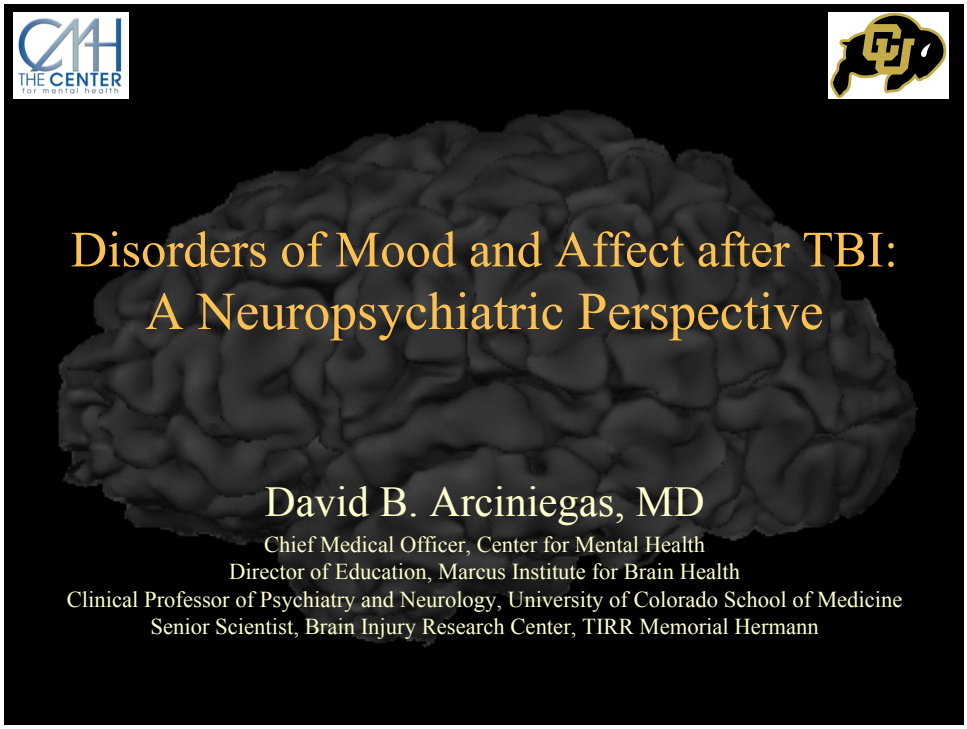
Disorders of Mood and Affect after TBI:
A Neuropsychiatric Perspective
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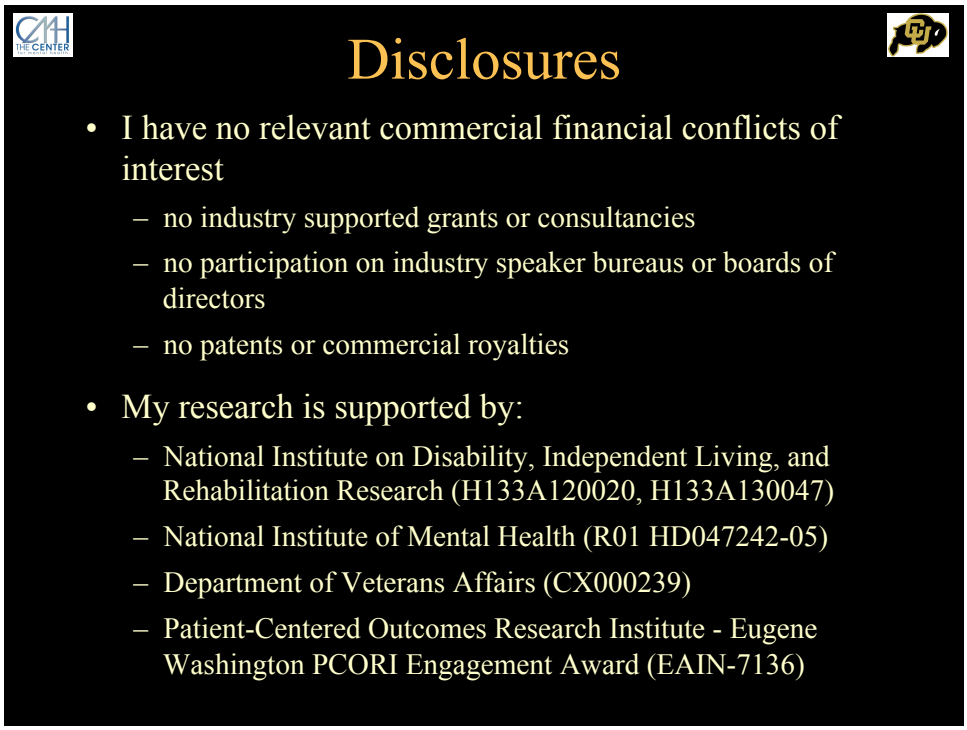
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Goals and Objectives

- Review the nosology, phenomenology, and neurobiology of emotion and emotional regulation
- Describe the disorders of mood and affect that occur common among persons with TBI
- Apply a neuropsychiatric approach to the evaluation and treatment of posttraumatic disorders of mood and affect

Framing the Problem

- Disorders of mood and affect – i.e., disorders of emotional regulation – are common consequences of traumatic brain injury (TBI)
  - major depressive disorder: 25-64%
  - secondary mania: 1-8%
  - pathological laughing and crying: 5-11%
  - affective lability: 14-62%
  - irritability: 35-71%
- Frequently misunderstood in purely psychological terms, these disorders require consideration in a neurobiopsychosocial context

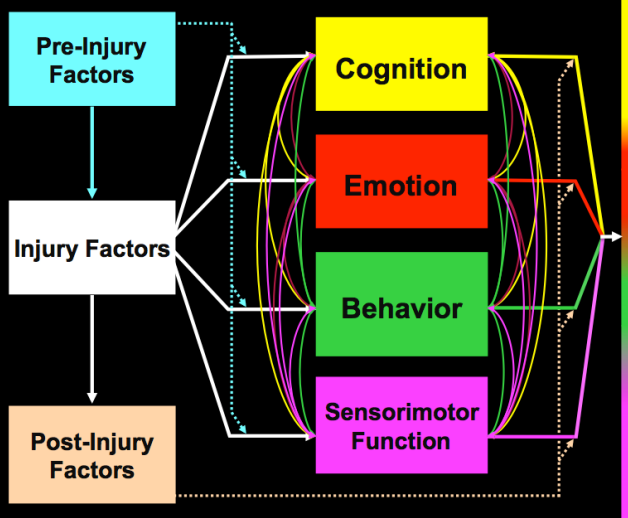
(Jorge et al. 1993; Whelan-Goodinson et al. 2010; Seel et al. 2010; Kim et al. 2007; Koponen et al. 2002; Hibbard et al. 1998; Fedoroff et al. 1992; Jorge and Robinson 2004; Gould et al. 2011; Tateno et al. 2003; Bombardier et al. 2010; Hart et al. 2012; Deb and Burns 2007; Rapoport et al. 2003; Bay et al. 2009; Demakis et al. 2010; Seel et al. 2010; Koponen et al. 2004; Caspi et al. 2003; Jorge and Arciniegas 2014; Arciniegas and Wortzel 2014)

Framing the Problem

- Development and persistence of these disorders involves a complex set of interactions between:
  - pre-injury factors
    - eg, psychiatric history, genetics, psychosocial influences)
  - injury factors
    - eg, type, severity, and location of injury)
  - post-injury factors
    - eg, neurobiological, psychosocial, and medical complications and comorbidities)

(Jorge et al. 1993; Whelan-Goodinson et al. 2010; Seel et al. 2010; Kim et al. 2007; Koponen et al. 2002; Hibbard et al. 1998; Fedoroff et al. 1992; Jorge and Robinson 2004; Gould et al. 2011; Tateno et al. 2003; Bombardier et al. 2010; Hart et al. 2012; Deb and Burns 2007; Rapoport et al. 2003; Bay et al. 2009; Demakis et al. 2010; Koponen et al. 2004; Caspi et al. 2003; Jorge and Arciniegas 2014; Arciniegas and Wortzel 2014)

Factors Affecting Neuropsychiatric Outcome after TBI



Framing the Problem

- Disorders of mood, especially depressive disorders, develop as a result of a complex interplay between effects of neurotrauma, neurogenetics, psychological, social, and other environmental factors on the *enduring* function of the distributed neural networks that generate and regulate emotion
- By contrast, disorders of affect tend to more directly reflect disturbances in the structural and functional networks involved in the moment-to-moment (i.e., *transient*) regulation of emotional responses

(Arciniegas and Topkoff 2000; Arciniegas et al. 2005; Beresford et al. 2005; Cummings et al. 2006; Parvizi et al. 2006; Kim et al. 2007; Oster et al. 2007; Rabins and Arciniegas 2007; Wortzel et al. 2008; Silver et al. 2009; Arciniegas 2013; Arciniegas and Wortzl 2014)

Definitional Issues

- Theoretical and neuroscientific accounts of emotion and emotional disturbances – framed clinically into mood disorders and disorders of affect – have advanced substantially over the last hundred years, and especially the last two decades
- These advances are reshaping the way in which disturbances of emotional generation, expression, experience and regulation are studied, evaluated, and treated
- Before discussing emotional disturbances after TBI – and with the aim of accurately distinguishing between mood disorders and disorders of affect – we must establish a common frame of reference

(James 1890; Ekman 1972, 1999; Plutchik 1980, 1984; LeDoux 1991, 1996; Damasio 1994; Dolan 2002; Phillips, Drevets, Rauch, and Lane 2003; Ochsner and Gross 2005; Mackinnon and Pies 2006; Phelps 2006;Mayberg 2007;Pessoa 2008; Fusar-Poli et al. 2009; Kringelbach and Berridge 2010; Price and Drevets 2010)

Etymology of Emotion

- From Latin *emovere* 'move out, remove, agitate,' from *ex-* 'out' + *movere* 'to move'
- 1579: 'a (physical) moving, stirring, agitation,' from Middle French *emotion*, from Old French *emouvoir* 'stir up'
- 1660: first recorded use of emotion to denote a sense of 'strong feeling'
  - 1808: extended to 'any feeling'
- 1857: *Emotional* – 'liable to emotion'
- 1917: *Emote* offered as back-formation of emotion

(Harper 2001)

Emotion and Emotional Feeling

- Emotional expression and emotional experience are distinct and separable types of psycho-physiological phenomena:
  - Emotional expression (objective): visceral/autonomic activity, motor behavior, vocalization
  - Emotional experience (subjective): awareness of objective phenomena and the images, cognitions, and contexts with which they are associated
- The cognitive neuroscience literature distinguishes between objective and subjective psycho-physiological phenomena using the terms *emotion* and *emotional feeling*, respectively

Emotion and Feeling

- EMOTION: a neural impulse that moves an organism to action, prompting automatic reactive behavior (autonomic and/or motor) that has been adapted through evolution as a mechanism to meet a survival need
  - *literally the 'ex-movere' components of these psychophysiological phenomena*
- EMOTIONAL FEELING: emotion that is brought into cognitive awareness (i.e., made conscious), and particularly through frontal systems, producing a psychological experience tied to the physiological process of emotion

(Damasio 1994, 2003; Cornelius 1996; Prinz 2004; Arciniegas 2013)

Emotion and Emotional Feeling

Basic Emotion	Adaptive Behavior
Anger	Destruction
Fear	Protection
Sadness	Reintegration
Joy	Reproduction
Disgust	Rejection
Surprise	Orientation
Expectancy	Exploration
Acceptance	Incorporation

(Plutchik 1980, 1984, extending Ekman 1972)

Emotional Traits vs. States

- Emotional traits (temperaments): innate and lifelong tendencies to experience certain types of emotions and emotional feelings
  - moderately heritable
  - observable in early in childhood
  - crystallize during the second and third years of life
  - remain relatively stable throughout life thereafter
  - contribute to personality
  - may bias toward developing a variety of psychiatric conditions, especially depression and anxiety disorders
- Emotional states: relatively transitory emotions and emotional feelings

Cattell RB 1966; Mehrabian 1996; Morris et al. 2009; Rossi and Pourtois 2011; Gros et al. 2007; Sasayama et al. 2011; Mian et al. 2011; Doyle et al. 2011; de Winter et al. 2007

Dimensions of Emotions and Emotional Feelings

- Frequency
- Valence (pleasantness)
- Arousal (activating) qualities
- Intensity
- Potency (amenability to voluntary control)
- Predictability/unpredictability

(Larsen and Diener 1987; Bachorowski and Braaten 1994; Woyshville et al 1999; Fontaine et al. 2007; Pelissolo et al. 2007; Goudbeek and Scherer 2010)

This Emotional Life…

- Klaus Scherer and colleagues (2004), using the basic emotions described by Ekman (1972, 1999) studied 1,030 subjects for the purpose of identifing the absolute and relative frequencies of emotions and emotional feelings
- The ten most commonly reported categories of emotions and emotional feelings were organized into six "families:"
  - happiness (comprising happiness, joy, and contentment)
  - anger (comprising anger, irritation, and frustration)
  - anxiety
  - sadness
  - stress
  - despair

(Scherer KR et al.: Emotions in everyday life: probability of occurrence, risk factors, appraisal and reaction patterns. Soc Sci Inform. 2004 Dec;43(4):499-570)

Modal Emotions and Emotional Feelings

- Responses falling into the happiness and anger categories were more frequent (by a factor of four) than all other emotions and emotional feelings
- Among the others, anxiety was more common than sadness, both of which were more common than stress or despair
- These observations suggest that a "happy-angry" (or "satisfied-irritable") continuum more closely approximates the everyday emotion life of most healthy people better than the "happy-sad" continuum taught and used social-psychological and psychiatric research and practice

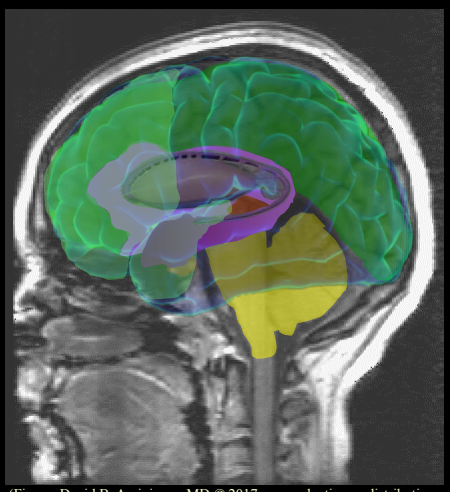
(Scherer KR et al.: Emotions in everyday life: probability of occurrence, risk factors, appraisal and reaction patterns. Soc Sci Inform. 2004 Dec;43(4):499-570)

Neuroanatomy of Emotion and Emotional Feeling

- Emotion and emotional feeling are predicated on the complex actions of and interactions between several selective distributed networks in the brain
  - limbic and paralimbic circuits
  - frontal-subcortical circuits
  - neuroendocrine and autonomic circuits
- The "server" for emotional information processed in these networks is the limbic and paralimbic circuits

(Mayberg 1997; Mega, Cummings, Salloway, Malloy 1997; Arciniegas and Beresford 2001; Seminowicz et al 2004; Drevets et al. 2008; Holtzheimer and Mayberg 2011)

Essential Neurobehavioral Anatomy



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Telencephalon *– neocortex; functionally organized in conjunction with the white matter and subcortical nuclear complexes to which these areas are connected*

Basal Ganglia *– caudate, putamen, globus pallidus (interna and externa), and (functionally) substantia nigra*

Limbic System *– a 'ring' of structures on the medial aspect of each hemisphere including the entorhinal-hippocampal complex, amygdala, cingulate gyrus, other medial temporal structures, ventral striatum, nucleus accumbens, thalamus (esp. dorsal and anteromedial), epithalamus, hypothalamus, limbic midbrain area, and other brainstem nuclei*

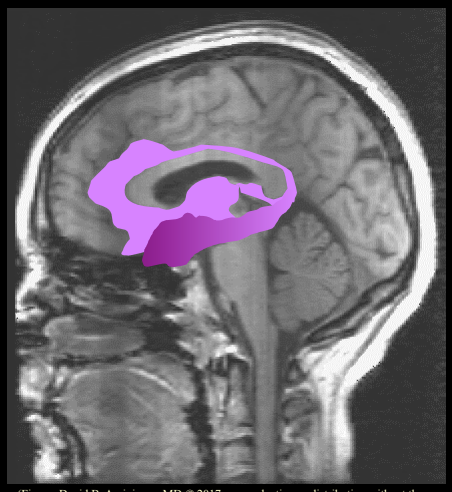
Diencephalon *– thalamus, hypothalamus, pituitary gland, pineal gland*

Reticular Formation *– collection of brainstem nuclei running from the rostral midbrain to the medulla, and with its functional components:*

Mesencephalon *– midbrain*
Metencephalon *– pons and cerebellum*
Myelencephalon *– medulla*

Sagittal view of the left hemisphere of the brain. Color overlays correspond to the major neuroanatomic areas listed to the right of the image. Those relevant areas listed in their relative neuropsychiatric hierarchy.

Limbic Cortex



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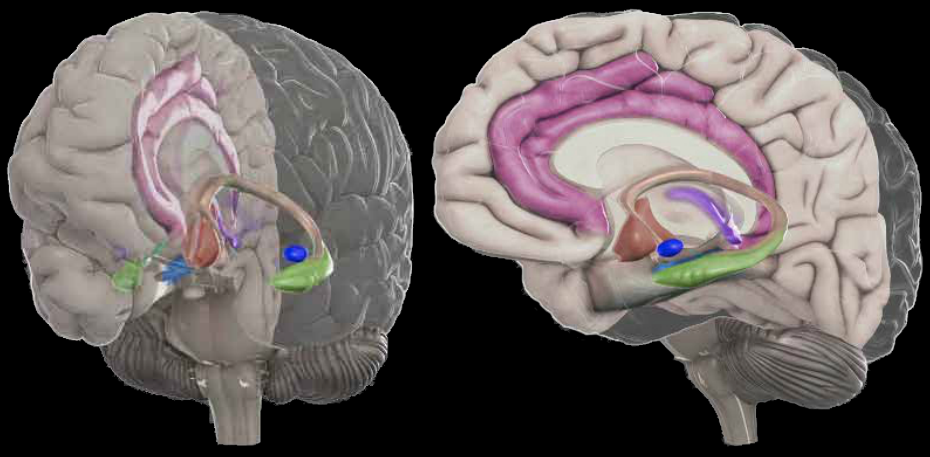
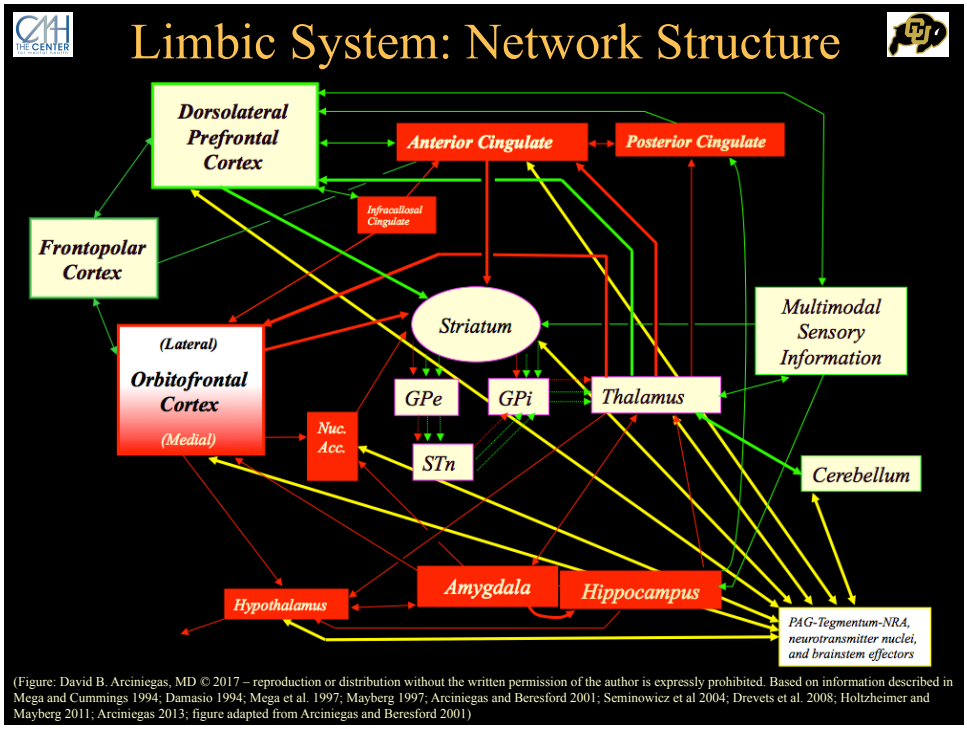
- At its core – or as the 'network hub' in this system – is the ring (fr. Latin, 'limbus') of structures (illustrated in purple in this figure) on the medial aspect of each hemisphere
- Although sometimes referred to as a "lobe" of the brain, the limbic system is more correctly understood as a network of structures comprised by neocortical areas, diencephalic structures, and midbrain elements
  - **entorhinal-hippocampal complex**
  - **amygdala**
  - **other medial temporal gyri**
  - **anterior cingulate gyrus**
  - thalamus (dorsal and anteromedial)
  - hypothalamus
  - limbic midbrain area

Sagittal view of the left hemisphere of the brain. Color overlays correspond to the major neuroanatomic areas listed to the right of the image. Those relevant areas listed in their relative neuropsychiatric hierarchy.

Limbic System



Near-coronal (left) and sagittal (right) views of the limbic system. Colors: pink – cingulate cortex; dark blue – amygdala; light blue – entorhinal cortex; green – hippocampus; tan – fornix and mammillary bodies; purple – epithalamus; brown – hypothalamus. Figure adapted from The G2C Brain, Cold Spring Harbor Laboratory (http://www.g2conline.org/2022).



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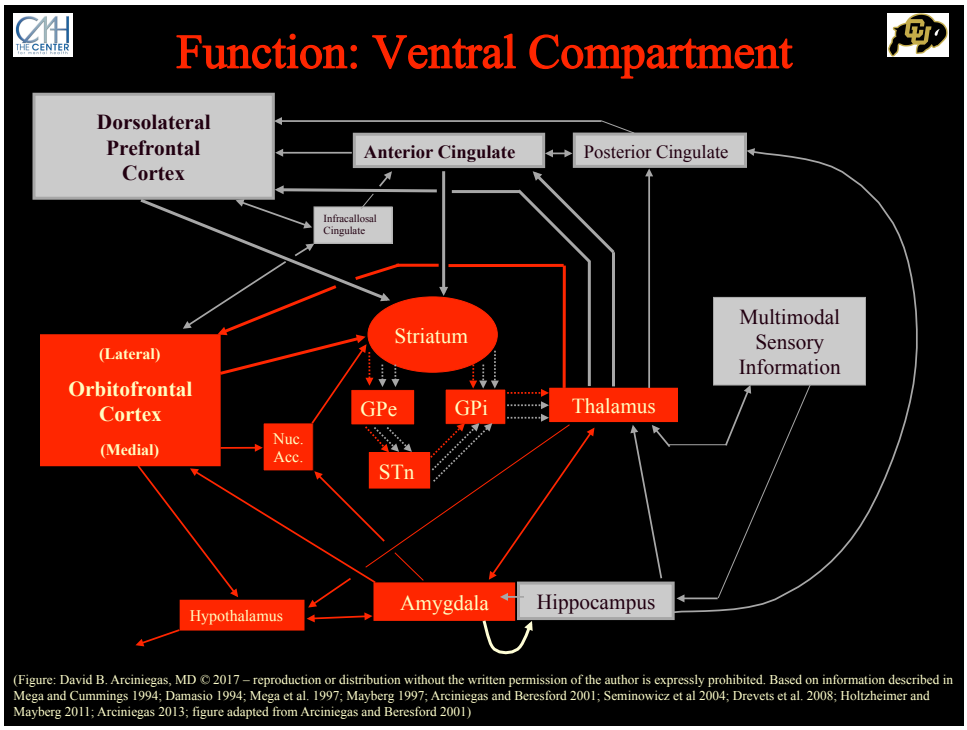

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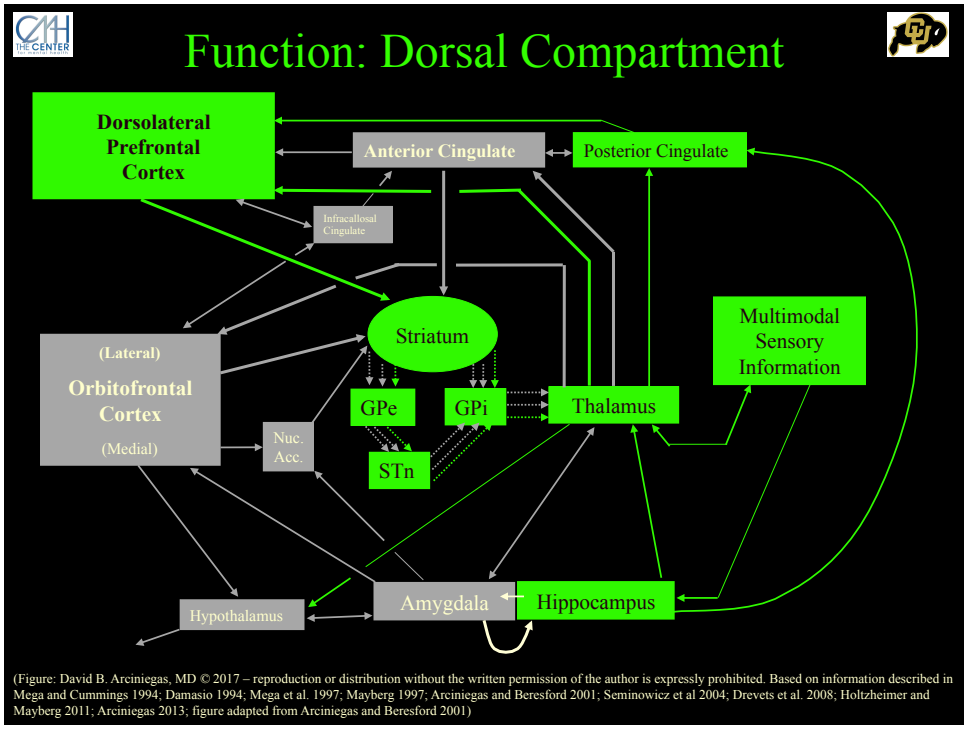

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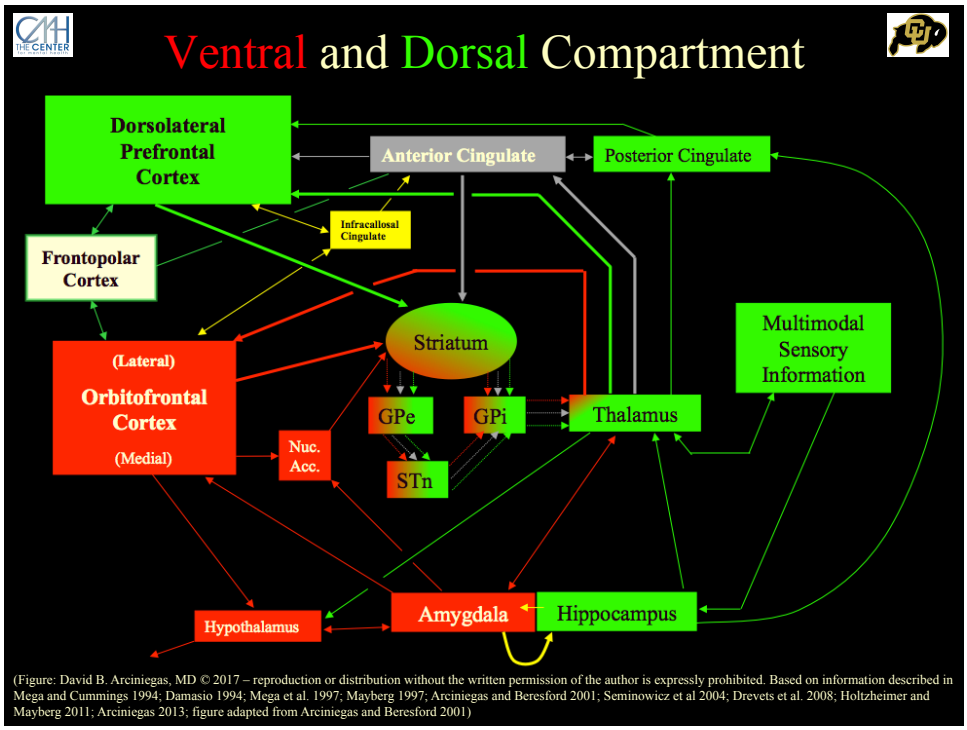

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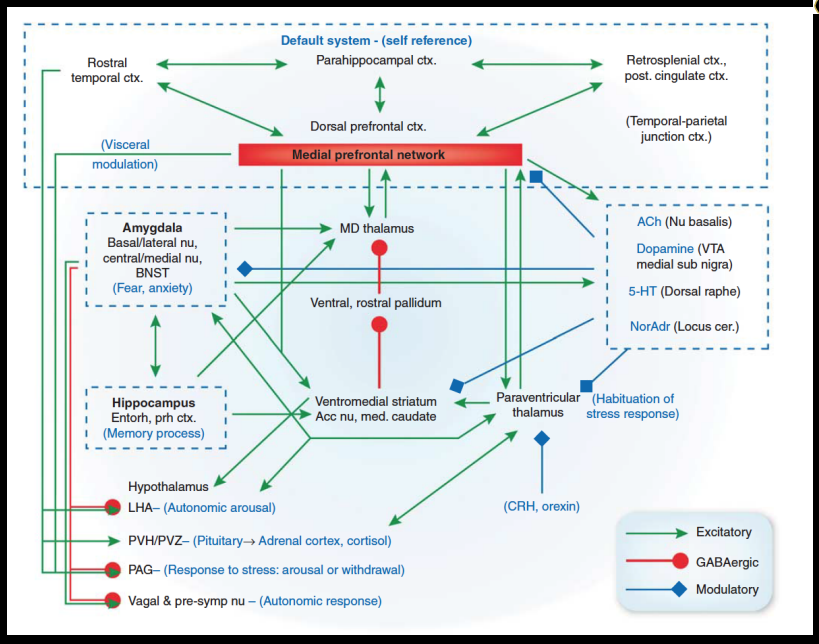


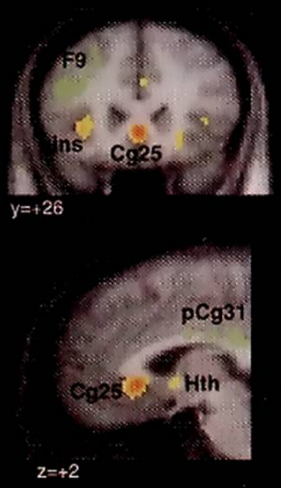
(Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010 Jan;35(1):192-216)

KEY CONCEPTS

- Emotion (the *ex-movere* function) is represented in a ventral limbic-paralimbic network
- Emotional feeling (conscious awareness of emotion and its associations) is represented in a dorsal limbic-paralimbic-cortical network
- The ventral network drives the dorsal network but also is amenable to modulation by it
- Emotion and emotional feeling are not strongly lateralized, but disturbances of emotion may arise from lateralized damage/dysfunction

Imaging Sadness

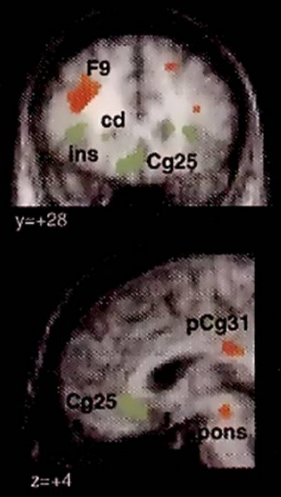
- Sadness increases limbic and paralimbic blood flow and a decrease in dorsolateral prefrontal blood flow
  - in patients with major depression
  - in healthy controls in a "transient induced sadness" experiment



(George et al. 1995; Schneider et al. 1995; figure adapted from Mayberg et al. 1997)

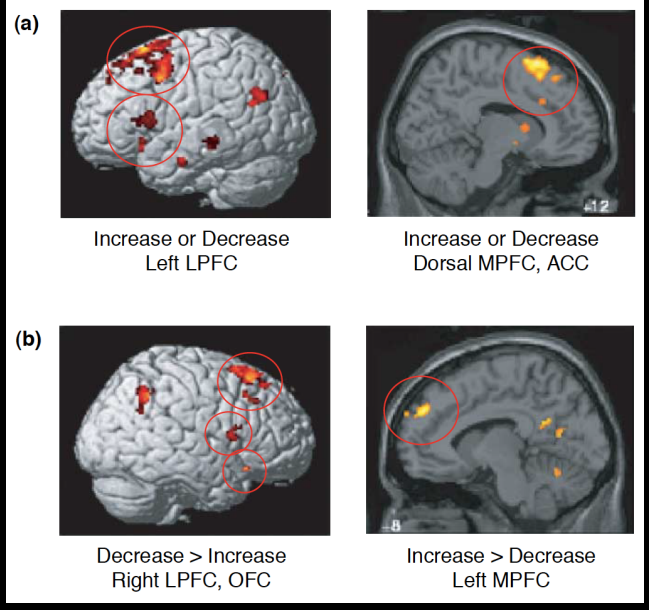
Imaging Sadness

- Resolution of sadness is associated with normalization of blood flow and metabolism in the dorsolateral prefrontal cortex and anterior (infracallosal) cingulate
  - regardless of whether that resolution is of persistent sadness or transient sadness



(George et al. 1995; Schneider et al. 1995; figure adapted from Mayberg et al. 1997)

Imaging Emotional Regulation

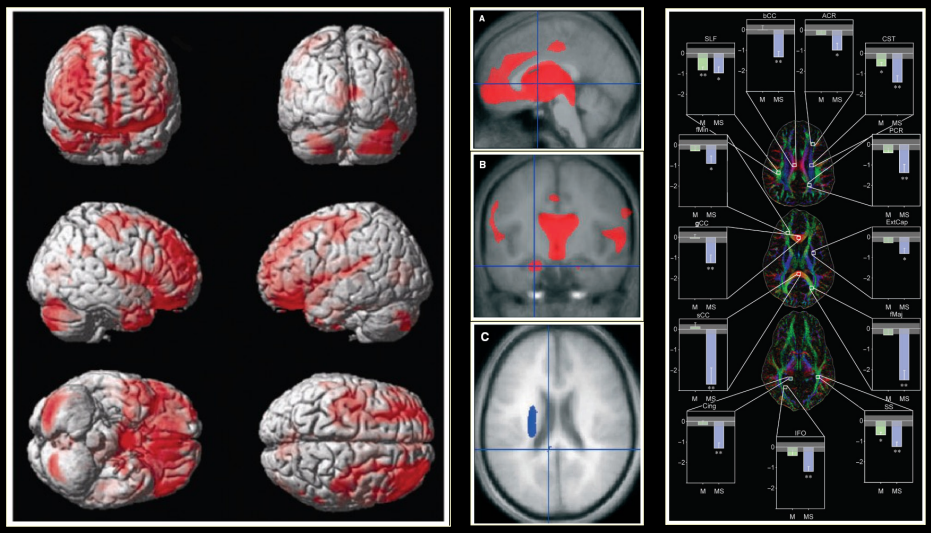


(a): Regardless of whether the goal is to increase or decrease emotion, lateral prefrontal and anterior cingulate cortices are activated.

(b): When the goal is to decrease emotion, right dorsolateral and ventrolateral prefrontal as well as right orbitofrontal cortex is more active than are left-hemispheric structures (left panel). By contrast, when the goal of control is to increase emotion, left lateral and dorsomedial prefrontal cortical regions are differentially recruited when imaging worsening experiences and outcomes (right panel).

Adapted from Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005 May;9(5):242-9.

Regional Vulnerability to TBI



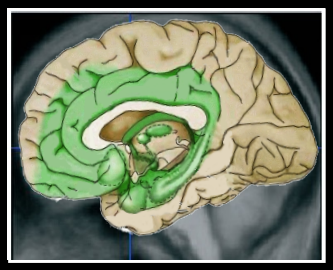
Yeates et al.: Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. Psychol Bull. 2007 May;133(3):535-56.

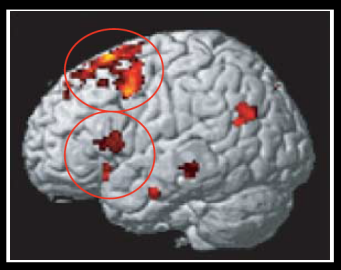
Salmond et al.: Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain. 2005 Jan;128(Pt 1):189-200.

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.

Emotion, Feeling, and TBI: Overlapping Neuroanatomies

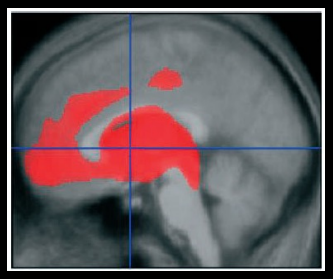
Purves et al. 2001

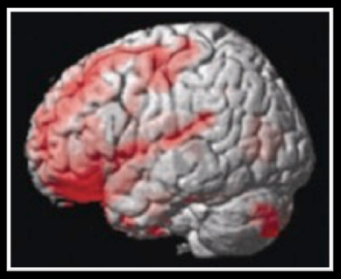




Ochsner and Gross 2005

Salmond et al. 2005





Yeates et al. 2007

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Matthews et al. 2010

- Used fMRI and DTI to study depression in the late periods (i.e., > 1 year) following blast-related concussion
- During emotion-related processing:
  - increased activity in the bilateral amygdala and related paralimbic-subcortical structures
  - decreased activity in left dorsolateral prefrontal cortices
  - decreased integrity of white matter tracts connecting dorsal frontal lobe to other structures

(Matthews et al. 2010)

Lateralization?

- Lateralization hypotheses are not supported strongly by meta-analyses of neuroimaging studies of > 4,000 healthy individuals processing emotional faces
  - all emotional conditions, irrespective of stimulus valence, produce **bilateral** activations of the ventral and dorsal compartments as well as the posterior sensory areas involved in visual processing
  - valence-specific lateralization to the left amygdala during processing of negative emotions was observed, as was a 'left/approach' and 'right/withdrawal' pattern of imaging activation to emotional faces

(Fusar-Poli et al. 2009; Arciniegas, Cummings, Coffey 2011)

Lateralization?

- However, the response of monoamine receptor systems to injury (e.g., stroke) or neurodegeneration may be lateralized
  - there is evidence that right, but not left, hemisphere injuries are associated with robust upregulation of biogenic amine receptors
- If so, then emotion and emotional feeling may not be strongly lateralized under normal circumstances but regulation disturbances and valence-specific disorders of mood and affect may arise in response to lateralized cerebral insults

(Sackeim 1982; Mayberg 1988; Morris et al. 1996; Robinson 2007; Arciniegas, Cummings, Coffey 2011)

Mood and Affect

- Mood and affect are sometimes used as synonyms for emotion and emotion feeling
  - mood: subjective state, or emotional feeling
  - affect: expression of feeling, or emotion (*ex movere)*
- This practice is not consistent with the definitions of mood and affect described in DSM-III-R and its successors and is inconsistent with the neuropsychiatric approach to the evaluation and treatment of mood disorders and disorders of affect

(American Psychiatric Association 1987, 1994, 2000, 2013; personal communication, Robert L. Spitzer, MD, Chair of the Work Group to Revise DSM-III and Special Advisor to the Task Force on DSM-IV; 15-August-2005

Mood and Affect

- DSM-IV-TR definitions:
  - Mood: "a pervasive and sustained emotion that colors the perception of the world"
  - Affect: "a pattern of observable behaviors that is the expression of a subjectively experienced feeling state"
- Both include objective (emotion) and subjective (emotional feeling) elements

(American Psychiatric Association 1987, 1994, 2000, 2013; personal communication, Robert L. Spitzer, MD, Chair of the Work Group to Revise DSM-III and Special Advisor to the Task Force on DSM-IV; 15-August-2005

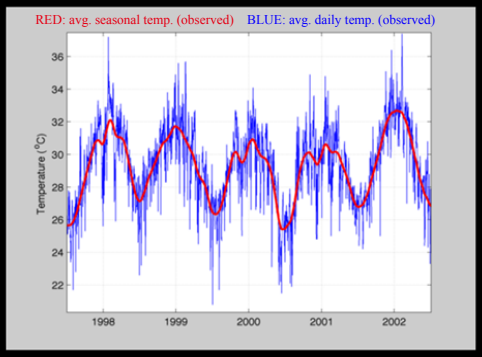
Mood and Affect

- DSM-IV-TR definitions (cont.):
  - "In contrast to *mood*, which refers to a more pervasive and sustained emotional 'climate',

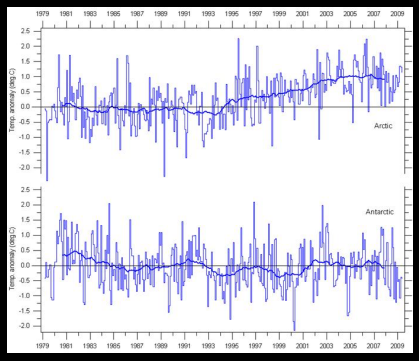
    affect refers to more fluctuating changes in the emotional 'weather'."
- Mood and affect are distinguished from one another ***on temporal grounds***
  - both have subjective (experienced) and objective (expressed) components
  - it is the relative durations of these emotional states that distinguishes them from each other

(American Psychiatric Association 1987, 1994, 2000, 2013; personal communication, Robert L. Spitzer, MD, Chair of the Work Group to Revise DSM-III and Special Advisor to the Task Force on DSM-IV; 15-August-2005

'Meteorological Metaphor'



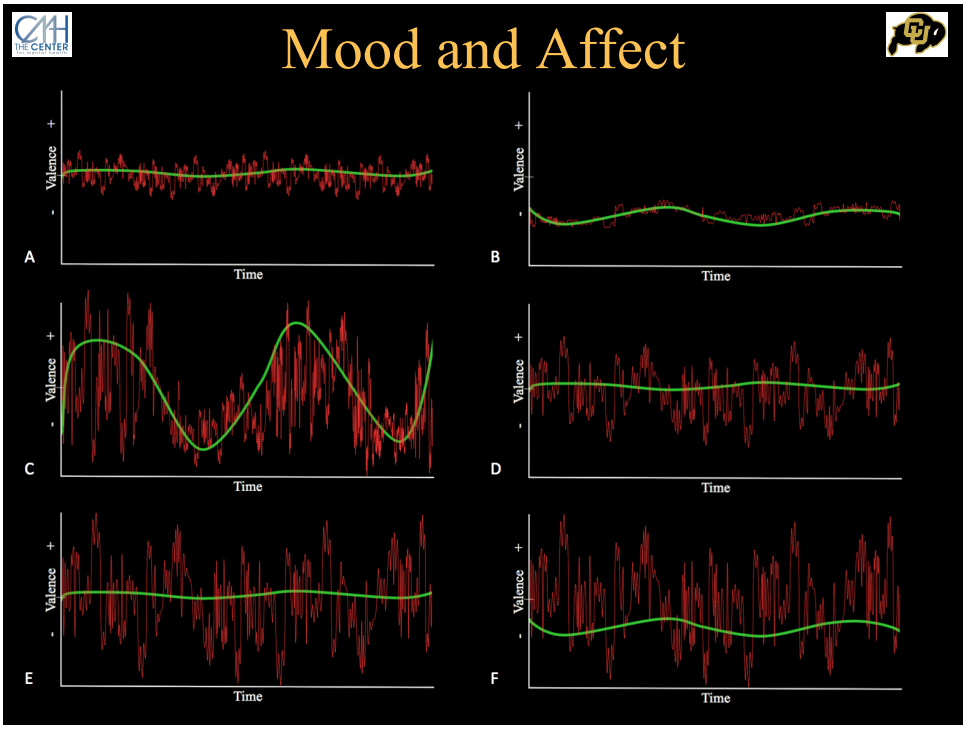
Example air temperatures in a temperate climate over a five-year period (1998-2002)



Example of air temperatures in an artic climate over a 30-year period (1979-2009)

(Sources: left: http://www.pacificclimatefutures.net/en/help/climate-projections/understanding-climate-variability-and-change/ and right: http://appinsys.com/globalwarming/GW_NotGlobal_files/image012.jpg)

Mood and Affect



Emotion, Emotional Feeling, Mood and Affect

	Emotion (Expression)	Emotional Feeling (Experience)
Mood	*"A pervasive and sustained emotion…*	*…that colors the perception of the world."*
Affect	*"A pattern of observable behaviors that is the expression of…*	*…a subjectively experienced feeling state."*

(American Psychiatric Association 1987, 1994, 2000, 2013; Arciniegas and Topkoff 2000; Arciniegas et al. 2005; Wortzel et al. 2008; Arciniegas 2013)

Emotion, Emotional Feeling, Mood and Affect

	Emotion (Expression)	Emotional Feeling (Experience)
Mood	Pervasive and sustained autonomic activity, visceral activity, neurohormonal, neurochemical processes, body posture, gestures, behaviors, facial expressions, vocalizations (*ex movere* phenomena that are present most of the day, nearly every day, over a period of days to weeks)	Emotion-related sensorimotor phenomena and associated cognitions that are present most of the day, nearly every day, over a period of days to weeks; these establish tendencies with which self and others are experienced (i.e., coloring of perception of the world)
Affect	Transient autonomic activity, visceral activity, neurohormonal, neurochemical processes, body posture, gestures, behaviors, facial expressions, vocalizations, the occurrence of which is superimposed and may be modified by the emotional background in which they occur (i.e., mood)	Transient emotion-related sensorimotor phenomena and associated cognitions (a momentary subjectively experienced feeling state)

(American Psychiatric Association 1987, 1994, 2000, 2013; Arciniegas and Topkoff 2000; Arciniegas et al. 2005; Wortzel et al. 2008; Arciniegas 2013)

Mood and Affect

MOOD:

1) How does the patient feel emotionally most of the time?
2) How does the patient appear to feel emotionally most of the time? (observed by someone who knows the patient well or, in the absence of a knowledgeable informant, to the examiner assessing for 'background' emotion)

AFFECT:

1) How does the patient feel emotionally right now?
2) How does the patient appear to feel right now?
3) What variability, if any, is there in how the patient feels or appears to feel from moment-to-moment?

Basic Emotions:

- Happiness (comprising happiness, joy, and contentment)
- Anger (comprising anger, irritation, and frustration)
- Anxiety
- Sadness
- Stress
- Despair
- Disgust
- Surprise

Disorders of Mood

- The cardinal feature of a mood disorder is one or more sustained episodes of pervasively abnormal emotion and/or feeling ('climate shift')
  - **Manic episodes:** abnormally and persistently elevated, expansive, or irritable mood *lasting at least 1 week*
  - **Hypomanic episodes:** abnormally and persistently elevated, expansive, or irritable mood *lasting at least 4 days*
  - **Depressive episodes:** feels sad *and/or* appears tearful *most of the day nearly every day for at least 2 weeks*
  - **Mixed episodes:** criteria for manic and depressive episodes are met *nearly every day for at least 1 week*

(American Psychiatric Association 1987, 1994, 2000; 2013)

Disorders of Affect

- The cardinal feature is disturbance of moment-to-moment emotion (the 'emotional weather')
  - pathological laughing and crying
  - essential crying
  - *witzelsucht*
  - episodic irritability/ dyscontrol
  - ?: panic attacks/panic disorder
  - ?: "organic aggressive syndrome"
  - placidity (in apathy states or Klüver-Bucy-like syndromes)

(Green et al. 1987; Dark et al. 1996; Arciniegas and Topkoff 2000; Smith et al. 2004; Arciniegas et al. 2005; Cummings et al. 2007; Wortzel et al. 2008)

Disorders of Mood and Affect after TBI

- Mood disorders
  - Depressive disorders
    - Major depressive disorder
    - Dysthymic disorder
    - Depressive disorder NOS
  - Depressive disorder due TBI
  - Mood disorder NOS
  - Secondary mania
  - Bipolar disorders
    - Bipolar I disorder
    - Bipolar II disorder
    - Cyclothymic disorder
    - Bipolar disorder NOS
  - Substance-induced mood disorders
- Disorders of affect
  - Pathological laughing and crying
  - Affective lability
  - Essential crying
  - *Witzelsucht*
  - Episodic irritability/dyscontrol
  - Panic attacks
  - Placidity in Klüver-Bucy-like syndromes

Major Depressive Disorder

Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). **(Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **(Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.[1]

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

(American Psychiatric Association 2013)

Post-TBI Mood Disorders & Related Problems

	Pre-TBI	Post-TBI	Non-TBI
Mood disorders			
Major depression	17%	61%	6%
Dysthymia	1%	3%	3%
Bipolar disorder	0%	2%	1%
Anxiety disorders			
Posttraumatic stress disorder	6%	19%	8%
Obsessive-compulsive disorder	1%	19%	3%
Panic disorder	4%	14%	2%
Generalized anxiety disorder	1%	9%	4%
Phobias	4%	10%	13%
Substance use disorder	40%	28%	17%
One Axis I disorder	34%	36%	
Two or more Axis I disorder	17%	44%	
Any Axis I disorders	51%	80%	

Hibbard MR, Uysal S, Kepler K, Bogdany J, Silver J. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil. 1998;13(4): 24-39. **Replicated by** Whelan-Goodinson R, Ponsford J, Johnston L, Grant F. Psychiatric disorders following traumatic brain injury: their nature and frequency. J Head Trauma Rehabil 2009;24(5):324-332.

Depressive Disorders after TBI

	Not controlling for alcohol abuse		Controlling for alcohol abuse	
	Odds ratio	95% CI	Odds ratio	95% CI
Major depression	2.4	1.7-3.4	2.3	1.6-3.2
Dysthymia	2.0	1.2-3.1	1.7	1.1-2.7
Bipolar disorder	1.4	0.6-3.0	1.1	0.5-2.5
Obsessive-compulsive disorder	2.1	1.3-3.4	2.0	1.2-3.2
Panic disorder	2.8	1.5-5.2	2.5	1.3-4.6
Any phobia	1.7	1.3-2.4	1.6	1.2-2.3
Drug abuse/dependence	1.8	1.2-2.5	1.5	1.0-2.1
Alcohol abuse/dependence	2.2	1.7-2.8		
Schizophrenia	1.8	1.0-3.3	1.7	0.9-3.0
Suicide attempt	5.7	3.7-8.7	4.5	2.8-7.1

Table 4. The association between psychiatric disorders and TBI after controlling for sociodemographic variables (age, sex, marital status, and SES) and quality of life variables. From the New Have Epidemiologic Catchment Area Study (n=5034). Adapted from Silver et al. (2001).

(Adapted from Silver et al., 2001)

Neurobiological Risk Factors for Depression after TBI

- Proximity to left frontal pole is directly proportional to the severity of depression
- Laterality of injury (left)
  - left dorsolateral prefrontal cortex
  - left ventrolateral prefrontal cortex
  - left basal ganglia
- Injury-induced serotonergic dysfunction

(Lispey et al. 1983; Mobayed and Dinan 1990; Jorge et al. 1993; Glenn et al. 2001; Rapoport et al. 2002; Dikmen et al. 2004; Robinson et al. 2004; Koponen et al 2006; Matthews et al. 2010; Rao et al. 2010)

Treatment of Depression after TBI

- Education, reassurance, and frequent support reduces adverse long-term outcomes after TBI, including depression
- Peer support programs increase knowledge about TBI, improve general outlook, enhance coping with depression, and improve quality of life
- CBT may improve depressive symptoms; even in the absence of their change, CBT may improve coping with these and other symptoms
- Engaging both the patient and also their family members therefore is essential in the treatment of depression following TBI

(Bell et al. 2008; Snell et al. 2009; Bombardier et al. 2009; Hibbard et al. 2002; Anson and Ponsford 2006a; Anson and Ponsford 2006b; Groom et al. 1998; Harris et al. 2001; Leach et al. 1994)

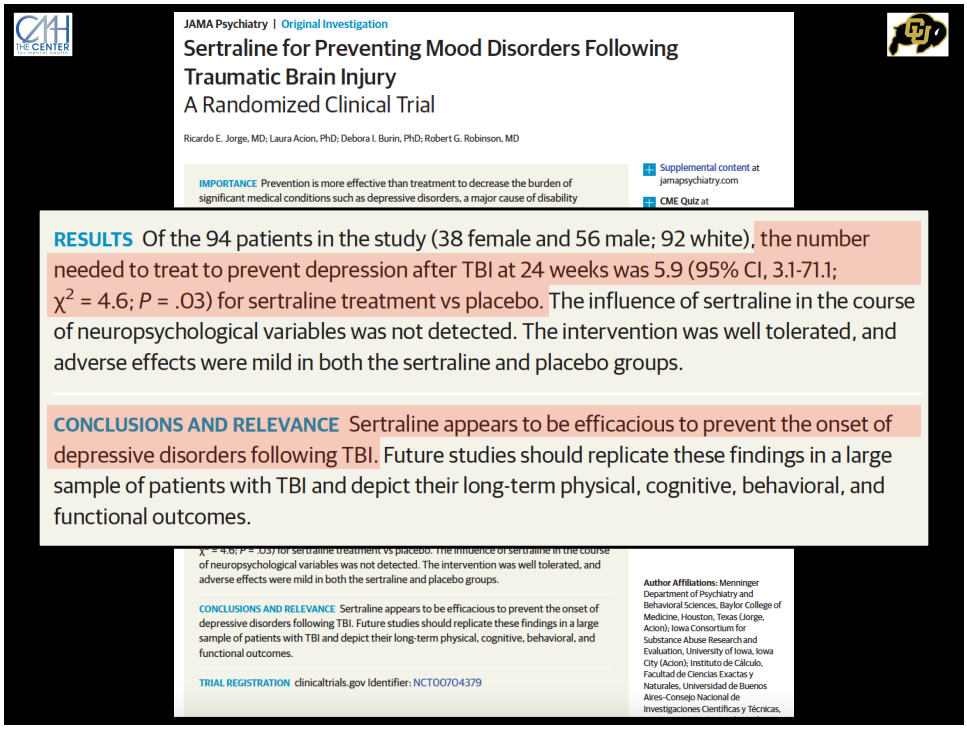
J Head Trauma Rehabil
Vol. 31, No. 4, pp. E21–E32

Pharmacotherapy for Depression Posttraumatic Brain Injury: A Meta-analysis

Objective: To examine the effectiveness of pharmacotherapy for the treatment of depression following traumatic brain injury (TBI). **Design:** Systematic review and meta-analysis. Multiple electronic databases were searched to identify relevant studies examining effectiveness of pharmacotherapy for depression post-TBI. Clinical trials evaluating the use of pharmacotherapy in individuals with depression at baseline and using standardized assessments of depression were included. Data abstracted included sample size, antidepressant used, treatment timing/duration, method of assessment, and results pertaining to impact of treatment. Study quality was assessed using a modified Jadad scale. **Results:** Nine studies met criteria for inclusion. Pooled analyses based on reported means (standard deviations) from repeated assessments of depression showed that, over time, antidepressant treatment was associated with a significant effect in favor of treatment (Hedges $g = 1.169$; 95% confidence interval, 0.849-1.489; $P < .001$). Similarly, when limited to placebo-controlled trials, treatment was associated with a significant reduction in symptoms (standardized mean difference = 0.84; 95% confidence interval, 0.314-1.366; $P = .002$). **Conclusion:** Pharmacotherapy after TBI may be associated with a reduction in depressive symptomatology. Given limitations within the available literature, further well-powered, placebo-controlled trials should be conducted to confirm the effectiveness of antidepressant therapy in this population. **Key words:** *depression*, *meta-analysis*, *pharmacotherapy*, *traumatic brain injury*

R_X of Depression: Medications

	Starting Dose	Target Total Daily Dose	Special Considerations
Selective Serotonin Reuptake Inhibitors			
Citalopram	5-10 mg daily	10 - 60 mg	Relatively short half-life; few drug-drug interactions
Escitalopram	5-10 mg daily	5 - 20 mg	Relatively short half-life; few drug-drug interactions; may be modestly more anxiolytic than citalopram
Sertraline	25 mg daily	25 - 200 mg	Relatively short-half life; modest sexual dysfunction; increased serum carbamazepine levels
Fluoxetine	10 mg daily	10 - 60 mg	Long half-life of primary active metabolite, norfluoxetine; possible excessive activation; inhibits multiple cytochrome 450 enzymes, increase the risk of problematic drug-drug interactions
Paroxetine	5-10 mg daily	10 - 50 mg	Risk of discontinuation syndrome; anticholinergic effects; weight gain; drug interactions; discontinuation syndrome may be worse than for other SSRIs
Stimulants			
Methylphenidate	5 mg twice daily	5 - 60 mg	Low but nontrivial risk of anorexia, insomnia, and dependence/abuse; may usefully augment partial responses to SSRIs
Dextroamphetamine	5 mg twice daily	5 - 60 mg	Low but nontrivial risk of anorexia, insomnia, and dependence/abuse; may usefully augment partial responses to SSRIs
Tricyclic Antidepressants			
Nortriptyline	25 mg daily	25 - 150 mg	Relatively less anticholinergic than older TCAs
Desipramine	50 mg daily	50 - 200 mg	Relatively less anticholinergic than older TCAs
Other Antidepressants			
Mirtazapine	15 mg daily	15 - 45 mg	Initial dose may be sedating, and usually is administered prior to sleep; may usefully augment partial responses to SSRIs
Bupropion XL	150 mg daily	150 - 450 mg	Possible dose-related seizure risk; generally entails lower risk of treatment-related sexual dysfunction than SSRIs
Venlafaxine XR	37.5 mg daily	37.5 - 225 mg	Hypertension may be treatment-limiting for some patients; usual neurological symptoms ("twitching" or "shock-like" sensations) are sometimes report; potentially difficult discontinuation syndrome



JAMA Psychiatry | Original Investigation

Sertraline for Preventing Mood Disorders Following Traumatic Brain Injury

A Randomized Clinical Trial

Ricardo E. Jorge, MD; Laura Acion, PhD; Debora I. Burin, PhD; Robert G. Robinson, MD

IMPORTANCE Prevention is more effective than treatment to decrease the burden of significant medical conditions such as depressive disorders, a major cause of disability

RESULTS Of the 94 patients in the study (38 female and 56 male; 92 white), the number needed to treat to prevent depression after TBI at 24 weeks was 5.9 (95% CI, 3.1-71.1; $\chi^2 = 4.6$; $P = .03$) for sertraline treatment vs placebo. The influence of sertraline in the course of neuropsychological variables was not detected. The intervention was well tolerated, and adverse effects were mild in both the sertraline and placebo groups.

CONCLUSIONS AND RELEVANCE Sertraline appears to be efficacious to prevent the onset of depressive disorders following TBI. Future studies should replicate these findings in a large sample of patients with TBI and depict their long-term physical, cognitive, behavioral, and functional outcomes.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00704379

Supplemental content at jamapsychiatry.com

CME Quiz at

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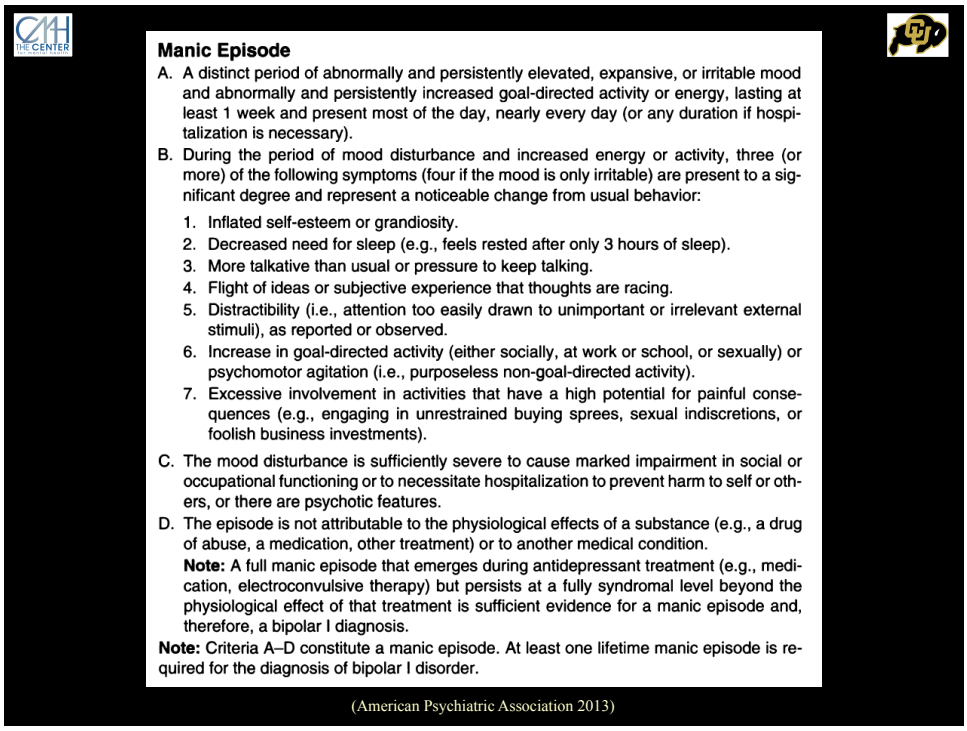


Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

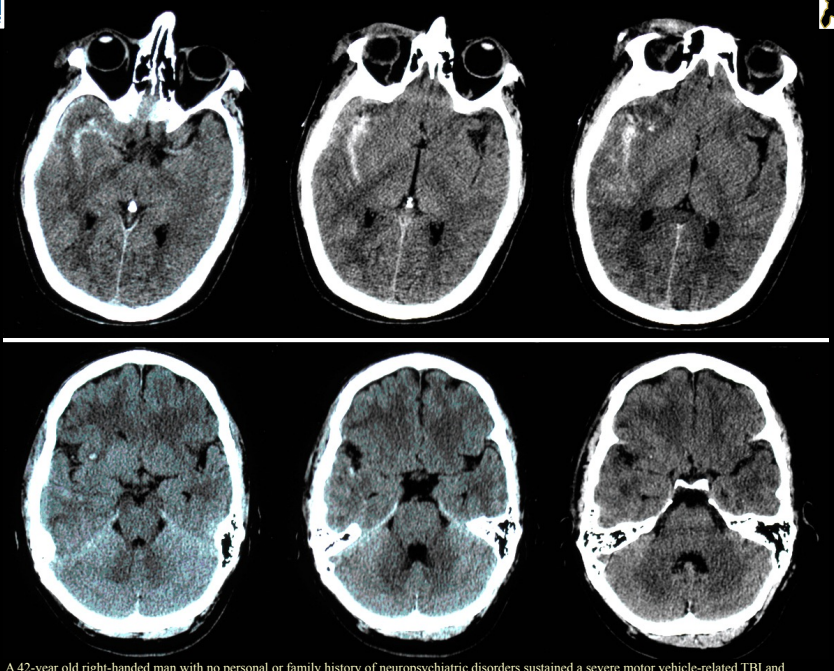
Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

(American Psychiatric Association 2013)

Neurobiological Risk Factors for Mania after TBI

- Not clearly related to personal or family history of psychiatric (including bipolar) disorder, pre- or post-injury psychosocial function, post-injury neurological or cognitive problems (including epilepsy)
- Consistent association with injury to:
  - right basoventral areas
  - anterior temporal cortex (right)
  - orbitofrontal cortex (right)
  - subcortical structures in circuits with libmic and paralimbic areas, including caudate, and thalamus

(Jorge et al. 1993; Shukla et al. 1987; Malaspina et al. 2001; Silver et al. 2001; Jorge et al. 1993; Malaspina et al. 2001; Silver et al. 2001; Mustafa et al. 2005; Starkstein et al. 1987, 1988; 1990; Robinson et al. 1988; Oster et al. 2007)



A 42-year old right-handed man with no personal or family history of neuropsychiatric disorders sustained a severe motor vehicle-related TBI and developed mania about 2 months post-injury. (Figure from Oster et al. 2007)

Psychological Treatment of Mania after TBI

- There are no published studies of psychotherapies for the treatment of posttraumatic mania
- Supportive counseling and family therapy may be reasonable to employ, but their effectiveness for secondary mania and/or adaptation to co-occurring bipolar disorder and TBI are not presently established

(American Psychiatric Association 2002; Hirschfeld 2002; Jorge and Arciniegas 2014)

R_X of Mania: Medications

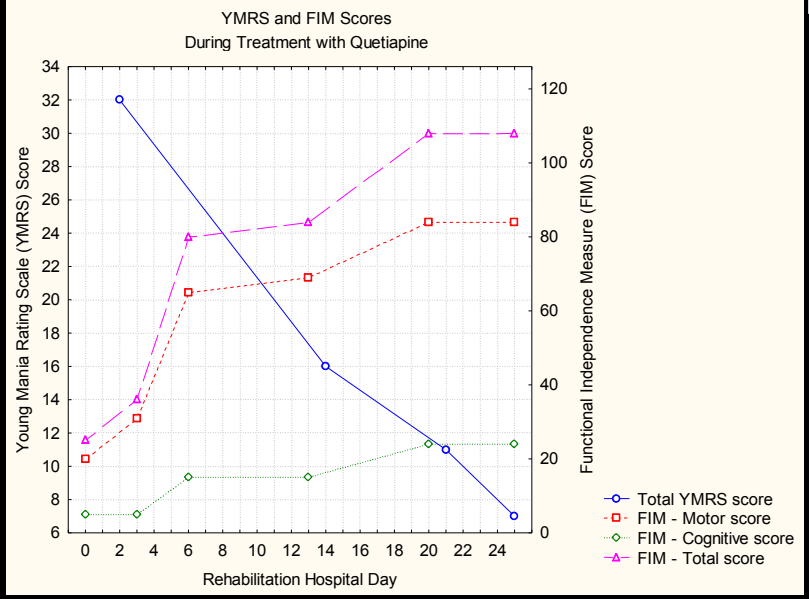
- No RCTs of pharmacotherapies for mania after TBI – only case reports and small case series
  - valproate or quetiapine are probably best first-choices for posttraumatic mania
  - carbamazepine is second-line
  - no reports demonstrating benefits of lamotrigine or other mood-stabilizing anticonvulsants

(Starkstein et al. 1987; Stewart et al. 1988; Bouvy et al. 1988; Kim et al. 2002; Pope et al. 1988; Monji et al. 1999; Yassa et al. 1994; Mustafa et al. 2005; Oster et al. 2007; Daniels and Felde 2008; Murai et al. 2003; American Psychiatric Association 2002; Hirschfeld 2002; Jorge and Arciniegas 2014; Cittolin-Santos et al. 2017)

R_X of Mania: Medications

- There are individual case reports for haloperidol, lithium, and several other atypical antipsychotics, alone or in combinations
- Unfortunately, as many of these report problems with these treatments as they do benefits
- In this population, atypical antipsychotics, particularly as adjuncts to valproate, appear preferable to treatment with lithium, haloperidol, or benzodiazepines

(Starkstein et al. 1987; Stewart et al. 1988; Bouvy et al. 1988; Kim et al. 2002; Pope et al. 1988; Monji et al. 1999; Yassa et al. 1994; Mustafa et al. 2005; Oster et al. 2007; Daniels and Felde 2008; Murai et al. 2003; American Psychiatric Association 2002; Hirschfeld 2002; Jorge and Arciniegas 2014; Cittolin-Santos et al. 2017)



Plot of Young Mania Rating Scale (YMRS) and Functional Independence Measure (FIM) scores by acute rehabilitation hospital day. Treatment with quetiapine 150 mg daily targeting secondary mania was initiated on rehabilitation hospital day 2; quetiapine was titrated to a total daily dose of 850 mg daily by rehabilitation hospital day 14 and to a final dose of 900 mg daily on rehabilitation hospital day 19. (Figure from Oster et al. 2007)

Electroconvulsive Therapy

- When medications are ineffective or poorly tolerated, or if depression or secondary mania becomes life-threatening, ECT (electroconvulsive therapy) may be required
  - ECT is an effective treatment for primary and secondary depressions and severe mania
  - ECT is safe even among persons with posttraumatic epilepsy, cognitive impairment, and other neurological consequences of TBI
  - nondominant unilateral ECT is the preferred technique

(Crow et al. 1996; Kant et al. 1999; Ruedrich et al. 1983; Zwil et al. 1992; American Psychiatric Association 2001)

Disorders of Affect

- The cardinal feature is disturbance of moment-to-moment emotion (the 'emotional weather')
  - pathological laughing and crying
  - essential crying
  - *witzelsucht*
  - episodic irritability/ dyscontrol
  - ?: panic attacks/panic disorder
  - ?: "organic aggressive syndrome"
  - placidity (in apathy states or Klüver-Bucy-like syndromes)

(Green et al. 1987; Dark et al. 1996; Arciniegas and Topkoff 2000; Smith et al. 2004; Arciniegas et al. 2005; Cummings et al. 2007Wortzel et al. 2008)

Pathological Laughing and Crying

- The prototypical disorder of affect is pathological laughing and crying PLC
  - also described as pseudobulbar affect, emotional incontinence, or emotional dyscontrol PLC
- PLC is associated with neurologic conditions, such as TBI, and involves a severe disturbance in moment-to-moment disturbance of emotion - and, in most cases, some degree of disturbance in emotional feeling as well
- PLC does not entail sustained, excessive, and pervasive disturbances of emotional and emotional feeling characteristic of mood disorders (eg, depression, dysthymia, secondary mania), although it may co-occur with them

(Wilson 1924; Arciniegas and Topkoff 1999; Olney 2011; Lauterbach et al. 2013; Wortzel and Arciniegas 2014)

Pathological Laughing and Crying

A. Frequent brief episodes of involuntary and uncontrollable crying and/or laughing

B. Episodes of crying and laughing may involve an episode-congruent emotional feeling, but do not necessarily reflect and do not produce a persistent change in the prevailing mood

C. Episodes are excessively intense with respect to the stimulus that incites them, and may be inappropriate to the context in which they develop (i.e., laughing when crying would be expected or *vice versa*)

D. Episodes reflect a change from usual affect regulation

E. There is evidence of an underlying neurological condition

F. The episodes are subjectively distressing and/or produce clinically significant impairments in social, occupational, or other important aspects of function

(Arciniegas and Topkoff 1999; Arciniegas et al. 2000; Wortzel et al. 2007, Wortzel et al. 2008)

Pathological Laughing and Crying

- The reported frequency of PLC during the first year after injury is 5% to 11%
  - common clinical experience suggests that the frequency of PLC may be less than these reported frequencies and tends to decline further in the late post-injury period
- The prevalence of PLC in the late period following TBI is not known
  - however, for some individuals – especially those with relatively severe TBI involving the dorsolateral and anterior frontal cortices, internal capsule, and/or pontocerebellar structures – PLC may become a chronic condition

(Zeilig et al. 1996; Tateno et al. 2004; Rabins and Arciniegas 2007; Lauterbach et al. 2013; Wortzel and Arciniegas 2014)

Pathological Laughing and Crying

- Although PLC may occur with depression, scores on measures of this problem (e.g., Pathological Laughing and Crying Scale) are not correlated with scores on depression measures
- Improvement of PLC occurs independently of improvement in depression
- Suggests that PLC and depression are distinct disturbances of emotional regulation

(Schiffer et al. 1985; Robinson et al. 1993; Arciniegas and Topkoff 2000; Wortzel et al. 2008)

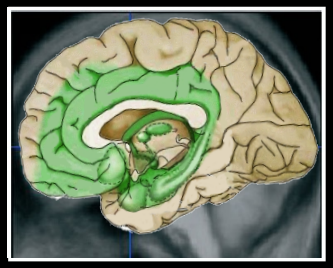
Lesion Location in PLC

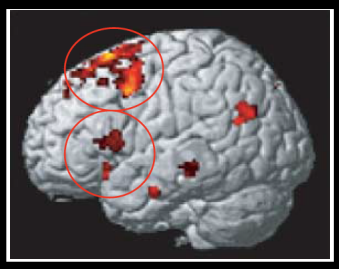
- Lesions to pathways that interfere with dorsal compartment communication with ventral compartment and brainstem effector regions
  - frontopontine projections, cerebello-thalamo-fronto-pontine circuit, cerebello-pontine projections
- Lesions in these pathways release the ventral compartment from descending control
- Parvizi et al. (2001) propose that the cerebellum participates in the modulation of laughing and crying by adjusting these behaviors to social context

(Reviewed in Arciniegas et al. 2005, Rabins and Arciniegas 2007)

Emotion, Feeling, and TBI: Overlapping Neuroanatomies

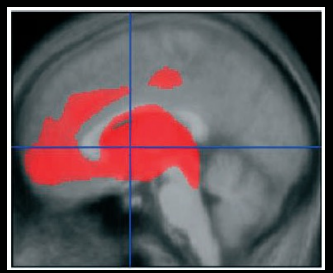
Purves et al. 2001

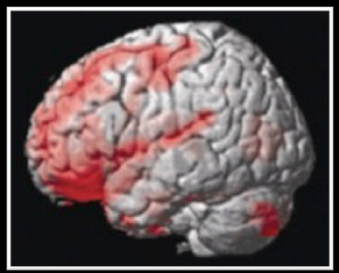




Ochsner and Gross 2005

Salmond et al. 2005





Yeates et al. 2007

Pathological Laughing and Crying

- Careful application of the diagnostic criteria to the clinical history and observations are usually sufficient to establish a diagnosis of PLC
- The Pathologic Laughter and Crying Scale (PLACS) provides two screening questions that facilitate the identification of episodes of emotional dyscontrol – including PLC
- Use of the full measure may facilitate distinguishing PLC from other disorders of affect (affective lability, essential crying, *witzelsucht*) as well as mood disorders

(Robinson et al. 1993)

Pathological Laughing and Crying Scale (PLACS)

Rarely	Occasionally	Quite often	Frequently
0	1	2	3

1. Have you recently experienced sudden episodes of laughter in the past two weeks?
2. Have you recently experienced sudden episodes of crying in the past two weeks?

If the patient responds affirmatively to question 1, questions 3-8 are asked. If the patient responds affirmatively to question 2, questions 11-18 are asked.

Questions regarding laughing spells:

3. Have the episodes of laughter occurred without any cause in your surroundings?
4. Have the episodes of laughter lasted for a long period of time?
5. Have the episodes of laughter been uncontrollable by you?
6. Have the episodes of laughter occurred as a result of a feeling of happiness?
7. Have the episodes of laughter occurred in excess of a feeling of happiness?
8. Have the episodes of laughter occurred as a result of a feeling of sadness?
9. Have the episodes of laughter occurred with any emotions other than happiness or sadness (nervousness, anger)?
10. Have the episodes of laughter caused you any distress or social embarrassment?

Questions regarding crying spells:

11. Have the episodes of crying occurred without any cause in your surroundings?
12. Have the episodes of crying lasted for a long period of time?
13. Have the episodes of crying been uncontrollable by you?
14. Have the episodes of crying occurred as a result of a feeling of sadness?
15. Have the episodes of crying occurred in excess of a feeling of sadness?
16. Have the episodes of crying occurred as a result of a feeling of sadness?
17. Have the episodes of crying occurred with any emotions other than happiness or sadness (nervousness, anger)?
18. Have the episodes of crying caused you any distress or social embarrassment?

(Robinson et al. 1993)

Ictal Displays of Affect

- Dacrystic (quiritarian) seizures
  - complex partial seizure featuring ictal crying
  - more common in patients with right hemisphere seizure foci
- Gelastic seizures
  - complex partial seizure with ictal laughing
  - more common in patients with left hemisphere or hypothalamic seizure foci
    - classic association is with hypothalamic hamartomas in adolescent males

(Luciano et al. 1993; Pearce 2004; Sackheim et al. 1982)

Ictal Displays of Affect

- The displays of crying and laughing in dacrystic and gelastic seizures, respectively, may be difficult to distinguish from those of PLC
- However, dacrystic and gelastic seizures are:
  - followed by a brief period of post-ictal confusion
  - usually associated with ictal epileptiform EEG findings
  - often associated with interictal epileptiform EEG findings
- The consequences and treatments of epilepsy and PLC are distinct, making it imperative to distinguish between these conditions

(Luciano et al. 1993; Pearce 2004; Sackheim et al. 1982)

Treatment of PLC

- SSRIs are first-line treatments
- Mirtazapine or amantadine may useful second-line treatments
- Dextromethorphan/quinidine is a reasonable consideration when SSRIs have failed to reduce PLC
- TCAs (nortriptyline) are third-line

(Klein et al. 1989; Tortella et al. 1989; Yamamoto et al. 1995; Narita et al. 1996; Arciniegas and Topkoff 2000; Bermack et al. 2001; Peeters et al. 2004; Bermack et al. 2005; Dhir et al. 2007; Wortzel et al. 2008; Jorge and Arciniegas 2014)

Psychosocial Interventions

- There are no psychotherapeutic interventions that reduce the frequency or severity of PLC
- However, the development and persistence of PLC can be embarrassing, socially disabling, and difficult to tolerate for affected persons and their families
- Patient and family education regarding PLC, its causes, and available treatments is an essential element of treatment

(Worztel et al. 2008)

Affective Lability

- Affective lability (also known as emotional lability) refers to a tendency to be easily overcome with intense emotions in response to personally or socially meaningful stimuli or events that ordinarily would induce more modest emotional responses
- Affective lability manifests as brief, nonstereotyped episodes of congruent emotional expression and experience that are not discretely paroxysmal, of variable intensity, and partially amenable to voluntary control or interruption by external events (ie, distractors)
- Affective lability characteristically involves crying or laughing but may also entail anxiety and/or irritability

(Poeck 1969; Siever and Davis 1991; Arciniegas and Topkoff 2000; Beresford et al. 2005; Henry et al. 2008; Wortzel et al. 2008; Arciniegas 2013; Arciniegas and Wortzel 2014)

Affective Lability

- Although episodes of affective lability are not stereotyped to the same degree as those of PLC, they involve emotional expressions and experiences that are more stereotyped than normal
- Similar to PLC, affective lability does not necessarily reflect the presence of a mood disorder and does not produce a persistent change in emotion and emotional feeling (ie, mood)

(Woyshville et al. 1999; Arciniegas and Topkoff 2000; Wortzel et al. 2008; Arciniegas 2013; Arciniegas and Wortzel 2014)

Affective Lability

- The reported prevalence of affective lability among persons with TBI is highly variable, at least in part reflecting differences in case definitions, assessment methods, injury severity, time since injury, and ascertainment biases
- Among persons with mild TBI, affective lability may be as high as 28% in the first week to three months after injury
- Among persons with severe TBI, the prevalence of affectively lability (referred to as "mood swings" or "lability of mood" in some reports) range from:
  - 33-46% in the early post-injury period
  - 14-62% in the late post-injury period

(Villemure et al. 2011; King et al. 1995; Cicerone et al. 1995; Meterko et al. 2012; Kreutzer et al. 1996; MiKinlay et al. 1981; Pelegrin-Valero et al. 2001; Deb et al. 1999; reviewed in Arciniegas and Wortzel 2014)

Affective Lability

- Affective lability is not specific to TBI or to traditionally defined neurologic disorders - it is observed in a broad range of psychiatric and medical problems
  - particularly depressive and dysthymic episodes, manic and hypomanic episodes, euthymic period of bipolar disorder, substance use disorders (intoxication or withdrawal), and among individuals with idiopathic personality disorders
- This broad differential diagnosis must be considered before separately diagnosing and treating affective lability

Harvey et al. 1989; Arciniegas and Topkoff 2000; Henry et al. 2001; Koenigsberg et al. 2002; Beresford et al. 2005; Mackinnon et al. 2006; Henry et al. 2008; Reich et al. 2009; Solhan et al. 2009; Parmentier et al. 2012;

Affective Lability

- The evaluation of affective lability among individuals capable of providing reliable self-report is guided usefully by the Affective Lability Scale (ALS) or the CNS-LS (an abbreviated form of the ALS)
  - as the CNS-LS is the shorter measure, it is more practical for use in daily practice
  - note that the CNS-LS, commonly used to screen for pseudobulbar affect (PBA), is in fact a screen for affective lability, not PLC/PBA
- Among persons with severe cognitive impairments or self-awareness deficits, the NPI is an informant-based interview identifies affective lability via items in the dysphoria, elation, and irritability/lability subscales
  - the NPI-Q is presently an element of the National Institutes of Neurological Diseases and Stroke - General Common Data Elements (CDE)

Harvey et al. 1989; Cummings et al. 1994; Solhan et al. 2009; Arciniegas and Wortzel 2014; Kaufer et al. 2000)

Affective Lability

- Psychological interventions include counseling and education focused on improving self-efficacy and self-regulation
- Pharmacotherapies include:
  - first-line: SSRIs
  - second-line: methylphenidate, tricyclic antidepressants (nortriptyline), amantadine
  - third-line: dextromethorphan/quinidine

(Arciniegas and Topkoff 2000; Wortzel et al. 2008; Wilson 2008; Arciniegas and Wortzel 2014)

Irritability

- 'Irritability' refers both to an internal experience (ie, becoming annoyed easily) as well as overt expressions reflecting that experience (ie, showing anger)
- Irritability and associated symptoms (eg, annoyance, impatience, anger, loss of temper) are common in the general population and tend to increase in frequency and/or severity after mild, moderate, or severe TBI

(Bohnen et al. 1992; Dikmen et al. 1996; van der Naalt et al. 1999; Kim et al. 1999; Alderman 2003; Scherer et al. 2004; Ettenhofer et al. 2009; Ettenhofer and Barry 2012; Yan et al. 2013; Arciniegas and Wortzel 2014)

Attribution of Irritability to TBI

- As a result of the commonplace occurrence of irritability and associated symptoms in the general population, clinicians should be very cautious about attributing irritability solely to TBI
- Pre-injury emotionality, comorbid psychiatric disorders (especially dysphoric depression, irritable mania/hypomania, mixed mood episode, anxiety disorders, posttraumatic stress disorder), substance use, pain, and medications may contribute to or entirely explain irritability among persons with TBI
- Each of these will usually be a more appropriate first target of treatment than irritability itself, and their effective treatment may obviate treatments targeting irritability specifically

(Linn et al. 1994; Iverson et al. 1997; Fann et al. 2000; Tateno et al. 2003; Jorge et al. 2004; Baguley et al. 2006; Johansson et al. 2008; Halbauer et al. 2009; Scherer et al. 2010; Seel et al. 2010; Castano Monsalve et al. 2012; Maguen et al. 2012; Arciniegas and Wortzel 2014)

Posttraumatic Irritability

- Early post-injury irritability is characterized by 'snappiness,' with irritability arising in response to nearly any stressor or frustration; this problem tends to resolve over time after TBI
- Late post-injury irritability is characterized by recurrent, transient, ego-dystonic outbursts that are triggered by unpredictable and trivial stimuli and represent a change from pre-injury affective responding (ie, such responses are "out of character")
- Emotional state between episodes of irritation, in general, is otherwise euthymic

(Eames 2001; Alderman 2003; Arciniegas and Wortzel 2014)

Irritability after Mild TBI

- Among persons with mild TBI, irritability is a common postconcussive symptom in the early post-injury period
- In most individuals with such injuries, posttraumatic irritability improves over time such that it occurs at a frequency comparable to that among persons without TBI

(McKinlay et al. 1981; Dikmen et al. 1986; Bohnen et al. 1992; Cicerone et al. 1995; Deb et al. 1999; Rapoport et al. 2002; Meterko et al. 2012; American Psychiatric Association 2013; Yang et al. 2013; Arciniegas and Wortzel 2014)

Irritability after Moderate-to-Severe TBI

- In their sample of 55 subjects, McKinlay et al. (1981) observed first-year post-injury irritability in 63-71%
- Deb et al. (1999) observed first-year post-injury irritability in 35% of 196 individuals with hospitalization-requiring TBI of at least complicated mild severity
- In both of these and other studies, posttraumatic irritability frequently co-occurred with other symptoms of emotional and behavioral dyscontrol, including impatience, mood swings (ie, affective lability), and verbal outbursts

(McKinlay et al. 1981; Dikmen et al. 1986; Bohnen et al. 1992; Cicerone et al. 1995; Deb et al. 1999; Rapoport et al. 2002; Meterko et al. 2012; Yang et al. 2013; Arciniegas and Wortzel 2014)

Insight and Irritability after TBI

- Yang et al. (2012, 2013) observed greater self-reported irritability among persons with mild TBI than among those with moderate to severe TBI, and the reported frequencies of irritability among persons with moderate to severe TBI did not differ from those of healthy comparators
- Caregiver-reported irritability among persons with moderate to severe TBI was comparable with that self-reported by those with mild TBI, both of which were higher than the frequency reported by persons without TBI
- Deficits in self-awareness among persons with moderate to severe TBI drove this discrepancy in self-reported versus informant-reported posttraumatic irritability
- Different methods of neuropsychiatric evaluation may be required to identify, characterize, and monitor changes in posttraumatic irritability in persons with mild versus moderate-to-severe TBI

(Brooks et al. 1987; Kim et al. 1999; Yang et al. 2012; Yang et al. 2013; Arciniegas and Wortzel 2014)

Evaluation of Irritability after TBI

- For persons with preserved insight/self-awareness after TBI, self-report measures of posttraumatic irritability include:
  - Neurobehavioral Symptom Inventory (NINDS TBI CDE)
  - Irritability Questionnaire
  - National Taiwan University Irritability Scale
- For persons with impaired insight/self-awareness after TBI, informant- and/or clinician-based assessment measures of posttraumatic irritability include:
  - Neuropsychiatric Inventory – NPI, NPI-NH, NPI-Q (NINDS General CDE), NPI-C

(Cummings et al. 1994; Cicerone et al. 1995; Wood et al. 2000; Kaufer et al. 2000; Cantagallo et al. 2002; Kilmer et al. 1119; Craig et al. 2008; de Medeiros et al. 2010; Ciurli 2011; Castano Monsalve 2012; Yang et al. 2011; NINDS 2013; Meterko et al. 2012; Arciniegas and Wortzel 2014)

Treatment of Irritability after TBI

- Nonpharmacologic intervention are first-line treatments, especially among patients with mild or moderate irritability symptoms and relatively preserved cognition
  - counseling and supportive psychotherapy
  - manualized anger self-management training developed specifically for persons with TBI
  - Group cognitive behavioral therapy, modified to accommodate posttraumatic cognitive impairments
  - structured rehabilitation interventions that focus concurrently on improving emotional self-regulation and functional cognitive performance

(Walker et al. 1998; Leon Carrion et al. 2001; Rees and Bellon 2007; Cicerone et al. 2008; Cattelani et al. 2010; Caracuel et al. 2012; Hart et al. 2012; Arciniegas and Wortzel 2014)

Treatment of Irritability after TBI

- Severe irritability and associated symptoms may require adjunctive pharmacotherapy
- When an individual with posttraumatic irritability is unable to engage effectively in symptom-targeted nonpharmacologic treatments, pharmacotherapy may be the principal method of treatment
- Effective pharmacotherapy may facilitate participation in counseling, psychotherapy, or behavioral therapies
- Published case reports and case series report improvements in posttraumatic irritability during treatment with sertraline, valproate, methylphenidate, carbamazepine, quetiapine, aripiprazole, buspirone, propranolol, and homeopathic medications – most of which had other symptoms as their primary targets

(Elliott 1977; Gualtieri 1991; Wroblewski et al. 1997; Kant et al. 1998; Chapman et al. 1999; Azouvi et al. 1999; Kim and Bijlani 2006; Umene-Nakano 2013; Arciniegas and Wortzel 2014)

J Head Trauma Rehabil

Effectiveness of Amantadine Hydrochloride in the Reduction of Chronic Traumatic Brain Injury Irritability and Aggression

Background: Following traumatic brain injury (TBI), individuals may experience chronic problems with irritability or aggression, which may need treatment to minimize the negative impact on their relationships, home life, social interactions, community participation, and employment. **Objective:** To test the a priori hypothesis that amantadine reduces irritability (primary hypothesis) and aggression (secondary hypothesis) among individuals greater than 6 months post-TBI. **Methods:** A total of 76 individuals greater than 6 months post-TBI referred for irritability management were enrolled in a parallel-group, randomized, double-blind, placebo-controlled trial of amantadine ($n = 38$) versus placebo ($n = 38$). Study participants were randomly assigned to receive amantadine hydrochloride 100 mg twice daily versus equivalent placebo for 28 days. Symptoms of irritability and aggression were measured before and after treatment using the Neuropsychiatric Inventory Irritability (NPI-I) and Aggression (NPI-A) domains, as well as the NPI-Distress for these domains. **Results:** In the amantadine group, 80.56% improved at least 3 points on the NPI-I, compared with 44.44% in the group that received placebo ($P = .0016$). Mean change in NPI-I was −4.3 in the amantadine group and −2.6 in the placebo group ($P = .0085$). When excluding individuals with minimal to no baseline aggression, mean change in NPI-A was −4.56 in the amantadine group and −2.46 in the placebo group ($P = .046$). Mean changes in NPI-I and NPI-A Distress were not statistically significant between the amantadine and placebo groups. Adverse event occurrence did not differ between the 2 groups. **Conclusions:** Amantadine 100 mg every morning and at noon appears an effective and safe means of reducing frequency and severity of irritability and aggression among individuals with TBI and sufficient creatinine clearance. **Key words:** *aggression*, *agitation*, *amantadine*, *brain injuries*, *dopamine*, *irritability*

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Amantadine Effect on Perceptions of Irritability after Traumatic Brain Injury: Results of the Amantadine Irritability Multisite Study

Abstract

This study examines the effect of amantadine on irritability in persons in the post-acute period after traumatic brain injury (TBI). There were 168 persons ≥6 months post-TBI with irritability who were enrolled in a parallel-group, randomized, double-blind, placebo-controlled trial receiving either amantadine 100 mg twice daily or equivalent placebo for 60 days. Subjects were assessed at baseline and days 28 (primary end-point) and 60 of treatment using observer-rated and participant-rated Neuropsychiatric Inventory (NPI-I) Most Problematic item (primary outcome), NPI Most Aberrant item, and NPI-I Distress Scores, as well as physician-rated Clinical Global Impressions (CGI) scale. Observer ratings between the two groups were not statistically significantly different at day 28 or 60; however, observers rated the majority in both groups as having improved at both intervals. Participant ratings for day 60 demonstrated improvements in both groups with greater improvement in the amantadine group on NPI-I Most Problematic ($p < 0.04$) and NPI-I Distress ($p < 0.04$). These results were not significant with correction for multiple comparisons. CGI demonstrated greater improvement for amantadine than the placebo group ($p < 0.04$). Adverse event occurrence did not differ between the two groups. While observers in both groups reported large improvements, significant group differences were not found for the primary outcome (observer ratings) at either day 28 or 60. This large placebo or nonspecific effect may have masked detection of a treatment effect. The result of this study of amantadine 100 mg every morning and noon to reduce irritability was not positive from the observer perspective, although there are indications of improvement at day 60 from the perspective of persons with TBI and clinicians that may warrant further investigation.

Key words: agitation; aggression; amantadine; brain injuries; irritability

Essential Crying

- A lifelong and hereditary propensity to easy crying
- Congruent affective expression and experience
- May be embarrassing but not functionally impairing
- May lie on the continuum between affective lability and normal affective variability

(Green and Bernat 1999; Green et al. 1987)

Witzelsucht

- Roughly translated from German as "seeking, or addicted to, wit," it is used to refer to a pathological tendency to engage in trivial joking
- Characterized by frequently and inappropriately elevated or giddy affect in which the patient experiences most everything as genuinely funny, frequently laughs, and makes childish, facetious, or sarcastic remarks
- Caregivers and others generally do not find the patient's remarks funny, but instead tend to experience them as rude, socially inappropriate, and/or latently hostile

(Berkovic SF, Andermann F. Pathological laughing. In Joseph AB, Young RR, eds. Movement Disorders in Neurology and Neuropsychiatry. Oxford, UK: Blackwell Science, Inc; 1999. Duchowny MS. Pathological disorders of laughter. In McGhee PE, Goldstein JH, eds. Handbook of Human Research, Vol II. New York, NY: Springer-Verlag; 1983.

Witzelsucht

- Distinguished from PLC and affective lability by:
  - admixture of irritability and mirth
  - absence of discrete and stereotype paroxysmal displays of affect
  - the purposeful (even if uncontrollable) and complex character of the behavior
- Most commonly seen in patients with frontal lobe disease or injury
  - especially right frontal lobe tumors or trauma

(Berkovic and Andermann 1999; Duchowny 1983)

Summary

- Emotion and emotional feeling describe the objective and subjective psychophysiologic processes, respectively, that move us to action and allow us to experience and interpret the meaning of such movements
- These processes are divided into two clinical types on temporal grounds
  - sustained baseline emotion and feeling: mood
  - moment-to-moment emotion and feeling: affect

Summary

- Emotion and feeling derive from a complex set of limbic, paralimbic, and cortical-subcortical networks
- Emotions are generated within, maintained by, and inexorable from the same systems subserving social intelligence/comportment, motivation, and executive function
- Their neuroanatomy and neurochemistry overlaps substantially with those of TBI

Summary

- The DSM criteria for mood disorders appears useful for their diagnoses among persons with TBI
- The DSM does not describe disorders of affect, among which PLC is prototypic
- Effective treatment of persons with these conditions following TBI depends on accurate diagnosis

Summary

- Some of these problems (esp. depression) may be influenced, but not explained, by the presence of pre-injury psychiatric problems
- Disorders of mood and affect following TBI are amenable to pharmacologic treatment
- Depression may improve with psychological interventions
  - it is unclear whether or to what extent posttraumatic mania, PLC, and affective lability are amenable to non-phamacologic treatment

Summary

- Additional research is needed to:
  - define more fully the epidemiology, neurobiology, and psychosocial contributors to post-TBI disorders of mood and affect
  - identify pharmacologic and non-pharmacologic treatments for these problems
    - multicenter, randomized, placebo-controlled studies are needed
  - identify predictors of response to medications, psychological interventions, or both in this population