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32_Neurophysiology

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01 - 1. Physiology of Neuronal Activity

1. Physiology of Neuronal Activity

02 - A. Action Potentials

A. Action Potentials

03 - B. Synaptic activity

B. Synaptic activity

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1. Physiology of Neuronal Activity A. Action Potentials An action potential is initiated at the axonal hillock when the synaptic signals received by the dendrites and soma are sufficient to raise the intracellular resting membrane potential from -70 mV to the threshold potential of -55mV. At -55mV, the Na⁺ channels present at the axon's initial segment will open. The subsequent Na⁺ influx causes rapid reversal of the membrane potential from the negative values to +40 mV. When the membrane potential reaches +40mV, the Na⁺ channels close and the voltage-gated K⁺ channels open. As K⁺ ions move out of the axon, the cell membrane gets "repolarized". B. Synaptic activity A synapse is a junction between 2 nerve cells. Three types of synapses are noted in the nervous system. □ Chemical synapses: Presynaptic neuron releases a chemical molecule on stimulation. This molecule acts on the next neuron to bring on a molecular effect or to propagate the impulse further downstream. o Depending on the effects noted on the postsynaptic neuron, a chemical synapse could be classified as either excitatory or inhibitory. Postsynaptic neurons are depolarized by activity at the excitatory synapses; inhibitory synaptic activity serves to hyperpolarize them. o In some instance the postsynaptic changes induced by an excitatory synapse may be sufficient to induce an action potential, but may serve to facilitate the likelihood of generating an action potential with further stimulation. This process is called facilitation. Due to this, additional input from several other presynaptic cells through other synapses may result in a spatial summation effect leading to an action potential. Similarly recurrent stimulation by the same synapse can result in temporal summation that leads to an action potential. □ Electrical synapses: They bring on the response by electrical communication without chemical exchange. □ Conjoint synapses: These have both electrical and chemical properties.

04 - 2. Neural basis of
physiological functions

2. Neural basis of
physiological functions

05 - A. Eating

A. Eating

06 - B. Temperature

B. Temperature

07 - C. Pain

C. Pain

© SPM Course 2. Neural basis of physiological functions

A. Eating The hypothalamus has 2 centers that control feeding behaviour. Ventromedial hypothalamus acts as the satiety centre while lateral hypothalamus acts as the feeding centre. Neurochemical substances such as ghrelin and neuropeptide Y act as mediators of increased appetite (orexigenic). Leptin, cholecystokinin and serotonin act as mediators of satiety (anorexigenic). Ghrelin is the only orexigenic substance produced outside of the CNS – it is synthesized in the gastric mucosa; adipose cells synthesize leptin. Food and food cues increase dopaminergic activity in nucleus accumbens (reward centre). Destruction of dopamine pathways reduces eating behaviour. In obesity, D2 receptors are reduced in the striatum.

B. Temperature The hypothalamus has 2 centers that control body temperature. Preoptic anterior hypothalamus acts as a hypothermic centre while posterior hypothalamus acts as a hyperthermic centre. Stimulating preoptic anterior hypothalamus results in parasympathetic-mediated sweating and vasodilation, resulting in hypothermia. Stimulating posterior hypothalamus results in sympathetic drive, shivers and vasoconstriction, leading to hyperthermia. Body temperature varies diurnally; Lesions in the median eminence reduces the diurnal temperature variation. Certain drugs can induce malignant hyperthermia, but not through hypothalamic mechanism. An abnormal excitation-contraction coupling in skeletal muscles is responsible for this defect. Hyperthermia is also seen in Neuroleptic Malignant Syndrome (NMS) induced by neuroleptic use or levodopa withdrawal.

C. Pain Thalamus plays a crucial role in pain perception while higher cortical centres are central to the localization and interpretation of pain signal. Thin unmyelinated C fibres or sparsely myelinated A-delta fibres carry pain sensation to dorsal horn of the spinal cord. Fast transmission takes place along lateral spinothalamic route to aid localization while slow transmission takes place through reticulothalamic tract to aid subjective sensation. Opioid receptors in dorsal horn and possibly those in brain stem (periaqueductal grey matter) modulate pain intensity. Descending fibres from serotonergic raphe nuclei also modulate pain perception; this may explain the role of tricyclic drugs in reducing chronic pain.

08 - D. Thirst

D. Thirst

09 - E. Abnormalities in physiological drives

E. Abnormalities in physiological drives

© SPMM Course Thalamic pain syndrome can occur in cases of stroke involving thalamoperforating branches of posterior cerebral artery. Patients have contralateral loss of sensation with burning or aching pain triggered by light cutaneous stimulation. D. Thirst Subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) are circumventricular organs playing a crucial role in the perception of thirst. The hypothalamic paraventricular nucleus is also involved in the regulation of thirst. Angiotensin II acts as a neurotransmitter to propagate thirst signals to hypothalamus. Hypotension also stimulates thirst through pathways originating from the baroreceptors on aorta and carotid. Anti diuretic hormone (ADH) increases water reabsorption at renal tubules and thus helps maintain body's fluid balance. The syndrome of inappropriate secretion of ADH (SIADH) may result from damage to paraventricular and supraoptic hypothalamic nuclei, or due to the use of drugs such as carbamazepine or chlorpromazine. Some tumours such as carcinoma of lung can also produce excess ADH. Low sodium and reduced osmolarity is noted in the presence of normal renal excretion of sodium and high urine osmolality. E. Abnormalities in physiological drives Disorder Clinical features Kluver-Bucy syndrome Bilateral lesions of amygdala and hippocampus results in placidity with decreased aggressive behaviour. Prominent oral exploratory behaviour and hypersexuality. Hypermetamorphosis (objects are repeatedly examined as if they were novel) is also seen. LaurenceMoon-Biedl Syndrome Obesity and hypogonadism along with low IQ, retinitis pigmentosa, and polydactyly. Diabetes insipidus is also seen. Autosomal recessive with genetic locus at 11q13 in most cases. No hypothalamic lesions have been found. Prader-Willi Syndrome Hypotonia, obesity with hyperphagia, hypogenitalism, mental retardation, short stature, impaired glucose tolerance. Abnormal control of body temperature and daytime hypersomnolence is related to hypothalamic disturbances. A reduction in oxytocin neurons and satiety neurons is noted. Associated with paternal deletion (genomic imprinting) at 15q11-q13 Kleine-Levin Syndrome Compulsive eating behaviour with hyperphagia, hypersomnolence, hyperactivity, hypersexuality and exhibitionism. A hypothalamic abnormality sometimes preceded by a viral illness; often resolves by the third decade of life. Psychogenic polydipsia Excessive water consumption in the absence of hypovolemia or hypernatremia. May lead to water intoxication and serious electrolyte imbalance.

10 - 3. Neurodevelopment

3. Neurodevelopment

11 - A. Neurogenesis

A. Neurogenesis

12 - B. Neuronal

MigrationMyelination

B. Neuronal

Migration/Myelination

13 - C. Synaptic pruning

C. Synaptic pruning

© SPMM Course 3. Neurodevelopment A. Neurogenesis Early fetal life is a prolific period of neurogenesis. An active zone of nerve cell production is seen immediately around the ventricles of the neural tube. This is called a subventricular zone. Neurons produced here migrate outwards to the cortical plate. Thalamic axons that project to the cortical plate initially synapse on a transient layer of neurons called the subplate neurons. In normal development, the axons subsequently detach from the subplate neurons and proceed superficially to synapse on the true cortical cells. The subplate neurons then degenerate. In some patients with schizophrenia an abnormal persistence of subplate neurons has been noted, suggesting a failure of axonal path-finding. It is now known that continuous neurogenesis takes place in certain brain regions (particularly the dentate gyrus of the hippocampus and olfactory bulb) in adults. Stress reduces hippocampal neurogenesis; enriched environments, exercise and antidepressants promote hippocampal neurogenesis. There is some controversy around whether adult neurogenesis is observed in other brain regions. B. Neuronal Migration/Myelination Neuronal migration takes place in the first 6 months of gestation. Two types of migration are noted: radial and tangential. Radial migration is the primary mechanism by which excitatory neurons reach the cortex. Radial glial cells form scaffolding through their foot processes to guide the migrating neuronal cells. Successive populations of migrating neurons travel past the previously settled neurons (inside out pattern) to form radial stacks of cells (Rakic's cortical columns). Most inhibitory interneurons in the external and internal granular layers are tangentially migrated neurons. Abnormalities in neuronal migration result in neurons failing to reach the cortex and residing in ectopic positions. This is called heterotopia. Myelination begins prenatally at around 4th gestational month; it is largely complete in early childhood (by 2 years), but does not reach its full extent especially in association cortices until late in the third decade of life. C. Synaptic pruning Synaptogenesis occurs very rapidly from the second trimester through the first ten years of life. The peak of synaptogenesis occurs within the first 2 postnatal years. By mid-childhood, more neurons and cellular processes are established than required for adult's brains. Thereafter a process of pruning or synaptic elimination takes place to select and preserve the most useful while eliminating the unnecessary neuronal connections in the adult's brain. This synaptic pruning continues through the early teen years. Neuronal numbers can be studied using a wide variety of markers including the density of D2 receptors. Before 5 years of age, D2 receptor density is greater than adult levels but regresses during the second

14 - D. Cerebral plasticity

D. Cerebral plasticity

© SPMM Course decade. Dopamine receptors continue to decrease in adult years, but at a considerably slower rate of 2.2% reduction per decade. This rate is faster in males than in females. In schizophrenia, the rate of D2 receptor loss is faster (6.0% loss per decade) than in healthy men. While excessive or prolonged pruning is associated with schizophrenia, relative under-pruning is implicated in autism, wherein the size of certain brain regions may be larger than in healthy controls. D. Cerebral plasticity Cerebral plasticity refers to the capability of the brain to be molded. Cortical sensory maps change with variations in sensory input. Patients with phantom limb also show reorganization of sensory maps after amputation so that the representation of the amputated limb may occur on the cortical face area. Repeated practice also leads to a reorganization of brain's functional regions. Such an effect is seen in musicians, jugglers and other professionals who repeatedly undertake a learned motor task.

15 - 4. Neuroendocrinology

4. Neuroendocrinology

16 - A. Pituitary gland

A. Pituitary gland

© SPM Course 4. Neuroendocrinology A. Pituitary gland The pituitary gland has an anterior and posterior lobe. The anterior lobe secretes many hormones that are regulated by regulatory neurohormones produced by parvocellular neurons of the hypothalamus. The posterior lobe releases 2 hormones that are synthesized in the magnocellular cells of supraoptic nuclei and paraventricular nuclei of the hypothalamus. □ Growth hormone excess causes acromegaly in adults or gigantism in children; low levels are associated with dwarfism. Exercise, sleep and stress increase GH release. The GH response to GHRH and the normal sleep-associated release of GH are altered in depression and anorexia nervosa. □ Prolactin release is inhibited by dopamine from the hypothalamus; TRH, on the other hand, may facilitate the release of prolactin. Prolactin levels are increased during pregnancy, nursing and during sleep and exercise. Antipsychotics remove the inhibitory control of dopamine by blocking D2 receptors in the tuberoinfundibular tract. This leads to hyperprolactinaemia, gynecomastia in males and galactorrhea in females. Long standing prolactin increase may lead to osteoporosis. □ Vasopressin (ADH) and oxytocin are peptides differing from each other in only two amino acids in their sequences. Vasopressin is thought to play a role in attention, memory, and learning. Release of vasopressin is increased by pain, stress, exercise, morphine, nicotine, and barbiturates and is decreased by alcohol. Oxytocin is implicated in mammalian bonding behavior, particularly in the initiation and maintenance of maternal behavior, social bonding, and sexual receptivity.

Region Hormonal output Anterior pituitary o GH - growth hormone o LH - luteinizing hormone (a gonadotrophin) o FSH - follicle stimulating hormone (a gonadotrophin) o ACTH - adreno corticotrophic hormone (corticotrophin) o TSH - thyroid stimulating hormone (thyrotropin) o Prolactin Posterior pituitary o Vasopressin (ADH - antidiuretic hormone) o Oxytocin Hypothalamus o CRH - corticotrophin releasing hormone o GHRH - growth hormone releasing hormone o GnRH - gonadotrophin releasing hormone o TRH - thyrotrophin releasing hormone o SST - somatostatin (inhibits GH) o PIF - prolactin inhibitory factor (dopamine)

17 - B. Thyroid gland

B. Thyroid gland

18 - C. Adrenal Cortex

C. Adrenal Cortex

© SPMM Course B. Thyroid gland TRH from the hypothalamus stimulates the secretion of TSH from the pituitary. TSH in turn stimulates the thyroid gland to synthesize and release thyroxine T4 and triiodothyronine T3. T4 is the predominant form of thyroid hormone, but T3 is biologically more potent. T4 is converted into T3 by target organs as well as the brain. Exogenous administration of TRH produces a brisk response by increasing TSH concentration. In patients with depression, a blunted response to TRH administration is seen. Mania, alcohol withdrawal and anorexia can also cause blunted TRH response. The addition of T3 and T4 as supplements to antidepressant treatment has been shown to accelerate response in some patients, particularly women. Exogenous administration of thyroid hormones (e.g. in resistant depression) increases serotonergic transmission with decreased 5-HT_{1A} sensitivity and increased 5-HT_{2A} sensitivity. Nerve growth factor genes are activated by T3 during early development but not in the adult's brain. Lithium produces hypothyroidism especially in middle-aged women who are predisposed to carry antithyroid autoantibodies. Hypothyroidism is sometimes implicated in rapid cycling mood pattern in previously stable bipolar patients. Hyperthyroidism is associated with symptoms of generalized anxiety disorder. Hypothyroidism Physical symptoms: Tachycardia, weight loss, heat intolerance, sweating. Mental symptoms: Anxiety, irritability, poor concentration, agitation, emotional lability. Hypothyroidism Physical symptoms: Fatigue, weight gain, cold intolerance, dry skin. Mental symptoms: Depression, reduced activity (psychomotor retardation), reduced libido and poor memory.

C. Adrenal Cortex CRH from the hypothalamus stimulates ACTH release from the anterior pituitary. ACTH in turn stimulates the release of cortisol from the adrenal cortex. Cortisol thus produced in turn inhibits both CRH and ACTH in a negative feedback loop to maintain homeostasis. This is called Hypothalamic-Pituitary-Adrenal (HPA) axis. HPA axis is involved in regulation of stress response. With chronic stress the HPA feedback fails and continuous excess of cortisol is produced with deleterious consequences to the hippocampus where glucocorticoid receptors are abundant. Decreased hippocampal neurogenesis with atrophy of hippocampal dendrites results in shrinkage of the hippocampus. This disrupts long-term potentiation (LTP) and leads to impaired memory performance. A compensatory increase in dendritic arborization of

19 - Dexamethasone suppression test (DST)

Dexamethasone suppression test (DST)

© SPMM Course neurons in the basolateral amygdala may occur, contributing to a memory bias towards negative events in chronic stress. Hypercortisolism (Addison's disease) Hypocortisolism (Cushing's syndrome) Physical symptoms: Apathy, fatigue, and depression Physical symptoms: Fatigue, weight gain, cold intolerance, dry skin Mental symptoms: Anxiety, irritability, poor concentration, agitation, emotional lability. Mental symptoms: Depression, mania, confusion, and psychotic symptoms.

A diurnal variation in cortisol levels occurs in humans, with peak cortisol levels occurring around 6:00:00 AM. Hypercortisolemia with the loss of the normal diurnal variation have been reported in depression (especially in melancholic depression with the somatic syndrome), in some patients with mania (especially psychotic), obsessive-compulsive disorder and schizoaffective disorder. In PTSD hypocortisolemia is seen in a subgroup of patients; this may be due to aberrant feedback to the pituitary due to excessive glucocorticoid receptors – probably a genetic vulnerability. Low cortisol is also seen in chronic fatigue and fibromyalgia. Dexamethasone suppression test (DST) o Exogenous corticosteroids such as dexamethasone will suppress endogenous cortisol production if the HPA axis is intact. o In DST, 1mg dexamethasone is given at 11PM with baseline cortisol sampling; on the next day at 8AM, 4PM and 11PM cortisol levels are measured again. If any one sample has >5mcg/L of cortisol, this indicates DST non-suppression. This demonstrates the failure of feedback suppression of ACTH/CRH and continuous production of endogenous cortisol despite administration of exogenous steroid (dexamethasone). o DST non-suppression is seen in depression and other psychiatric hyper cortisolemic states (also in organic hyper cortisolemic states such as Cushing's). o The sensitivity of the DST for detecting major depression is modest (about 40%- 50%) but is higher (about 60%-70%) in very severe depression with psychotic as well as melancholic features. o DST non-suppression is non-specific to depression and is also seen in mania and schizoaffective disorder. In addition, a number of major medical conditions, pregnancy, severe weight loss and use of alcohol and certain other drugs (hepatic enzyme inducers that reduce dexamethasone availability - barbiturates, anticonvulsants, and others) can also produce DST non-suppression. o Despite the presence of depression, DST may suppress cortisol if the patient has Addison's or hypopituitarism or taking steroids, high-dose benzodiazepines or

indomethacin. o DST non-suppression does not increase the likelihood of antidepressant response. A negative test is not an indication for withholding antidepressant treatment. o Some data suggest that patients with DST non-suppression are less likely to respond to a placebo than those who show a suppression response.

20 - D. Pineal gland

D. Pineal gland

© SPMM Course o Continued failure to suppress cortisol despite the apparent recovery from depression suggests an increased risk for relapse, poor prognosis and possibly later suicidal behaviour.

D. Pineal gland The pineal gland is also called epiphysis. It contains pinealocytes that secrete both serotonin (in the day) and melatonin (in the night). The gland also contains calcium deposits that become more prominent with age (corpora arenacea or brain sand). The pineal gland contains the highest concentration of serotonin in the body. Melatonin is synthesized from serotonin by the action of serotonin-N-acetylase and 5-hydroxyindole-O-methyltransferase. The major regulator of melatonin synthesis is the light-dark cycle, with synthesis increased during darkness. The pineal gland is regulated by a major α -adrenergic mechanism, and α -antagonists such as propranolol decrease melatonin synthesis. Melatonin regulates circadian rhythms. It has both synchronizing and phase-shifting properties in the regulation of biological rhythms.

ENDOCRINE CHANGES & SLEEP

Start of sleep – increased testosterone Slow wave sleep – increased GH & SST; reduced cortisol
REM sleep – reduced melatonin Early morning sleep – increased prolactin.

Circadian rhythm development in the first 1 month involves the emergence of the 24-hour core body temperature cycle; by 2 months progression of nocturnal sleeping is noted and in 3 months, melatonin and cortisol rhythms are established.

21 - 5. Physiology of sleep

5. Physiology of sleep

22 - A. Measurement

A. Measurement

23 - B. Architecture

B. Architecture

24 - NREM sleep

NREM sleep:

© SPMM Course 5. Physiology of sleep A. Measurement

- Actigraphy: This is used to quantify circadian sleep-wake patterns and to detect movement disorders during sleep; it uses a motion sensor.
- Polysomnography (PSG): This includes EEG, electromyogram (EMG), electrooculogram EOG. ECG, oximetry and respiratory monitor can also be added. PSG helps in the diagnosis and monitoring of sleep apnoea, narcolepsy, restless legs & REM behavioural disorder. Some of the terms used in PSG are
 - o Sleep latency: time from 'lights out' to sleep onset.
 - o REM latency: Time from sleep onset to first REM episode. Normally ~90 minutes in adults.
 - o Non-REM latency: Time from sleep onset to first Non-REM episode.
 - o Sleep efficiency: $(\text{Total sleep time} / \text{total time in bed}) \times 100$.
 - o Multiple sleep latency test: This is used to assess daytime somnolence and daytime REM onset in narcolepsy.

B. Architecture The average length of sleep is approximately 7.5 hours per night. Sleep is made up of non-rapid eye movement (NREM) and rapid eye movement (REM) phases. NREM sleep:

- o 75% of adult sleep is NREM. Most physiological functions are markedly lower in NREM than in wakefulness (decreased muscle tone, respiration, temperature and heart rate).
- o NREM is classified as stages 1 to 4 with increasing amplitude and decreasing frequency of EEG activity. Stages 3 & 4 together constitute slow wave sleep (SWS). SWS dominates initial part of the sleep.
- o Features of non-REM sleep includes
 - Increased parasympathetic activity (decreased heart rate, systolic blood pressure, respiratory rate, cerebral blood flow)
 - Abolition of tendon reflexes
 - The upward ocular deviation with few or no movements.

- 5% of sleep • Drowsy period. When awoken from this stage one denies being asleep.
- Shows low voltage theta activity, sharp V waves.

Stage 1 NREM sleep

- 45% of sleep • Shows the development of sleep spindles and K complexes.

Stage 2 NREM sleep

- 12% of sleep • Shows <50% delta waves.

Stage 3 NREM sleep

- 13% of sleep • Shows >50% delta waves.

- Physiological functions are at the lowest

Stage 4 NREM sleep

DREAMS

Dreaming occurs at all stages of sleep, but the content varies. In non-REM sleep the dreams are thought-like as though the person is solving a problem. In REM sleep the dreams may be illogical and bizarre.

25 - REM sleep

REM sleep

26 - C. Brain activity

C. Brain activity

© SPMM Course □ Reduced recall of dreams if awaken. (Sleep terror is an NREM disorder. When awake after sleep terror episodes, children appear confused and do not recall what terrified them). REM sleep □ 25% of adult sleep is REM. Darting eye movements are noted in REM despite other muscles being paralysed. REM sleep is characterized by a high level of brain activity and physiological activity similar to those in wakefulness. □ In REM sleep behavioural disorder, muscular paralysis does not occur resulting in violent movements coinciding with brain activity. □ EEG shows low-voltage, mixed-frequency (theta and slow alpha) activity similar to an awake state. Sawtooth waves are also seen. □ In a typical night, a person cycles through five episodes of non-REM/REM activity. The REM episodes increase in length as the night unfolds. □ Features of REM sleep: □ Increased sympathetic activity (increased heart rate, systolic blood pressure, respiratory rate, cerebral blood flow) □ Autonomic functions are active with penile erection or increased vaginal blood flow □ Increased protein synthesis □ Maximal loss of muscle tone with occasional myoclonic jerks □ Vivid recall of dream if awaken. (Nightmares occur in REM sleep – hence they are well recollected). C. Brain activity Apart from various oscillatory patterns, some specific patterns of electrical activity are also noted during sleep. □ Sleep spindles □ Waves with upper alpha or lower beta frequency, seen in many stages but especially in stage 2. The waveform resembles a spindle with an initial increase in amplitude that decreases slowly □ Duration usually <1second. □ They usually are symmetric and are most obvious in the parasagittal regions. □ K complex: □ K complex waves are large-amplitude delta frequency waves, sometimes with a sharp apex. □ They can occur throughout the brain but more prominent in the bifrontal regions. □ These may be mediated by thalamocortical circuitry. □ Usually symmetric, they occur each time the patient is aroused partially from sleep. □ Semiarousal often follows brief noises; with longer sounds, repeated K complexes can occur. □ Runs of generalized rhythmic theta waves sometimes follow K-complexes; this pattern is termed an arousal burst. □ V waves: □ V waves are sharp waves that occur during sleep. They are largest and most evident at the vertex bilaterally and are usually symmetrical. □ Multiple V waves tend to occur especially during stage 2 sleep.

27 - D. Regulation

D. Regulation

28 - Hypothalamic controls

Hypothalamic controls

29 - Ascending Reticular Activating System Neurotr

Ascending Reticular Activating System - Neurotransmitters

© SPMM Course □ Often they occur after sleep disturbances (e.g., brief sounds) and, like K complexes, may occur during brief semiarousals.

D. Regulation Hypothalamic controls □ The master clock of the brain is the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus - this orchestrates circadian rhythms and is synchronized by signals from the retina. □ SCN is reset each day by signals of light from the retina. Specialized melanopsin-containing retinal ganglion cells project via retinohypothalamic tract to the SCN. This provides light input independent of vision. □ In the absence of solar guidance, the 24-hour sleep-wake cycle will gradually increase to approximately 26 hours -this is called freerunning. □ Pineal melatonin secreted during darkness can also reset the SCN. Thus, melatonin promotes sleep in those with delayed sleep onset or jet lag. □ The ventrolateral preoptic nucleus (VLPO) is called the sleep switch nucleus. It has projections to the main components of the ascending arousal system. The VLPO induces sleep by putting the brakes on the arousal nuclei. People with damage to their VLPO have chronic insomnia. □ The VLPO must be inhibited so that people can wake up. This is brought about by a negative feedback from the monoaminergic system. The switching to arousal is then stabilised by orexin (also called hypocretin) neurons in the hypothalamus. Orexin neurons are mainly active during wakefulness and reinforce the arousal system. Patients with narcolepsy have reduced number of orexin neurons, leading to repeated somnolence during the day.

Ascending Reticular Activating System - Neurotransmitters

Neurotransmitter	Cell Bodies	Function
Cholinergic	Midbrain-pons nuclei	REM on neurons. Activation brings on REM sleep
Noradrenergic	Locus coeruleus	REM off neurons. Activation reduces REM sleep.
Dopaminergic	Periaqueductal gray matter D2	possibly enhances REM sleep
Serotonergic	Raphe nuclei 5HT2	stimulation possibly maintains arousal
Histaminergic	Tuberomammillary nucleus H1	stimulation possibly maintains arousal

SLEEP & AGEING

Newborns sleep about 16 hours a day. They spend >50% of sleep time in REM sleep. Sleep onset REM is also seen in neonates.

By 3-4 months of age, the pattern shifts so that the total percentage of REM sleep drops to less than 40, and entry into sleep occurs with an initial period of NREM sleep. By late teens adult pattern of sleep is established.

This distribution remains relatively constant until old age. Absolute reduction occurs in both slow-wave sleep and REM sleep in older persons. An increase in frequency of awakenings after sleep onset also occurs with age.

30 - E. Drugs and Disorders

E. Drugs and Disorders

© SPMM Course E. Drugs and Disorders Disorder / drugs Changes Alcohol □ Increase SWS (chronic use – loss of SWS) □ Reduce initial REM but increase second half REM Alcohol withdrawal □ Loss of SWS □ Increased REM □ Intense REM rebound Anxiety disorders □ Increased stage 1 sleep (light sleep) □ Reduced REM, normal REM latency □ Reduced slow wave sleep Benzodiazepines □ Decrease sleep latency □ Increase sleep time □ Reduce stage 1 sleep □ Increase stage 2 sleep □ Reduce REM and SWS □ REM rebound on cessation □ Prevent the transition from lighter stage 2 sleep into deep, restorative (stages 3 and 4) sleep. Cannabis □ Increase SWS □ Suppress REM Carbamazepine □ Suppresses REM and increases REM latency □ Increases SWS Dementia □ Increased sleep latency & fragmentation □ Reduced sleep time Depression □ Loss of SWS slow wave sleep (first half) □ Increased REM (leading on to Early awakening) □ Reduced REM latency Lithium □ Suppresses REM and increases REM latency □ Increases SWS Opiates □ Decrease SWS & REM □ Withdrawal REM rebound Schizophrenia □ Inconsistent reduction in REM latency and slow wave sleep. □ N.B.: Antipsychotics have variable effects SSRIs □ Alerting due to 5HT₂ stimulation □ May reduce REM latency □ Variable effects of REM suppression Stimulants □ Reduce sleep time by decreasing both REM sleep and SWS □ REM rebound on cessation (except modafinil) Tricyclics □ REM suppression (especially Clomipramine) □ Increased SWS and stage 1 sleep Z hypnotics □ Less effect on sleep architecture; Zopiclone may increase SWS

31 - 6. Neurophysiological measurements

6. Neurophysiological measurements

32 - A. EEG

A. EEG

33 - Wave forms noted in EEG

Wave forms noted in EEG

© SPMM Course 6. Neurophysiological measurements A. EEG □ EEG records the electrical activity of the brain. In psychiatric practice, it is primarily used to rule out seizures, monitor ECT and in polysomnogram for sleep disorders. □ Standard EEG uses 21 electrodes placed on the scalp. Placement of the electrodes is based on the 10/20 International System of Electrode Placement. This system measures the distance between readily identifiable landmarks on the head and then locates electrode positions at 10 percent or 20 percent of that distance in an anterior-posterior or transverse direction. □ Activation procedures could be used to bring up abnormal discharges. □ Strenuous hyperventilation (most common, safe) □ Photic stimulation using an intense strobe light □ 24 hours of sleep deprivation can lead to the activation of paroxysmal EEG discharges in some cases □ EEG recording during sleep (natural or sedative induced) can also be used when the wake tracing is normal. Wave forms noted in EEG

Waves Frequency Notes Beta

“ 13Hz Some seen at frontal, central position in the normal waking EEG Alpha 8 to 13 Hz Dominant brain wave frequency when eyes are closed and relaxing; occipitoparietal predilection. Disappears with anxiety, arousal, eye opening or focused attention. Dominance reduces with age. Theta 4 to 8 Hz A Small amount of sporadic theta seen in waking EEG at frontotemporal area; prominent in drowsy or sleep EEG. Excessive theta in awake EEG is a sign of pathology. Delta <4 Hz Not seen in waking EEG. Common in deeper stages of sleep; the presence of focal/generalized delta in awake EEG is a sign of pathology. Mu 7-11 Hz Occurs over the motor cortex. It is related to motor activity, characterized by arch like waves; gets attenuated by movement of the contralateral limb Lambda Single waves A single occipital triangular, symmetrical sharp wave produced by visual scanning when awake (e.g. reading) or in light sleep

□ Beta and alpha are called fast waves; theta and delta are slow waves. Newborns Newborns •Dominant delta and theta waves Infants Infants •Irregular medium- to high-voltage delta activity Early childhood Early childhood •Alpha range develops in posterior areas Midadolescence

Midadolescence • EEG essentially has the appearance of an adult tracing by 12-14 years. Adults
Adults • Normal dominant alpha rhythm

34 - Abnormalities in EEG

Abnormalities in EEG

© SPMM Course Abnormalities in EEG EEG in various disorders Absence seizures (petit-mal) Regular 3 Hz Complexes Alzheimer's dementia Rarely normal in advanced dementia; may be helpful in differentiating pseudodementia from dementia Angelman's syndrome

1. EEG changes are notable by the age of 2.
2. Prolonged runs of high amplitude 2-3 Hz frontal activity with superimposed interictal epileptiform discharges - all ages
3. Occipital high amplitude rhythmic 4-6 Hz activity facilitated by eye closure, is seen under the age of 12 years.
4. There is no difference in EEG findings in AS patients with or without seizures
Antisocial personality disorder Increased incidence of EEG abnormalities in those with aggressive behaviour ADHD Up to 60% have EEG abnormalities (spike/spike-waves) Borderline personality disorder Positive spikes: 14- and 6 per second seen in 25% of patients CJD Generalised periodic 1-2 Hz sharp waves are seen in nearly 90% patients with sporadic CJD. Less often in familial / hormonal transplant-related forms. NOT seen in a variant form. Closed head injuries Focal slowing (sharply focal head trauma) Focal delta slowing (subdural hematomas) Diffuse atherosclerosis Slowed alpha frequency and increased generalized theta slowing Herpes simplex encephalitis Episodic discharges are recurring every 1-3 seconds with variable focal waves over the temporal areas. Huntington's dementia Initial loss of alpha; later flattened trace Infantile spasms (seen in tuberous sclerosis) Hypsarrhythmia [diffuse giant waves (high voltage, >400 microvolts) with a chaotic background of irregular, asynchronous multifocal spikes and sharp waves]. Clinical seizures are associated with a marked suppression of the background - called the electrodecremental response Infectious disorders Diffuse, often synchronous, high voltage slowing (acute phase of encephalitis) Metabolic and endocrine disorders Diffuse generalized slowing. Triphasic waves: 1.5 to 3.0 per second highvoltage slow-waves especially in hepatic encephalopathy. Neurosyphilis The non-specific increase in slow waves occurring diffusely over the scalp. Panic disorder Paroxysmal EEG changes consistent with partial seizure activity in one-third; focal slowing in about 25% of patients Seizures Generalized, hemispheric, or focal spike/ spike-wave discharge. Stroke Focal or regional delta activity Structural lesions Focal slowing / focal spike activity

35 - Effect of drugs on EEG

Effect of drugs on EEG

36 - B. MEG

B. MEG

37 - C. ERP

C. ERP

© SPMM Course □ Diffuse slowing of background is the most common EEG abnormality; it is nonspecific and signifies the presence of encephalopathy. Focal slowing suggests local mass lesions; e.g. edema, haematoma or focal seizure. □ Epileptiform discharges when seen interictally, can be considered as hallmark of seizure disorder. But this is not a common finding. If this is lateralized and periodic, it may suggest an acute destructive brain lesion.

Effect of drugs on EEG

B. MEG □ Magnetoencephalography (MEG) is used to measure the magnetic fields produced by electrical activity in the brain □ In contrast to electric fields, magnetic fields are less distorted/impeded by the skull and scalp. □ The scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only its tangential components. Thus, MEG may selectively measure the activity in the sulci, whereas scalp EEG measures activity both in the sulci and at the top of the cortical gyri. C. ERP □ An ERP is a change in electrical brain activity stereotyped and time-locked to an event (e.g., stimulus), although it can also occur for the omission of an expected stimulus. ERPs allow the investigation of specific types of information processing by the brain. □ ERPs are small relative to the spontaneous brain activity (background EEG) that is they have a low signal-to-noise ratio. To increase the signal-to-noise ratio, an often-used method is ERP averaging

Psychotropics

Antipsychotics

Slowing of beta activity with increase in alpha, theta and delta activity

Antidepressants

Slowing of beta activity with increase in alpha, theta and delta activity

Lithium

Slowing of alpha or paroxysmal activity

Anticonvulsants

No effect on awake EEG

Primarily sedating drugs – decrease alpha

Barbiturates

Effects are opposite to that of alcohol. Increased beta activity upon intoxication; generalized paroxysmal activity and spike discharges (even without overt fits) in withdrawal states. Benzodiazepines

Increased beta; decreased alpha. Overdose leads to diffuse slowing

Opioids

Decreased alpha activity; increased voltage of theta and delta waves; in overdose, slow waves are seen. Primarily recreational drugs – increase alpha

Alcohol

Increased alpha activity; increased theta activity. Withdrawal increases beta. Delirium tremens has beta (fast) wave activity – other deliria have increased slow waves. Marijuana

Increased alpha activity in frontal area of brain; overall slow alpha activity

Cocaine

Same as marijuana; longer lasting. Nicotine

Increased alpha activity; in withdrawal, marked decrease in alpha activity

Caffeine

In withdrawal, increase in amplitude or voltage of theta activity

© SPMM Course □ ERPs have polarity (positive [P] or negative [N]) and latency (the moment of peak occurrence after stimulus presentation, which is often indicated by the number attached to the labels of ERP activity). □ The temporal resolution of EEG, MEG and ERP analysis is much higher than that of other neuroimaging methods like functional MRI, SPECT and PET, but these techniques

lack the high spatial resolution of the MR techniques. □ According to the time of occurrence ERPs, can be classified as early, mid latency and late. □ The P300, a positive late ERP component around 300 ms after stimulus presentation, is typically generated when a rare target stimulus is imbedded with more frequent stimuli e.g. (auditory 'oddball' protocol). The P300 is related to the maintenance of working memory. Decrease in P300 amplitude is well established as a biological trait marker in schizophrenia. □ The Mismatch Negativity or MMN is a negative ERP component that is recorded between 100-200 ms in response to low-probability deviant sounds (oddball) in a sequence of standard sound stimuli, when the participant is not actively attending to the deviants. The MMN is best seen in the difference wave between the ERP in response to the standard and deviant sounds. The MMN reflects involuntary information processing in auditory context, i.e. the mnemonic comparison of a given stimulus with a previous one that has already built up a trace in memory. The violation of the previously formed memory trace produces the MMN. Decreased MMN amplitude is noted in schizophrenia. □ The Contingent Negative Variation (CNV) is a slow negative shift in the interval between two paired stimuli presented one after the other (S1 being the cue, S2 being the imperative stimulus prompting to respond). CNV reduction in central (midline) electrodes is noted in schizophrenia patients especially with long duration of illness with positive symptoms.

•Basic sensory pathways can be studied by recording early ERPs. •These are also called 'evoked potentials' (EPs) or brain stem evoked responses (BAER) •They occur in response to sounds (Auditory EP, AEP), flashes (Visual EP, VEP) or electrical stimulation (Somatosensory EP, SEP). Early ERPs Early ERPs • These occur after BAER. •The three well known midlatency ERPs are N100, P50 and P200. •Their amplitudes reduce with repetition (habituation response / sensory gating). Midlatency ERPs Midlatency ERPs •Cognitive pathways can be studied by recording of ERPs related to the execution of psychological events such as attention, emotion or memory tasks. •P300 and MMN are late ERPs Late ERPs Late ERPs

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