Subdivision of Depression

Temperament
Sleep
Light
Depression (Sub division)

The four possible common features of depressed mood are:

- the personality trait of Neuroticism;
- the state of malaise (fatigue, aching etc) which accompanies an illness with an activated immune system;
- demotivation due to lack of positive emotions (anhedonia);
- the syndrome of seasonal affective disorder (SAD).
Possible Treatment or Stabilising Agents

• **Neuroticism (depression with anxiety):** St John’s Wort
  Nutrients: Vitamin C, methylating nutrients, magnesium, 5 hydroxytryptophan

• **Malaise:** Reduce sleep disruption, shift work, regulate circadian rhythm: Reduce the action of immune cytokines:
  analgesics/pain killers such as aspirin, ibuprofen, paracetamol/acetaminophen and the opiates
  Nutrients: quercetin, dl-phenylalanine, tyrosine, mitochondrial nutrients, chromium picolonate, light therapy

• **Demotivation:** energizing agents such as caffeine and nicotine
  Nutrients: mitochondrial nutrients, dl-phenylalanine, tyrosine and cofactors, chromium picolinate

• **SAD:** bright light used in the early morning
  Nutrients: tryptophan and cofactors, methylating agents, melatonin

• Charlton BG Med Hypotheses 2009;72(1):1-7
Adjuvant Use Of Nutritional Medicines With Antidepressants

Various nutrients also have emerging evidence as effective adjuncts with antipsychotics and mood stabilizers. These include:

- omega-3 fatty acids,
- SAMe,
- folic acid/folacin
- l-tryptophan
Treatment And- Monitoring (S-DTM) Model

• Diagnosis

1. Recognition of a depressed, unhappy, low mood.

2. Introspective self–diagnosis of the sub-type of symptomatic and emotional cause of depressed mood.

3. Matching the symptoms and emotions to one of the four sub-types of ‘depression’.

4. Matching the sub-type of depression to the drug class which is most likely to alleviate those symptoms and emotions.

5. Researching the scientific literature on the effects, side effects and possible interactions of the drug class – and choose a (probably) safe first-line agent.
Treatment And- Monitoring (S-DTM) Model

- **Self-treatment**


- **Self-monitoring**
  
    7. Very careful monitoring for effects and side effects for the first 4 hours after taking the agent, and continued vigilance for several days. Keep a record. (e.g. Consider self-monitoring blood pressure when using psychostimulant type drugs.)
  
    8. If immediate problems of side effects or feeling worse after taking a drug, consider stopping immediately – or continue with vigilant self-monitoring.
  
    9. If no benefit at all after a few days consider increasing dose or stopping and trying another agent.
  
    10. If side effects are bad, or there is concern over dependence, or if unsure about whether or not the drug is having benefit, or if wanting to stop taking the drug; consider stopping the agent and self-monitoring the result of stopping – then consider restarting and monitor the results of restarting.
  
    11. Go through the process for each new agent tried. Avoid interactions between the drugs and nutrients.
A Model Of Suicidal Behaviour In War Veterans With PTMD.

- Polymorphism of dopamine receptor and detox enzymes
- Low birth weight and maternal malnutrition in pregnancy
- Temperamental predisposition, previous exposure to traumatic events, family history of psychological problems, history of mental disorders, psychosocial problems, and life adversity
- Pre-deployment stress include shortened tempers, difficulty sleeping and trouble concentrating.
- Time, duration and type of stressor, sense of controllability, degree of personal impact, immediate reactions to the event, presence of dissociation at the time of the traumatic event and persistence of life threatening events
- Perceived social support, stressful situations, ongoing threat to safety, the state of health, nutrition, alcohol and drug use, climate may affect the mental condition of a war veteran
- Most likely, precipitants of suicidal acts in war veterans include interpersonal losses or conflicts, financial trouble, and job problems

Brain Energy and Mood Disorders

Hypofrontanality
Mitochondria
Hypofrontanality

• The “hypofrontality” is a term denoting local reduced glucose turnover in regions of the brain

• Cerebral blood flow (CBF) is able to influence the glucose metabolism

• Patients with depressive disorder have reduced blood flow in the prefrontal cortex, anterior cingulate cortex and caudate nucleus

Inhibition Of Mitochondrial Respiratory Chain And Depression.

• After 40 days of mild stress the following were observed in animal studies:
  – a reduction in sweet food ingestion
  – increased adrenal gland weight, when compared to control group. Mitochondrial complex I, III and IV were inhibited in stress group only in cerebral cortex and cerebellum.
  – Complex II and creatine kinase were not affected in stressed group.

Astroglia

- Historically, research upon the CNS has almost been exclusively focused upon neurons. It is easy to forget that only a tenth of the total cell number in the brain is neurons. And the possibility that other cell types can be heavily involved in pathological processes, should definitively be considered.

- Almost all neurotransmitters and neuropeptide receptors are found on the astroglial processes, and these are in close proximity to synapses.

- This implies that antidepressant pharmacotherapy may have astroglia as target, and not necessarily neurons.
Brain Structure and Depression

• Abnormal sizes/volumes of different parts in the brain have been found in depressed patients

• Öngür et al. found significant glial reduction in the prefrontal cortex from patients with mood disorders, but not schizophrenia.

• Studies of post mortem brains of depressed individuals found 20–30% reduction in the mean density of glia in several layers of the dorsolateral prefrontal cortex, ≈15% reduction in the caudal orbitofrontal cortex, and a trend to reduction in the rostral orbitofrontal cortex, but this did not reach statistical significance.

• There were also several abnormalities regards neurons.
Panic Attacks/Disorder

Panic disorder (PD) is a complex condition that is further complicated by its numerous inducers, which include hypercapnia, hypoxia, sodium lactate, caffeine and cholecystokinin.
Distinguishing generalized anxiety disorder, panic disorder, and mixed anxiety states in older treatment-seeking adults.

Higher scores on measures of sympathetic arousal, agoraphobic avoidance, and rates of comorbid somatization disorder and alcohol dependence distinguished those with panic disorder from those with GAD.

Higher scores on measures of depression and hostility, but not trait anxiety or worry, distinguished the GAD group.

Results indicate that distinguishing features of GAD and PD in older treatment-seeking adults may be fewer and slightly different from those of younger adults.

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) Definition of 'Anxiety Disorders''

- Panic disorder, with and without agoraphobia
- Agoraphobia, without a history of panic disorder
- Social anxiety disorder (SAD)
- Specific phobia
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Acute stress disorder
- Generalised anxiety disorder (GAD)
- Anxiety disorder due to a general medical condition
- Substance-induced anxiety disorder
- Anxiety disorder not otherwise specified
autonomic nervous system showing typical panic responses in phobia and reflecting increased sympathetic nervous system activity

- hypothalamus
- brainstem
- upper spinal cord
- blood vessel
- increased blood pressure
- trachea - lungs
- hyperventilation
- heart
- increased heart rate
- stomach
- stomach secretions
- liver
- kidney
- bowel
- increased defaecation
- bladder
- increased urination

key
- peripheral organs
- areas of the brain
- response

- blood vessel
- pupils dilate

- skin
- piloerection
- sweating

- lower spinal cord

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The Areas Of The Brain Affected In Generalised Anxiety Disorder
The Areas Of The Brain Affected In Panic Disorder
The Areas Of The Brain Affected In Phobia

There is an increased incidence of panic disorder and major depression in patients with chronic obstructive pulmonary disease (COPD) compared with the general population: the existing studies suggest that clinically significant symptoms of depression and anxiety occur in approximately 50% of all COPD cases.

The Pulmonary Neuroepithelial Bodies (Nebs)
Hypoxia-sensitive Chemoreceptors
**Possible Mechanism of PD**

- In any inflammation, there is an interaction between the inflammatory mediators: bradykinin (BK), serotonin (5-HT), prostaglandin E(2) and acidic pH.

- As the inflammatory NEBs are sensitive to these substances, BK, which augments the airway hyper-response to diverse inducers (for example, hypercapnia, hypoxia, sodium lactate and caffeine), might cause these cells to release 5-HT along with peptides and pan-neuro-endocrine markers from their dense-core secretory granules.

- When 5-HT and BK cross the BBB, the release of 5-HT at the axonal terminals in the serotonergic neurons in the brain will be inhibited, since the 5-HT1 autoreceptors have a higher affinity for 5-HT than do the 5-HT2 receptors.

- It is easy to suppress the periaqueductal gray matter (PAG), which inhibits flight reactions to impending danger, pain or asphyxia.

- In short, the inhibition of serotonergic neurons might bring about flight reactions.

- Moreover, the periaqueductal gray (PAG) efferent pathways modulate cardiovascular-related sympathetic-outflow systems. PAG also serves as the midbrain link between the forebrain emotional-processing systems and the motor pathways that are used in the defence reaction. Therefore, 5-HT and BK might modulate the effects of the flight reaction in the central nervous system.
Possible Mechanism of PD

- BK has a dual effect on sympathoexcitation: firstly, it directly excites sympathetic neurons via B(2) receptors and induces the release of noradrenaline;
- BK with 5-HT is indirectly associated with the central noradrenergic system.
- Patients with PD therefore suffer from palpitations, tremulousness and excessive sweating, which are all symptoms produced by the β-adrenergic receptors, and these are compounded by the additional effects of the flight reaction and other inflammatory mediators (for example, fear of losing control, fear of dying, feeling of unreality, sensation of shortness of smothering, feeling of choking, paresthesias, nausea and anticipatory anxiety).
The Areas Of The Brain Affected In Obsessive Compulsive Disorder
Sleep and Panic Disorder

- A high percentage of panic disorder individuals report subjective sleep disturbances.

- 92.3% of patients with both nocturnal panic attacks and depression report striking extremes in sleep duration or insomnia.

- Nocturnal-sleep panic attacks and depression are independently as well as interactively associated with increased sleep disturbances in panic disorder.

- Although these findings are expected, they underscore the importance of assessing sleep functions, including over-sleeping, in panic disorder patients.

Sleep and Mood Disorders

Disturbed sleep is one of the hallmark signs of depression.
Clinical Psychology Training In Sleep And Sleep Disorders

• There is growing evidence to suggest that clinical psychologists would benefit from more training in sleep and sleep disorders.

• Sleep disturbances are commonly co-morbid with mental health disorders and this relationship is often bidirectional.

• In addition, psychologists have become integral members of multidisciplinary sleep medicine teams and there are not enough qualified psychologists to meet the clinical demand.

Sleep and Depression

• Human sleep data suggest that changes in REM sleep, mediated by the noradrenergic, serotonergic and cholinergic systems, are not only a consequence of depression, but can be seen as true endophenotype of the disease.
How Do We Measure Sleep

EEG
## Frequency and amplitude waves associated with the awake and sleep state.

<table>
<thead>
<tr>
<th>Stage</th>
<th>EEG Rate (Frequency)</th>
<th>EEG Size (Amplitude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>8-25 Hz</td>
<td>Low</td>
</tr>
<tr>
<td>Stage 1 NREM</td>
<td>6-8 Hz</td>
<td>Low</td>
</tr>
<tr>
<td>Stage 2 NREM</td>
<td>4-7 Hz</td>
<td>Medium</td>
</tr>
<tr>
<td>Stage 3 NREM</td>
<td>1-3 Hz</td>
<td>High</td>
</tr>
<tr>
<td>Stage 4 NREM</td>
<td>Less than 2 Hz</td>
<td>High</td>
</tr>
<tr>
<td>REM</td>
<td>More than 10 Hz</td>
<td>Low</td>
</tr>
</tbody>
</table>

- **Awake**: 30-80 Hz (these waves are more synchronised than the 8-25 Hz)
- **Stage 1 NREM**: Occasional "sleep spindles"
- **Stage 2 NREM**: Occasional "K" complexes
<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awake</strong></td>
<td>• “Alert” brain</td>
</tr>
<tr>
<td></td>
<td>• Muscles relatively tense</td>
</tr>
<tr>
<td><strong>Non-REM sleep</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>• Transition stage</td>
</tr>
<tr>
<td></td>
<td>• Light sleep</td>
</tr>
<tr>
<td></td>
<td>• Reduced brain-wave activity</td>
</tr>
<tr>
<td></td>
<td>• Slow eye movements</td>
</tr>
<tr>
<td>Stage 2</td>
<td>• Muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>• Decreased body temperature</td>
</tr>
<tr>
<td></td>
<td>• Reduced heart rate</td>
</tr>
<tr>
<td></td>
<td>• Sleep spindles on electroencephalograph</td>
</tr>
<tr>
<td></td>
<td>• K-complexes on electroencephalograph</td>
</tr>
<tr>
<td>Stages 3 and 4 (slow-wave sleep)</td>
<td>• Deep sleep</td>
</tr>
<tr>
<td></td>
<td>• High-voltage, low-frequency brain waves</td>
</tr>
<tr>
<td></td>
<td>• Restorative sleep</td>
</tr>
<tr>
<td><strong>REM sleep</strong></td>
<td>• Rapid eye movements</td>
</tr>
<tr>
<td></td>
<td>• Vivid dreaming</td>
</tr>
<tr>
<td></td>
<td>• Increased brain activity</td>
</tr>
<tr>
<td></td>
<td>• Increased heart rate</td>
</tr>
<tr>
<td></td>
<td>• Increased respiratory rate</td>
</tr>
<tr>
<td></td>
<td>• Active inhibition of voluntary muscles</td>
</tr>
</tbody>
</table>

**Note:** REM = rapid eye movement.
Hypnogram Of The Natural Sleep Cycle

REM sleep is indicated by the heavy bar.
**Sleep Cycle**

1. Interim between consciousness and sleep
   - Move to Stage 2 after 5-15 mins
   - Heart rate slows, brain does less complicated tasks

2. Increase in eye movement, heart rate, breathing, BP & temperature
   - After another 15 mins, move into non-REM sleep, the Delta stage

3. Move into REM sleep approx 90 mins after first feeling sleepy
   - Body makes repairs

4. Body temperature & BP decreases
   - BP = Blood Pressure

5. REM

---

(3, 2)
Sleep Spindles

- Melatonin which acts by promoting spindle formation.

- Word-pair learning relies on stage 2 sleep spindles and requires little SWS.

- Sleep spindles occur in humans with a “periodicity” of approximately 4 s.

- Sleep spindles (SS) are conducted by the thalamus during sleep and have an inhibitory effect on information rising through the thalamus to the cortex, probably representing the mechanism called Arousal Inhibitory Mechanism.
K complexes and Sleep

• K-complexes (KCs) are evoked delta frequency electroencephalogram (EEG) responses during sleep that occur when large numbers of healthy cortical cells burst fire in a synchronized manner.

• The KC amplitude and incidence are sensitive measures of normal healthy brain aging.

• Alcohol and aging reduces K complex firing
Micro- Arousals and K Complexes

- Micro-arousal (MA) are low-voltage fast-rhythm electroencephalographic (EEG) arousals associated with high-amplitude EEG bursts, delta-like or K-complexes.
- Slow and fast MA are not randomly scattered but appear structurally distributed within sleep representing state-specific arousal responses.
- MA preceded by slow waves occurs more frequently across the descending part of sleep cycles an types (coupled with mild autonomic activation) in the first cycles while fast type of arousals types (coupled with a vigorous autonomic activation) across the ascending slope of cycles prevails during the last third of sleep.
- MA are not isolated events but are basically endowed with a periodic nature expressed in non-rapid eye movement (NREM) sleep by the cyclic alternating pattern (CAP).
- Functional significance of arousal in sleep, and particularly in NREM sleep, is to ensure the reversibility of sleep, without which it would be identical to coma.
- Arousals may connect the sleeper with the surrounding world maintaining the selection of relevant incoming information and adapting the organism to the dangers and demands of the outer world.
K complexes and Dementia

- A lower probability of eliciting a K-complex correlates with greater dementia severity, as measured by the Mini Mental State Examination and Dementia Rating Scale

Stages of Sleep

• **Stage 1** is a transition between wakefulness and sleep; the slightest event can bring back the individual to wakefulness. Normally we spend approximately 5% of our sleeping time in stage 1. Beta waves give way to Alpha waves as the transition occurs from awake to sleep.

• **Stage 2** is the first “real” sleep stage and it represents over 50% of our total sleep time. Here theta waves (3-7Hz) start to appear. In stage 2, the eyes do not move, muscle tone is low compared to wakefulness. As the sleeper engages into stage 2 sleep the theta waves continue interspersed with two unusual wave phenomena that occur periodically every minute or so, the EEG sleep spindles and K-complexes.

  • The former is a sudden increase in wave frequency and the latter is a sudden increase in wave amplitude. These sleep spindles are transient EEG oscillations of about 12-16 Hz. Sleep spindles originate in the thalamus and have a sleep protective function by reducing sensory transmission to the cortex. They also are involved in brain plasticity processes during sleep.

• **Stage 1 and 2** are relatively ‘light” stages of sleep, and if someone is woken during this period of sleep they often report that they were not asleep.
Stages of Sleep

- **Stages 3 and 4** also called **Slow Wave Sleep (SWS)**; cover approximately 20% of our total sleeping time.

- The tall (high amplitude) and slow wave activity observed in the EEG is the hallmark of stage 3 and 4. They are called **delta waves with a frequency of 0.5-2 Hz** and a voltage in excess of 75 uV.

- Delta waves appear initially on only 20 to 50% of the recording (stage 3) and they slowly dominate the entire recording (stage 4). In these stages, sleep is very deep and it is difficult to be awakened by external events. If awakened, the individual is often confused, disorientated or frightened.

- There is evidence that stages 3 and 4 play an important role in mental and physical recuperation and regeneration. It is also interesting to note that sleepwalking and sleep talking is most likely to occur during delta sleep.
Stages of Sleep

• **REM** is the last stage of the sleep cycle. It is associated with a sudden and dramatic loss in muscle tone and rapid eye movement as recorded by the EMG and EOG.

• The skeletal muscles of a person in REM sleep are effectively paralysed.

• The brain wave pattern comprises a combination of alpha and beta waves and desynchronous waves.

• **It is in REM sleep that most dreaming occurs.**
Physiological Variables Associated with Sleep

- Muscle tone and spinal reflexes can be maintained during NREM, but are severely depressed during REM.
- Brain activity varies in different brain structures during sleep e.g. In the raphe nuclei and locus coeruleus, neuronal activity is maintained during NREM but stopped during REM, but in the occipital cortex neuronal activity is higher during REM than NREM.
- Cerebral blood flow increases dramatically when subjects pass from NREM to REM.
- Heart rate, respiration rate and blood pressure are more variable during REM than NREM.
- Dreaming is reported more frequently on awakenings from REM than on awakenings from NREM
- Penile erections occur during most REM periods.
<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Electrophysiology</th>
<th>Neurochemistry</th>
<th>Functional anatomy</th>
</tr>
</thead>
</table>
| **NREM:** Stage I  
Stage II  
SWS  
Stage III  
Stage IV | - Loss of α-EEG  
- Spindles/k-complex  
- Slow wave synchronous EEG | Aminergic & Cholinergic conc. LOW | ↓ Activity in pons, thalamic, limbic, frontal, temporal regions |
| **REM:** | - Increased EEG frequency  
- PGO waves  
- Muscle atonia | Aminergic conc. LOW, Cholinergic conc. HIGH | ↓↓ Activity in lateral prefrontal cortex, ↑ activity in visual, medial frontal, limbic system, anterior cingulate. |
THE DREAMING BRAIN

REM sleep produces a particular pattern of brain activity

- **Active**
- **Inactive**

**Parietal cortex** body sense and movement control

**Prefrontal cortex** rational thought

**Visual cortex**- areas that generate internal imagery are active, even without input from the eyes

**Thalamus** controls brain rhythms

**Hippocampus** memory regions (long term) - short-term memory become inactive, dreamer forgets what just happened.

**Hypothalamus** controls sleep onset and circadian rhythms

**Brain stem** controls switch between REM and non-REM sleep

**Amygdala** and surrounding tissues produce emotions - emotion up, judgment down, giving free rein to unconscious feelings and drives - the subconscious mind in Freudian theory

**SENSORY INPUT BLOCKED DURING REM**

**MOTOR OUTPUT BLOCKED DURING REM**
Bio-Rhythms or Cycles

- The body contains multiple systems that function in cycles. The duration of the cycles vary according to the system investigated. Heart rate, respiration, hormonal function, immunity, liver and gastrointestinal function, reproductive function and sleep/wake are all controlled by biorhythms.

- These rhythms permit the body to do the right thing efficiently and at the right time with some flexibility. However, these rhythms can be disrupted (through jetlag, shift work, drugs, irregular work hours and stress) thus impacting on sleep, performance and well-being.

- Most human behavioural and physiological processes are characterized by daily oscillations. Circadian rhythms are rhythms recurring once a day. Examples of circadian rhythms are body temperature and some hormonal cycles (melatonin, cortisol etc.).

- Rhythms with longer or shorter frequencies are called infradian and ultradian rhythms, respectively.
Schematic Representation Of Basic Processes Underlying Sleep Regulation:

**Homeostatic**
- W (Wakefulness) decreases as sleep propensity increases.
- S (Sleep) increases as sleep propensity increases.
- Time of day indicated as 7 AM to 11 PM.

**Circadian**
- W (Wakefulness) and S (Sleep) follow a diurnal pattern.
- W decreases and S increases during the day.
- Time of day indicated as 7 AM to 11 PM.

**Ultradanian**
- N (Naps) and R (Resuming Sleep) indicate periodic sleep cycles.
- Time of day indicated as 7 AM to 11 PM.
Sleepiness Measured Over a 24-hour Cycle

Sleep drive increases
A prolonged period of waking accumulates sleep pressure, increasing both the duration and the intensity of the subsequent sleep period.
Circadian Rhythms Of Sleep And Wakefulness In A Constant Light Environment.

Without exposure to environmental synchronizers these subject's sleep/wake rhythms couldn’t stay synchronized to the 24-hour day/night cycle.
Sleep and Aging

Phase Shift
Insomnia,
REM Sleep Disorder
Sleep Apnoea
Effect of Aging on Sleep

Box 1: Typical sleep changes with aging

- Decreased total nocturnal sleep time
- Delayed onset of sleep
- Advanced circadian phase: early to bed, early to rise
- Reduced slow-wave sleep
- Reduced rapid-eye-movement (REM) sleep
- Reduced threshold for arousal from sleep
- Fragmented sleep with multiple arousals
- Daytime napping
Aging and Sleep

• With age, important changes in sleep structure occur perhaps most characteristic is a phase advance of the normal circadian cycle. The result is a propensity toward an earlier sleep onset, accompanied by an earlier morning wake signal.

• With aging, the total amount of time asleep shortens:
  – infants and young children sleep an average of 16–20 hours per day;
  – adults, 7–8; and
  – people over 60 years of age, 6.5 hours daily.

• Delta sleep (stages 3 and 4), the deepest and most refreshing form of sleep, diminishes with age.

Sleep Pathologies In Older Patients

• **Insomnia**
  – **Elderly women** tend to report sleep disturbances more frequently than elderly men possible due to low estrogen
  – common causes of secondary insomnia are a variety of musculoskeletal disorders, nocturia related to benign prostatic hypertrophy in men and bladder instability with decreased urethral resistance in women, congestive heart disease, and chronic obstructive lung disease.
  – **Depression and anxiety disorders**, common among people over 65 years of age, frequently contribute to insomnia. Risk factors for depression in older people include loss of a spouse, retirement, social isolation, comorbid disease and onset of dementia.
  – Insomnia is also common in people who have Parkinson's disease and dementias
  – **Many drugs** and other ingested substances have been shown to cause or contribute to insomnia

• **Rem Disorders**
  – REM-sleep behaviour disorder is characterized by the loss of this normal muscle atonia. Affected people may display a variety of movements, E.g. A patient may get up and walk about, thrash limbs, flail arms or legs, or even engage in complex activity such as eating, while remaining in REM sleep.
  – Periodic leg movements and restless legs syndrome

Sleep-related Respiratory Disorders

• Snoring
  – In the large Cardiovascular Health Study, which included over 5000 people aged 65 years and older, 33% of men and 19% of women self-reported “loud” snoring.

• Obstructive sleep apnoea
  – It occurs in at least 4% of men and 2% of women aged 30–60 years. Among those over 60 years of age, prevalence rates as high as 45%–62% have been quoted.

Table 2: Medications and other substances that can contribute to insomnia in older patients

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects and points of advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Sleep induction Subsequent sleep disruption</td>
</tr>
<tr>
<td>Anticholinesterase inhibitors</td>
<td>Insomnia Disturbing dreams</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Sleep physiology altered Nightmares possible</td>
</tr>
<tr>
<td>Caffeine, decongestants</td>
<td>Stimulant effects • Advise patient to avoid evening use</td>
</tr>
<tr>
<td>Carbadopa, levadopa</td>
<td>Nightmares; insomnia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Stimulant effect; may cause agitation • Prescribe lowest possible dose</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Nocturia • Avoid late in day</td>
</tr>
<tr>
<td>Nicotine</td>
<td>• Encourage smoking cessation</td>
</tr>
<tr>
<td>Phenytoin (e.g., Dilantin)</td>
<td>Frequent insomnia</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Frequent insomnia</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Stimulant effect • Substitute metered-dose bronchodilators</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>• Check thyroid function</td>
</tr>
</tbody>
</table>

Note: SSRIs = selective serotonin reuptake inhibitors.
<table>
<thead>
<tr>
<th>Aspect</th>
<th>Restless legs syndrome</th>
<th>Periodic leg-movement disorder</th>
</tr>
</thead>
</table>
| **Clinical features** | • Unpleasant sensations in legs, usually at night  
                  • Described as “creeping,” “crawling” or painful  
                  • Improved by movement  
                  • Sleep-onset insomnia  
                  • Daytime fatigue | • Involuntary limb movements that recur at regular intervals (20-40 s) during the non-rapid-eye-movement stages of sleep  
                  • Patient often unaware of movements  
                  • Frequent arousal or awakening during sleep  
                  • Daytime fatigue |
| **Prevalence**  | • 2%-15% of general population  
                  • 10%-35% among people 65 years or older  
                  • More common in women than in men | • 5% among people aged 30-50 yr; up to 45% among those ≥ 65 yr  
                  • Equally common in women and men |
| **Diagnosis**   | Clinical                                     | Polysomnography showing repetitive muscle contractions              |
| **Associated factors** | • Accompanied by periodic leg-movement disorder in about 85% of cases  
                  • Family history (about half of affected people)  
                  • More common  
                  • Iron deficiency  
                  • Peripheral neuropathy  
                  • Renal failure | Accompanied by restless legs syndrome in around 25% of cases  
                  • Diabetes  
                  • Parkinson’s disease  
                  • Cigarette smoking  
                  • Use of alcohol, caffeine  
                  • Some medications |
| **Treatments**  | In frequent use  
                  • Dopaminergic agents  
                  • Dopamine agonists | In frequent use  
                  • Benzodiazepines  
                  • Anticonvulsants  
                  • Opioids  
                  • Some medications | Less frequently used  
                  • Dopaminergic agents  
                  • Dopamine agonists  
                  • Anticonvulsants  
                  • Muscle relaxants  
                  • Some medications |
Common Causes Of Sleep Problems In The Elderly

- **Poor sleep hygiene** – Examples of poor sleep hygiene are irregular sleep hours, consumption of alcohol before bedtime, and too much daytime napping.
- **Pain or medical illness** – Pain can keep you from sleeping well. In addition, many health conditions such as, a frequent need to urinate, arthritis, asthma, diabetes mellitus, osteoporosis, nighttime heartburn, menopause, and Alzheimer's can interfere with sleep.
- **Medications** – Seniors tend to take more medications than younger people. Combinations of drugs, as well as the side-effects of individual drugs, can impair sleep or even stimulate wakefulness.
- **Lack of exercise** – If you are too sedentary, you may not feel sleepy or feel sleepy all of the time. Regular exercise early in the day can promote good sleep.
- **Psychological stress or psychological disorders** – Significant life changes like the death of a loved one or moving from a family home can cause stress. Anxiety or sadness can also keep you awake, which can, in turn, cause more anxiety or depression.
- **Sleep disorders** - Restless Legs Syndrome (RLS), insomnia, and sleep-disordered breathing such as snoring and sleep apnea occur more frequently in older adults.
Sleep Molecules of the Brain

The sleep molecule of the brain is adenosine
Extracellular Adenosine Concentration Increases In The Wakeful State

Age may affect adenosine receptor function rather than number

Dag Stenberg et al. Journal of Sleep Research 2003, 12: 283
The Role Of Adenosine A1 And A2A In Sleep

A1 inhibits adenyl cyclase and A2A stimulate adenyl cyclase.
Molecular Networks Of Sleep-regulatory Substances Make Up The NREM Homeostat

Adenosine, Caffeine and Sleep

- **Adenosinergic** neurotransmission contributes to homeostatic sleep–wake regulation

- **Functional polymorphism** in the adenosine metabolizing enzyme, ADA, contributes to the high inter-individual variability in sleep structure and nonREM sleep intensity.

- The adenosine receptor antagonist, **caffeine**, potently attenuates the physiological EEG markers of nonREM sleep homeostasis during sleep, as well as during wakefulness.

Hans-Peter Landolt. *Bioc hematical P harmacology* 2008;7 5 :2 0 7 0 – 2 0 7 9
Melatonin

# Factors Influencing Human Melatonin Secretion

<table>
<thead>
<tr>
<th>Factors</th>
<th>Effect(s) on melatonin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>Suppression</td>
<td>&gt;30 lux white</td>
</tr>
<tr>
<td></td>
<td></td>
<td>460-480 nm most effective</td>
</tr>
<tr>
<td>Light</td>
<td>Phase-shift/ Synchronisation</td>
<td>Short wavelengths most effective</td>
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<tr>
<td>Sleep timing</td>
<td>Phase-shift</td>
<td></td>
</tr>
<tr>
<td>Posture</td>
<td>↑ standing (night)</td>
<td>Partly secondary to light exposure</td>
</tr>
<tr>
<td>Menstrual cycle</td>
<td>Inconsistent</td>
<td>↑ amenorrhea</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>↓ synthesis</td>
<td>Anti-hypertensives</td>
</tr>
<tr>
<td>SSRI’s</td>
<td>↑ fluvoxamine</td>
<td>Metabolic effect</td>
</tr>
<tr>
<td>Noradrenalin uptake inhibitor</td>
<td>↑ change in timing</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Mono-amine oxidase inhibitor</td>
<td>↑ may change phase</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>(\alpha)-adrenoceptor-antagonist</td>
<td>↓ alpha-1, ↑ alpha-2</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Variable</td>
<td>GABA mechanisms</td>
</tr>
<tr>
<td></td>
<td>↓ diazepam, alprazolam</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Oestradiol</td>
<td>↓? Not clear</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Possible changes ↑↓?</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Decreased</td>
<td>Dose dependent</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Increased</td>
<td>Delays clearance (exogenous)</td>
</tr>
<tr>
<td>Aspirin, Ibuprofen</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Increased</td>
<td>Metabolic effect</td>
</tr>
<tr>
<td></td>
<td>Possible phase change, Parkinson</td>
<td>Aromatic amino-acid decarboxylase-I</td>
</tr>
<tr>
<td>Benserazide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sleep and Depression
Sleep And Depression

- For patients with depression, disrupted sleep is of major significance.

- Both the treatment and the response to treatment are influenced by the quality and duration of sleep.

- In practice, between 40% and 95% of subjects with depression have poor sleep quality.

- These findings have been corroborated by physiological criteria from polysomnographic studies - 40% to 60% of outpatients and 90% of inpatients with depression have polysomnographic abnormalities.
Sleep and Depression

- Depressed patients have:
  - increased stage I sleep, decreased stage III and stage IV sleep, shorter NREM sleep duration, insomnia (involving difficulties falling asleep, sleep fragmentation and early morning awakenings)

- Common sleep-EEG alterations include:
  - decreased REM sleep latency, increased REM density and increased total time spent in REM sleep.

- Melancholic depression, is characterised by the aforementioned alterations, including poor sleep quality and decreased amounts of sleep

- Atypical depression is associated with an overall increased amount of sleep and fatigue-like behaviour during the day

OSA Diagnosis must be considered in Psychiatric Patients

- Sleep-disordered breathing is a common problem in the general population that in some cases shares overlapping symptoms with mood, anxiety, and psychotic disorders. The result may be a complex clinical presentation with diagnostic confusion and significant treatment challenges.

- Mental health professionals should be mindful of possible sleep-disordered breathing in patients with disrupted sleep or daytime sleepiness.

- Patients with chronic mental illnesses should be screened for possible sleep disorders.
Sleep-disordered Breathing and the Psychiatric Patient

• Obstructive sleep apnoea causes sleep disruption, daytime sleepiness, cognitive impairment, and depressive symptoms.

• Psychotropic medications may exacerbate sleep apnea.

• Depression, anxiety, and psychosis may undermine sleep apnoea treatment.
STOP-BANG OSA SCORING MODEL

**Snoring:**
Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

**Tired:**
Do you often feel tired, fatigued, or sleepy during the daytime?

**Observed:**
Has anyone observed you stop breathing during your sleep?

**Blood Pressure:**
Do you have or are you being treated for high blood pressure?

**BMI:**
BMI >35 kg/m2?

**Age:**
Age >50 years?

**Neck circumference:**
Neck circumference >40 cm?

**Gender:**
Gender male?

**High risk of OSA:** Answering yes to ≥3 items.
**Low risk of OSA:** Answering yes to <3 items.

OSA=obstructive sleep apnoea; BMI=body mass index
THE EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0=would never doze
1=slight chance of dozing
2= moderate chance of dozing
3=high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>-----------------</td>
</tr>
<tr>
<td>Watching television</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sitting, inactive, in a public place</td>
<td>-----------------</td>
</tr>
<tr>
<td>As a passenger in a car for 1 hour</td>
<td>-----------------</td>
</tr>
<tr>
<td>Lying down in the afternoon</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
</tr>
</tbody>
</table>

**Total Score:**
A score of ≥10 suggests excessive sleepiness

Collop NA, Neubauer DN. *Primary Psychiatry*. 2009;16(2):25-32
THE RELATIONSHIP OF OSA WITH PSYCHIATRIC SYMPTOMS AND DISORDERS

- Patients with OSA may complain of:
  - disrupted night-time sleep
  - excessive daytime sleepiness,
  - Fatigue
  - poor concentration and memory
  - irritability,
  - impairment in daytime functioning,
  - inability to enjoy usual activities
  - a general sense of discouragement.
  - express feelings of discouragement and depression
  - may question the value of living with their burdensome and often unexplained symptoms.
Does the OSA mimic a major depressive episode (MDE) or does the constellation of mood disorder symptoms demonstrate co-morbidity of OSA and major depressive disorder (MDD)?

Both are possible.
OSA, Depression & Serotonin

- OSA-related sleep stage alterations, such as decreased slow-wave and rapid eye movement (REM) sleep, and recurrent oxyhaemoglobin desaturation can exacerbate mental impairment and increase the risk for depressive disorders.

- **Serotonin** plays key a role in the neurobiology of depression and arousal as well as in the control of upper airway muscle tone during sleep.

- Decreased serotonin activity may increase the risk of developing depressive symptoms and, perhaps, increase the probability of pharyngeal collapsibility during sleep.

OSA or Depression?

• Problems arise when a mood disorder or related psychiatric condition is diagnosed, but the possibility of sleep-disordered breathing is not considered as a possible contributor to night-time sleep disruption or daytime fatigue and sleepiness.

• Although selected symptoms may improve with antidepressant therapy, the patient could be labelled as treatment resistant due to limited improvement in core daytime and night-time symptoms.

• Accordingly, sleep-disordered breathing should always be in the differential diagnosis of patients with complaints of disrupted night-time sleep or excessive daytime sleepiness.

• This is especially important since psychotropic medications may both directly and indirectly exacerbate sleep apnoea

• Collop NA, Neubauer DN. Primary Psychiatry. 2009;16(2):25-32
REM sleep and Depression

• REM sleep is associated with processing emotional memory and storage, i.e., emotional memory consolidation.

• Depression is commonly associated with alterations in REM sleep, including a faster progression into REM (reduced REM latency) and an increase in the amount of REM.

• REM abnormalities in depression may represent a maladaptive consolidation process of prior negative affective experiences, which, due to the increased REM amount and faster speed of entry into REM, could selectively and disproportionately reinforce negative memories at night, thereby potentiating the mood disorder.

• Masaki Nishida, Jori Pearsall et al. Cerebral Cortex 2009 19(5):1158-1166
Biochemistry Of REM Sleep Depression

- Neuro-chemically, levels of limbic and forebrain ACh are markedly elevated during REM Sleep.
- Ach is known to improve memory

- This procholinergic REM state may therefore result in a selective memory facilitation of affective memories

- **Noradrenergic input** from the locus coeruleus does not occur during this REM process thus resulting in poor modulation of negative emotional experiences during REM.
- This lack of input thus does not negate the resulting long-term state of chronic anxiety.

- Masaki Nishida, Jori Pearsall et al. Cerebral Cortex 2009 19(5):1158-1166
Sleep In Bipolar Patients

- Specific complaints may include:
  - frequent night-time awakenings,
  - poor quality of sleep,
  - reduction in total sleep time, and
  - nightmares.
  - insomnia when in depression, but
  - a significant percentage of patients also report
    hypersomnia symptoms with prolonged night-time sleep,
  - difficulty in wakening,
  - excessive daytime sleepiness.

Giglio LMF et al. Sleep and Breathing 2009;13(2):169-173
Depression, Pain, and Aging

• The prevalence of persistent pain increases with age.

• Painful conditions such as fibromyalgia, chronic low back pain, osteoarthritis, and neuropathic pain are frequently comorbid with depression.

• Anxiety, disordered sleep, fatigue, and cognitive impairment are frequent "co-travelers" with depression and pain in late life; these conditions require vigilant screening and treatment.

• Karp JF, Reynolds CF. Focus 2009; 7:17-27
PSTD and Sleep

• Post-traumatic stress disorder (PTSD) is associated with a dysregulation of REM sleep, with reports of increased sympathetic autonomic tone.

• There may similarly be an adverse consequence to such trauma-induced REM-sleep changes in PTSD, which if they persist, could counter-productively amplify, rather than ameliorate, the acquired affective experience.
Insomnia And Depression

• The following associations of the causal relationship between insomnia and depression have been reported:
  – Insomnia increases the risk of onset of depression.
  – Persistent insomnia is associated with a 40-fold increase in risk of depression.
  – Insomnia increases the risk of recurrence of depression.
  – A stable sleep-wake rhythm and good sleep hygiene are essential in the prevention of further relapses in depressed patients.
Insomnia and Depression

• Insomnia could also contribute to worsening of symptoms already caused by depression: – e.g. irritability, decreased cognitive functioning, poor executive functioning
Circadian rhythms and depression

- Disturbances in circadian rhythms play a role in the pathogenesis of depression.
- Cortisol and temperature levels are increased and melatonin levels are decreased – mainly due to amplitude reduction.
- Some patients respond dramatically to treatment modalities that manipulate circadian rhythms.
- Circadian rhythms return to normal after recovery.
Circadian Rhythms And Depression

• Sleep is regulated by two broad mechanisms: the circadian system, which generates 24-h rhythms of sleep propensity and a wake-dependent homeostatic sleep process whereby sleep pressure increases during wake and dissipates during sleep.

• There are two general ways in which disrupted circadian rhythms could lead to depression:
  – (i) disorganization within the circadian system could itself lead to neurobiological dysfunction
  – (ii) a circadian disturbance of the normal sleep-wake cycle could facilitate or exacerbate the depressed state.
Sleep and the Melatonergic System

• Profound disturbances in sleep architecture occur in major depressive disorders (MDD) and in bipolar affective disorders.

• Reduction in slow wave sleep, decreased latency of rapid eye movement (REM) sleep and abnormalities in the timing of REM/non-REM sleep cycles have all been documented in patients with MDD.

• Depressed patients exhibit disturbances in both the amplitude and shape of the melatonin secretion rhythm.

• Melatonin can improve the quality of sleep in these patients.

Chronobiologic Multistage Intervention (CMI) in Depression

- Comprised of the following techniques:
  - (i) partial sleep deprivation during the second half of the night (wake therapy – WT),
  - (ii) medium (green) wavelength light in combination with dawn simulation (DS),
  - (iii) bright light therapy (BLT),
  - (iv) sleep phase advance (SPA).

Lucian Moscovici, Moshe Kotler. Journal of Affective Disorders August 200;116(3):201-207
Sleep Deprivation as a Antidepressant

• **Before sleep deprivation**, responders have significantly elevated metabolism compared with non-responders, and normal controls, in the orbital medial prefrontal cortex, and in the ventral portions of the anterior cingulate cortex.

• **After sleep deprivation**, these hyperactive areas normalize in the responders. The magnitude of the clinical improvement is significantly correlated with decreased local glucose metabolic rate or cerebral blood flow most studies.

• The antidepressant benefits of sleep deprivation are correlated with endogenous release of dopamine.


Light
**Light and Cell Signalling**

- *Propagation* of photon signals in the organism could take place by direct tissue penetration, along cellular processes, e.g., axons and dendrites and inside the hollow core of cytoskeletal microtubules.
- The constant inner diameter of 15 nm of microtubules are capable of guiding light, free of thermal noise and loss.
- Light propagation in the brain depends on the nerve fibre orientation and is better along the axes of white matter tracts.
- Albumin is capable of transporting light along blood vessels.
Humoral Phototransduction.

- Light-induced luminescence of plasma components, such as albumin and free radicals, transports ambient light along the blood vessels. This emission could have photochemical and photobiological effects, e.g., photomodulation of enzymes.

- **Albumin fluorescence emission** could stimulate serotonin formation at **337nm**, modulated by bilirubin. Such mechanisms could be involved in the action of light therapy on serotonin formation, melatonin suppression and circadian rhythms, both in the pathophysiology of seasonal affective disorder and major depression, and in blood pressure regulation via photovasorelaxation.
Light-induced luminescence of 5ml plasma of three healthy volunteers. The plasma was illuminated for 1min with a mercury gas lamp. Photonemission was recorded in a Hamamatsu photomultiplier. Measurement started 17s after the illumination, cps=counts per second=emission.

Light-induced luminescence of 5 ml human serum albumin 30 g/100 ml at pH 7.4. The specimen was illuminated for 30 s. Measurement started 32 s after the illumination. Note that the emission is high despite a shorter illumination time and longer transfer time. Twenty-five minutes after the illumination, the emission is still higher than the background (shutter closed), cps = counts per second = emission.
Cellular Light

• Every metabolic reaction has a specific light emission spectrum that is determined by the energetic steps involved.

• The subcellular fraction with the highest metabolic activity are the mitochondria. The oxidation of NADH has a high capability to generate photons. According to Albrecht-Buehler mitochondria are the best candidates for a cellular light source

• Of all natural aminoacids, nature has chosen the aromatic ones with the strongest fluorescence, tryptophan, phenylalanine and tyrosine as precursors for the neurotransmitters involved in mood reactions: serotonin, dopamine and norepinephrine.

• Albumin fluoresces at 337nm, melatonin synthesis is inhibited at 464nm
Targets or modes of action for a photon signal could be metabolic processes.

Configurational changes in form of cis/trans transitions, e.g., rhodopsin,

- Photoactivation of enzymes, e.g.,
  - tryptophan-decarboxylase by 337 nm light,
  - activation and synchronisation of the cytochrome P-450 dependent monoxygenase system by blue light,
  - activation of glutamate-dehydrogenase by red light.
  - Photovasorelaxation could act on the blood circulation by near UV light.
  - Degranulation of neutrophils.
  - Cell orientation by red or near infrared light.
  - Influences on mitotic processes, e.g., “mitogenetic radiation” by UV light.
  - Among many other photochemical and photobiological reactions, also photosensitized singulet oxygen formation and nitric-oxide generation from nitrogen containing substances may play a role.

- From laser experiments with 3T3 cells Albrecht-Buehler concludes that the centrosome is an infrared detector, and calls it a “cellular eye”.
Melatonin

• Melatonin reduces neuronal loss and cytoskeletal deterioration, improving the psychological wellbeing of individuals.

• A major action of melatonin in the Central Nervous System is protection of the neuronal cytoskeleton from oxidative damage.

• Structural damage to the cytoskeleton is consequential in the function of neurons and is not uncommonly associated with psychological illness and with neurodegenerative diseases.

• Russel J. Reiter, Gloria Benitez-King Salud Mental 2009;32:3-11
Melatonin

- Melatonin is linked to mitochondrial health via interaction with complexes I and IV, whereby oxidative phosphorylation and electron transport efficiency are enhanced and cytochrome c oxidase activity (complex IV) and ATP production (complex V) are both increased.

- Melatonin sustains GSH levels in the mitochondria both by scavenging hydroxyl radicals directly, thereby sparing GSH, and by inducing the expression of γ-glutamylcysteine synthetase, the enzyme responsible for catalyzing the rate-limiting step of GSH synthesis.

- Melatonin also acts by up-regulating superoxide dismutase (SOD) and increasing glutathione peroxidase (GPx) and glutathione reductase (GRx) activities.

- Melatonin increases enzyme activities of all three enzymes, SOD, GPx, and GRx, in the developing liver upon daily red light treatment. The coordinated efforts of all three enzymes, in addition to catalase, are responsible for the detoxification of reactive oxygen and nitrogen species.

Light Effects On Melatonin

• Various analyses of the effects of light and LEDs on melatonin levels and rhythms in humans have shown that while shorter wavelengths of blue (430nm) and green (540nm) light suppress salivary melatonin and shift the melatonin rhythm,

• Red light (610 and 660nm) has no effect on melatonin suppression and slightly shortens the time before dim light onset of melatonin secretion.
Light Therapy
Dark Therapy

• Dark Therapy”, in which complete darkness is used as a mood stabilizer in bipolar disorder, roughly the converse of light therapy for depression

• Retinal photoreceptor, whose fibres connect only to the biological clock region of the hypothalamus, has been shown to respond only to a narrow band of wavelengths around 450nm.

• Amber-tinted safety glasses, which block transmission of these wavelengths, have already been shown to preserve normal nocturnal melatonin levels in a light environment which otherwise completely suppresses melatonin production.
Bipolar Disorder: A circadian Rhythm Disorder

• Clinicians have long recognized the pro-manic effects of sleep deprivation, but recent data have underscored the central role of circadian rhythms in Bipolar Disorder.

• Amongst patients with bipolar depression, a particular allele variation of the CLOCK gene is associated with higher activity levels in the evening, delayed sleep onset, and reduced amount of sleep at night, relative to patients with the more common allele; and these differences diminish with lithium treatment.
ADHD and Light

• Evening/late-night blue light exposure from electric lights, televisions, and computers may contribute to Attention Deficit Hyperactivity Disorder (ADHD).

• An 11-year-old with ADHD and apparent delayed sleep phase (bedtime later than 1 a.m. 80% of the time) was taken off methylphenidate and treated with morning light. The intent was to cause a “phase advance”, shifting his circadian rhythm toward an earlier bedtime.

• In one week, his sleep onset had advanced by 2h, and his Conner’s Teacher Global Index score (a standard measure of ADHD severity) had improved from 64 to 45.

• An open trial of light therapy for ADHD found similar results in 29 adults.
Temperament
The Role Of Temperament

- In all major mental disorder, there pre-exists an underlying temperamental extreme variance of the normal occurring types. (Each type facilitates a function in a characteristic way.)
- **Temperament is defined** as the inborn “How” of behaviour. Its somewhat controversial elements (i.e., sociability, compulsivity, intensity, other-orientedness, inner-orientedness, emotionality, “feeling the world,” “thinking the world” and possible others...) tend to occur in clusters of various, often distinct, combinations comprising the temperamental types conferring evolutionary advantages for the individual under particular circumstances as well as to the tribe.
Temperament

- Temperament plays a significant role in an individual’s life; it is partially involved in mate selection for the formation of procreational dyads as well as for lasting partnerships.

- It contributes to one’s lifestyle and vocational choice within the framework of contingency and circumstance.

- It also acts as a possible facilitator (when an extremely variant) in gifted and talented individuals to conduit their talents into creative channels by mechanisms not yet clear.

- It also, evolutionarily, contributes specific benefits to the group as a whole not only to the individual bearer.
Temperament

• In schizophrenia, the pre-existing extreme, temperamental variances constituting the premorbid personality and its components at the onset of the disorder are renamed the negative symptoms.

• They are present in various combinations: aloofness, apathy, with occasional explosivity, social uneasiness, self-absorption, egocentricity, absence of empathy, excessive “cerebricity” (e.g., thinking the world).
Temperament Variance and Mental Disorder

• Extreme temperamental variances for each disorder remain unaffected in remissions.

• For schizophrenia, they are now called “residual symptoms” which are often mixed with some lingering positive ones.

• In obsessive–compulsive disorder, there pre-exists specific extreme temperamental variances such as difficulties in accommodating ambiguity and displaying flexibility of response to a given situation and a mirthless attachment to exactitudes.

• In bipolar disorder, the pre-existing variances include an undue emotionality, acute sensitivity to even mild social stimuli, obsessiveness and an emotional entrainment perceived by the patient variously as an “inner, frozen landscape,” and “emotional shackles” Therapy: Dark Therapy

• In borderline disorder, the prime temperamental, extreme variant triggering the frequent, mercurial and brief, oscillatory symptoms across all the higher mental faculties is hyperintensity/hyper-reactivity in addition to a lack of empathy and undue self-absorption. The latter is often overlooked.

• In phobias, anxieties, and panic attacks, the extreme temperamental variances include the presence of excessive sociability and obedience to social gestalt, excessive empathy and sensitivity to social expectations and stimuli
The Role Of Periodic Relapses, Remissions And Shifts

• All major mental disorders regardless of treatment at least in the initial period, will remit and relapse while the underlying extreme temperamental traits remain the same.

• During a relapse, the clinical symptoms often shift from one “typical” syndrome to another, requiring a “new” diagnosis.

• These phenomena suggest a potential bimodality of the operating mode. They also suggest a causative role of the underlying temperamental variance as well as a common initial developmental origin.
Temperament and Neurotransmission

- These phenomena suggest that the overall operating mode of brain function is sustained by a complex and subtle interplay of many neurotransmitters and the multifunctional role of a single neurotransmitter.

- They also suggest that the mode is an emergent phenomenon of complexity. This is additionally suggested, by the delay in the appearance of pharmacotherapeutic results.
Mental Disorder Sequence

- If the extreme temperamental variance involves mainly a functional part of the brain dealing with mood modulation, it makes the candidate liable to the appearance of periodic occurrence of oscillations of mood expressed as a bipolar disorder.
- If it is in the area dealing with social interactions and connectedness, affective presence (sociability), thinking processes and coordination of feelings and ideas, it will express itself as schizophrenia.
- If it is in the “algorithmic” area of the brain that modulates orderliness, sequencing, scheduling, and sequencing actions, it will express itself mainly in the various phenomena of compulsions or obsessions.
- If it is in the area of the brain that oversees perception of danger from within (anxiety) or without (fear), it will then show up mainly in a panic attack, phobia, anxiety disorder and obsessive–compulsive disorder (OCD).
- In the latter, there is also a notable difficulty to bring closure to a thought or action and in addition, the frequent appearance of intrusive, rebellious, “nasty” thoughts which alternate with excessive piety and periods of slovenliness as well as neglect of one’s affairs.
Mental Disorder Sequence

- The following sequence of events lead to the occurrence of a major mental disorder;
  - individuals with inborn, extreme temperamental variances (with the implied, underlying, extreme structural variances) make up a group of vulnerable candidates. A certain percentage of these will develop a major mental disorder.
  - Whether a disorder may actually develop in a particular area/faculty of higher brain function depends as a probabilistic occurrence on two factors. One is the degree of the structural variance expressed as a temperamental extreme that confers vulnerability in that particular faculty in the brain (or even faculties in the presence of comorbidity.)
  - The other factor is the entire range of accumulated, environmental influences acting on the brain.
- A mental disorder will occur in some of these vulnerable individuals, usually in adolescence presumably triggered by hormonal and social pressures, pruning and possibly by other factors.
- Following the first occurrence (onset), usually but not always, the operating mode becomes permanently unstable and bimodal (e.g. switching phases periodically from normal to the pathological and back again) expressed as relapses and remissions.
Mental Disorder Sequence

• During the periodic appearance of the pathological phase of the overall mode, the particular faculty affected expresses itself mainly in an either–or fashion with the appearance of symptoms as clusters of oscillating, antithetical substitutes characteristic for each disorder.

• It is as if the conductor of an orchestra during a musical performance suddenly abandons the orchestra.

• The phenomena are akin to Parkinson’s disease where awkward, spastic, either-or, zombie-like, painful-to-observe, body movements have replaced normal elegance and grace of motion. The latter mediated by the basal ganglia.

• Intolerance of ambiguity present in all major mental disorders can be considered as the cardinal characteristic symptom of a compromised, entrained overall operating mode
Does Nutrition Effect Temperament

Neurotransmitters

Genes

Nutrition
DRD4, Frontal Asymmetry, and Temperament

- The dopamine D4 receptor (DRD4) gene (long allele vs. short allele) moderated the relation between resting frontal EEG asymmetry (left vs. right) at 9 months and temperament at 48 months.
- Children who exhibited left frontal EEG asymmetry at 9 months and who possessed the DRD4 long allele were significantly more soothable at 48 months than other children.
- Among children with right frontal EEG asymmetry at 9 months, those with the DRD4 long allele had significantly more difficulties focusing and sustaining attention at 48 months than those with the DRD4 short allele.
- Resting frontal EEG asymmetry did not influence temperament in the absence of the DRD4 long allele.
Neurotransmitters, Neuroendocrine Correlates Of Sensation-seeking Temperament In Normal Humans

- Correlations between sensation-seeking (SS) personality dimension and plasma concentrations of norepinephrine (NE), epinephrine, and NE-dependent testosterone (T), cortisol and prolactin (PRL) were studied in 74 physically and psychologically healthy male volunteers, in order to see whether or not the noradrenergic system is involved in the modulation of this personality trait.

- Novelty-seeking scores by the Temperament and Character Inventory and SS scores on a Visual Analog Scale were positively correlated with plasma NE, T and PRL levels, suggesting that NE and the downstream cascade of NE-dependent hormones, together with other monoaminergic changes, might be responsible for the development and the degree of this temperamental character.

Malnourishment and Temperament

• Undernourished Children Have Different Temperaments Than Better-Nourished Children in Rural Bangladesh

• Manageability, activity, emotionality, sociability, attention, soothability, and fear

• Helen Baker-Henningham et al Journal of Nutrition 2009;139(9): 1765-1771
Associations Between Anterior Cingulate Cortex Glutamate And Gamma-aminobutyric Acid Concentrations And The Harm Avoidance Temperament.

• The anterior cingulate cortex (ACC) has been implicated to play an important role in the human fear and anxiety

• Functional and structural characteristics of ACC have been suggested to be associated with the harm avoidance (HA) temperament, one of the important temperament dimensions

• HA scores correlated negatively with glutamate concentrations in ACC and positively with GABA concentrations in ACC

• Kim HJ et al Neurosci Lett 2009 Aug
Association Of Serum Uric Acid Levels With Emotional And Affective Temperaments

• Temperament relates to emotions and the prevailing mood or affective temperament.

• Uric acid (UA) is the end-product of purine metabolism and has been associated with psychological features such as high energy/drive, positive affect, achievement, good performance, higher social status and leadership.

• Externalized traits of temperament are associated with higher serum UA levels both in men and women.
Circulation and Mood Disorders
Stroke and Depression

- Severity of depression was significantly increased in patients with left anterior lesions as opposed to any other lesion location.
- The severity of depression correlated significantly with proximity of the lesion on CT scan to the frontal pole in the left anterior group.
- The right hemisphere lesion group showed the reverse trend: patients with right posterior lesions were more depressed than patients with right anterior lesions, who were unduly cheerful and apathetic.
- This suggests that intrahemispheric lesion location is in some way related to mood disorder in stroke patients and that there is a graded effect of lesion location on severity of mood change.
PCOS and Depression
POLYCYSTIC OVARIAN SYNDROME AND PSYCHOLOGICAL FUNCTIONING

• PCOS is the most common endocrine disorder in women of reproductive age, affecting 5% to 10% of females, ~50% of whom are obese.
• The syndrome is characterized by chronic anovulation and hyperandrogenism and is manifested by hirsutism, cystic acne, hair loss, insulin resistance, and weight gain.
• PCOS is also one of the primary causes of infertility.
• Women diagnosed with PCOS experience increased incidence of depression and report significantly decreased quality of life (QOL) and emotional well-being.
• Allison KC et al. Primary Psychiatry. 2009;16(3):35-40
PCOS and Depression

- Women with PCOS are significantly more depressed than controls, with >66% of participants with PCOS experiencing some level of depression.
- Women with PCOS, as compared to age-matched controls, reported higher levels of distress as assessed by the Symptom Checklist-Revised.
Anorexia Nervosa
The Time Course And Phenomenology Of Anorexia Nervosa

Walter H. Kaye, Julie L. Fudge & Martin Paulus
Nature Reviews Neuroscience 2009;10:573-584
The Role Of Serotonin Neural Function In Anorexia Nervosa.

Walter H. Kaye, Julie L. Fudge & Martin Paulus
Nature Reviews Neuroscience 2009;10:573-584
Cortical-striatal Pathways With A Focus On Taste

Dorsolateral prefrontal cortex

Orbitofrontal cortex

Anterior cingulate cortex

Amygdala

Affective relevance

Medulla

NTS

Brainstem

Sensory input

Chemoreceptors of the tongue

Spinal cord

Thalamic taste centre

Nucleus tractus solitarii.

Walter H. Kaye, Julie L. Fudge & Martin Paulus
Nature Reviews Neuroscience 2009;10:573-584
Impaired Balance Between Interoceptive And Reward Processing.

Walter H. Kaye, Julie L. Fudge & Martin Paulus
Nature Reviews Neuroscience 2009;10:573-584
Addiction

The glutamate homeostasis hypothesis of addiction
Corticostriatal Circuits In Addiction.

**Figure a:** Adapively regulated behaviour

- **dStr**, dorsolateral striatum;
- **GP**, globus pallidus;
- **SM**, sensorimotor cortex;
- **SN**, substantia nigra;
- **VL**, ventrolateral thalamus;
- **VP**, ventral pallidum;
- **VTA**, ventral tegmental area.

**Figure b:** Compulsive drug-seeking behaviour

- **PFC**, prefrontal cortex;
- **NAc**, nucleus accumbens;
- **Amy**, amygdala;
- **CNA**, central nucleus of the amygdala;
- **BLA**, basolateral amygdala.

_Human brain diagram highlighting corticostriatal circuits in addiction._

Peter W. Kalivas
_Nature Reviews Neuroscience 10, 561-572 (August 2009)_
Neuro-adaptations Produced by the Effects Of Chronic Cocaine Administration on the Function of the Nucleus Accumbens.

Peter W. Kalivas
Nature Reviews Neuroscience 10, 561-572 (August 2009)
The Septohippocampal Circuit
Plasma-bradykinin Concentrations and Generalized Anxiety Disorder

Points Of Proposed Interaction Of Melatonin With Cellular Metabolism During Red Light Therapy

Red light therapy restores glutathione redox balance.