary mania (not bipolar disorder)	<ul style="list-style-type: none"> <li>• Consistent association with injury to right basoventral areas, anterior temporal cortex (right), orbitofrontal cortex (right), subcortical structures in circuits connecting limbic and paralimbic areas, including caudate, and thalamus</li> </ul>
Pathological laughing and crying, affective lability (aka “pseudobulbar affect”), irritability	<ul style="list-style-type: none"> <li>• Lesions to pathways that interfere with dorsal compartment communication with ventral compartment and brainstem effector regions, including frontopontine projections, cerebello-thalamo-fronto-pontine circuit, cerebello-pontine projections</li> <li>• Lesions in these pathways release the ventral compartment (limbic and paralimbic areas) from descending (top-down) control by executive function centers (dorsolateral prefrontal cortices) and from modulation by posterior cerebellar hemispheres</li> </ul>
Disinhibition, aggression	<ul style="list-style-type: none"> <li>• Injury to white matter tracts connecting lateral orbitofrontal cortex to mediodorsal nucleus of the thalamus (for severe disinhibition)</li> <li>• Diminished connectivity between prefrontal cortices (especially medial and lateral orbitofrontal) and the amygdala</li> <li>• Lesions to pathways that interfere with dorsal compartment communication with ventral compartment and brainstem effector regions, including frontopontine projections, cerebello-thalamo-fronto-pontine circuit, cerebello-pontine projections</li> </ul>

# Brain Networks and Depression after Traumatic Brain Injury



Quinn DK, Story-Remer J, Brandt E, Fratzke V, Rieger R, Wilson JK, Gill D, Mertens N, Hunter M, Upston J, Jones TR, Richardson JD, Myers O, Arciniegas DB, Campbell R, Clark VP, Yeo RA, Shuttlesworth CW, Mayer AR. Transcranial direct current stimulation modulates working memory and prefrontal-insula connectivity after mild-moderate traumatic brain injury. *Frontiers in Human Neuroscience* (Section on Brain Imaging and Stimulation) *Front Hum Neurosci.* 2022;16:1026639

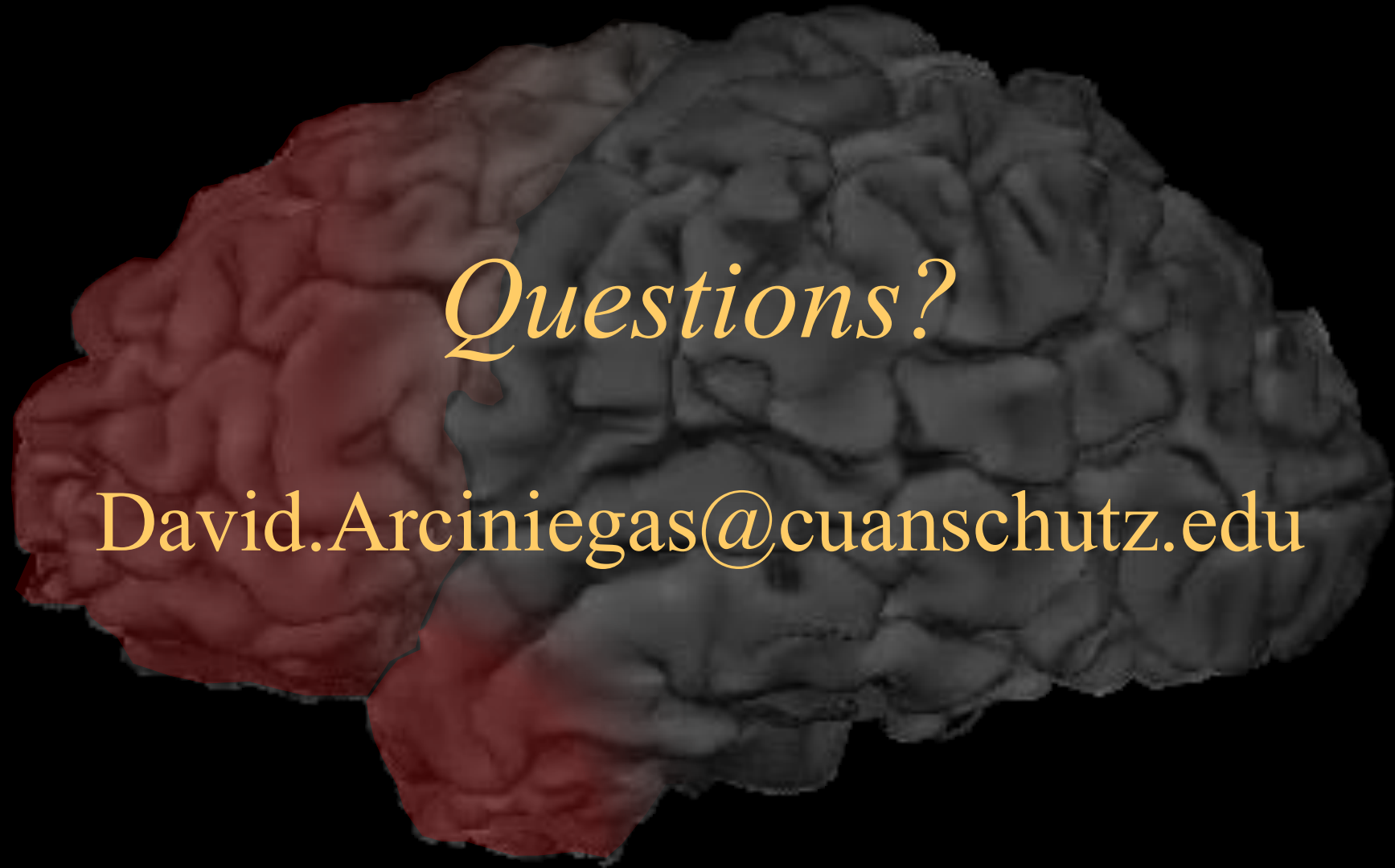


Siddiqi SH, Kandala S, Hacker CD, Bouchard H, Leuthardt EC, Corbett M, Morey RA, Brody FL. Precision functional MRI mapping reveals distinct connectivity patterns for depression associated with traumatic brain injury. *Sci Transl Med.* 2023 Jul 5;15(703):eabn0441.



# Summary and Recommendations

- Neuropsychiatric symptoms and syndromes after TBI are common and predictable adverse consequences of biomechanical forces and subsequent cytotoxic processes on neural systems that generate emotions and emotional expression (i.e., limbic and paralimbic networks) and that regulate those systems (i.e., prefrontal cortex, cerebellum, and white matter connections between them).
- The effects on these systems may directly induce neuropsychiatric symptoms and syndromes in the acute/subacute period after TBI, and they create persistent vulnerabilities for their development when coupled to psychological and environmental factors in the chronic period.
- Classical anatomic lesion and circuit/network models of brain-behavior relationships after TBI provide foundations for advanced neuroimaging studies of the emotional and behavioral sequelae of neurotrauma – which, in turn, create opportunities to better characterize the structural and functional neuroanatomy of neuropsychiatric symptoms and syndromes after TBI and to develop neurobiologically rational treatments for persons with them.



*Questions?*

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