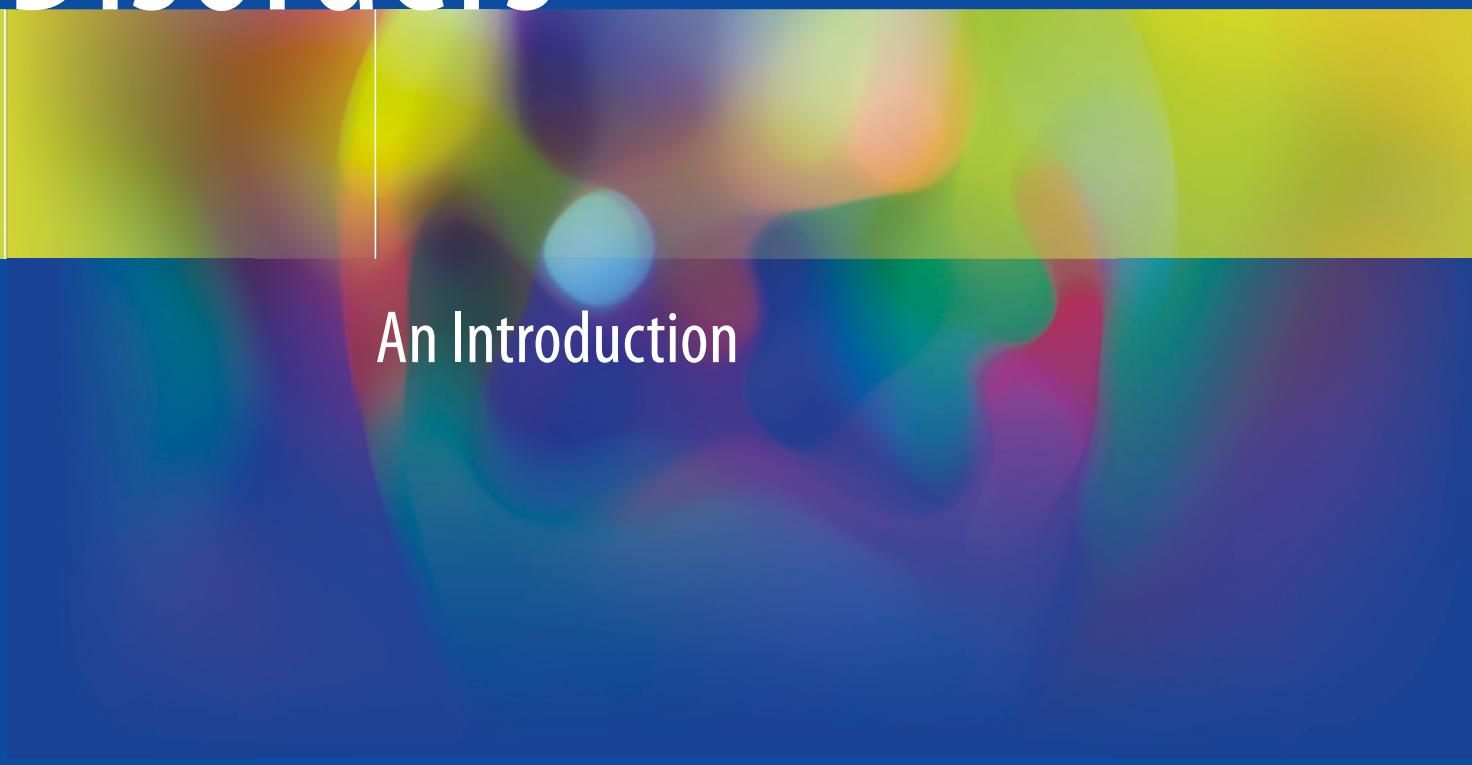
Jacob Raber · Franklin Sunzeri ·
Jennifer M. Loftis ·
J. Wesson Ashford *Editors*

Understanding and Treating Depressive Disorders



An Introduction

Springer

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Preface

A number of years ago, the NIH funded a Phase 1 Small Business Innovation Research grant that was the inception of our project in behavioral medicine called *Behavioral Medicine: A Research Compendium.* This project is a collaboration between professors at Oregon Health & Science University (OHSU), Stanford University, and the small business, Heather Hills Consulting.

Its objective is to revolutionize interdisciplinary learning among college-level graduate and medical students, faculty, and practitioners in allied behavioral medicine fields. We are doing so by eliminating obstacles to interdisciplinary collaboration that have been recognized within the NIH Roadmap for Medical Research and 2021–2025 Strategic Plan.

Behavioral medicine is the interdisciplinary field concerned with development and integration of behavioral, psychosocial, and biomedical science knowledge and techniques relevant to the understanding of health and illness, and the application of this knowledge and these techniques to prevention, diagnosis, treatment, and rehabilitation.

A wide range of consumers and health professionals are involved in behavioral medicine research and practice, including cardiologists, counselors, epidemiologists, exercise physiologists, family physicians, health educators, internists, nurses, nutritionists, pediatricians, psychiatrists, psychologists, and sociologists.

Behavioral medicine is taught through a variety of university programs. These include programs such as integrative biology that aims to discover complex interrelationships between organisms and the physical and biological environment in which they live and the highly integrative field of translational medicine. Integrative biology combines fields of genetics, genomics, physiology, ecology, systematics, and evolutionary biology to address critical problems related to the environment, ecosystems, human and animal health. There are literally hundreds of behavioral-medicine related programs at universities.

Unfortunately, resources for these courses are often ill defined and ad hoc. Based on the need for a comprehensive and tailored resource, the Compendium was developed.

The Compendium consists of a background science volume, volumes of applied science that cover areas of concentrated knowledge, and an interactive website. The Compendium begins by presenting a foundation in behavioral medicine. The focused volumes highlight a particular clinically relevant disorder. These include topics such as depression, anxiety disorders, post-traumatic stress disorder (PTSD), cardiovascular disease, cancer, autoimmune disorders, obesity, addictions, and violence.

This is the first of the focus volumes. Its goal is to shine light on the relationships discovered by the latest scientific investigations into understanding and treating depressive disorders. The volume *Understanding and Treating Depressive Disorders: An Introduction* includes a chapter on the neuroanatomical view for understanding, preventing, and treating mood disorders by Dr. Ashford, and a chapter on immune mechanisms and anti-inflammatory treatment strategies for mood disorders by Dr. Loftis.

To serve the greatest range of users, the most essential information germane to clinical depression is presented in this applied science focus volume. We begin with etiological considerations underpinning possible relationships between psychosocial variables and health. These include, but are not limited to, communication in the brain, molecular aspects, stress responses,

heritability, and disease-associated immune responses. Next, factors relative to the ability to modify behaviors are considered. These include topics such as epigenetics, neuroplasticity, conditioning, therapy genetics, critical periods, and motivation. Then, evidence for efficacy of treatment approaches is presented. These include such interventions as pharmacotherapy, psychotherapy, complementary interventions, and self-medication. We hope that with this approach, clinicians, researchers, and students with diverse experiences will acquire sufficient information to better understand and apply biopsychosocial theory and techniques.

Social interaction is an important part of this endeavor. For this reason, we have created an ancillary website offered to users of the Compendium. There are discussion boards to facilitate learning and dissemination of information, and to foster creativity. A window for feedback and input is part of the online website.

In summary, the Compendium aims to (1) facilitate an understanding of complex, interrelated issues despite users lacking knowledge of, or familiarity with, all the related science; (2) provide rigorously investigated citations and balanced narratives where conflicts in findings exist; and (3) use digital state-of-the-art technology to enhance the learning experience.

We want to acknowledge the very valuable contribution of Abigail O'Niel, a graduate student in the Behavioral Neuroscience graduate program in the laboratory of Dr. Raber at OHSU. She not only created the figures that appear in this focus volume, but she also provided the graduate student perspective and editorial feedback so important for the success of this project. We also want to acknowledge the support of the Springer Nature team, including Kiruthika Andappan, Julia Andrews, Margaret Moore, and Richard Lansing.

We thank Dr. Peter Kaufmann, formerly of the NHLBI division of the NIH, which sponsored the SBIR grant that provided the opportunity to initiate this project, for his belief in the goal of this project and who gave us the confidence to pursue it.

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The Neurophysiology of Depression, Interactions Between the Brainstem and Cerebral Cortex

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J. Wesson Ashford

Introduction

Depression has long been thought of as being a disorder of the frontal lobes. This perspective makes sense in the classic understanding of brain function since the frontal lobes generate movement, speech, thought, and planning dorso-laterally and emotions ventro-medially [1, 2]. See Fig. 25.1. If depression is seen with this view, depressive thoughts, lack of motivation, self-deprecating ruminations, and even suicidal ideation can be understood as generated by the frontal lobes. Even electroshock therapy and now trans-cranial magnetic stimulation target the frontal lobes with beneficial effect [3]. Further, special imaging of the frontal lobes has been used to find the most efficacious location for prefrontal targeting of transcranial magnetic stimulation [4]. Additionally, functional magnetic resonance imaging (fMRI) has shown distinct neurophysiological varieties (biotypes) of depression and specific symptoms involving the frontal lobes and limbic system, which can be categorized into four specific types of depression, defined by distinct patterns of dysfunctional connectivity in the limbic and frontostriatal networks[1] [5], and there are specific changes in the fronto-striatal salience network[2] found in individuals with depression [7].

Consider commonly used depression scales such as the *Hamilton Depression Rating Scale (HDRS)*[3] [10] and the *Geriatric Depression Scale (GDS)*[4] [12, 13], which list the most commonly recognized symptoms of depression. The items on these scales can be reviewed for estimating the neurological sources of depression-related symptoms.

HDRS Items:

- 1. Depressed Mood—sadness, hopeless, helpless, worthless
- 2. Work and Activities—thoughts and feelings of incapacity, fatigue, or weakness related to activities; work or hobbies
- 3. Social Withdrawal—loss of interest in activities
- 4. Genital Symptoms—loss of libido, menstrual disturbances
- 5. Somatic Symptoms—loss of appetite, GI symptoms
- 6–7. Weight—loss, gain
- 8–10. Appetite—increased eating, carbohydrate craving
- 11–14. Sleep Management: insomnia—early, middle, late, hypersomnia
- 15–16. Somatic Symptoms—heaviness, aches, loss of energy, fatigability

[1] In an endeavor to define depression subtypes, four biotypes have been suggested [5]. These are based upon fMRI data that attempts to correlate how distinct clinical symptom profiles might predict treatment responses as they relate to clustered patterns of dysfunctional connectivity. One of the goals is to use neuroimaging biomarkers to diagnose these subtypes.

[2] The frontostriatal salience network is involved in reward processing and the conscious integration of internal goals and environmental demands with autonomic responses and feedback [6]. It appears that the frontostriatal salience network is expanded almost two fold in the cortex of most individuals with depression [7, 8].

[3] There are several versions of the HDRS (aka Ham-D) varying from 17 to 29 questions. One of the limitations of the HDRS was the lack of assessing atypical symptoms. This version outlined here includes more of the symptoms such as increased eating. The HAM-D is considered to be a valid and sensitive clinimetric index [9].

[4] The GDS-15 scale referenced here is most accurate in screening for depression in older adults with normal cognitive functions vs. cognitively impaired [11].

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- 17. Feelings of Guilt—self-reproach, ideas of guilt or rumination
- 18. Suicide—feeling life is not worth living, death wishes, suicide ideation, plans, attempts
- 19–21. Anxiety—subjective tension and irritability, worrying, somatization, hypochondriasis
- 20. Anxiety—somatic
- 22. Insight—may deny being ill
- 23. Retardation—motor, speech, thought
- 24. Agitation—fidgetiness, cannot sit still, hand wringing

GDS Items:

1. Not feeling satisfied with life
2. Dropped many activities, interests
3. Feeling life is empty
4. Getting bored
5. Poor spirits most of the time
6. Afraid that something bad is going to happen
7. Feeling unhappy most of the time
8. Feeling helpless
9. Preferring to stay home
10. Concern about memory problems ("brain fog")
11. Not wishing to be alive
12. Feel worthless
13. Lacking energy
14. Feeling hopeless
15. Feeling not well off

These symptom lists have been developed from extensive experiences with depressed patients and selecting the items most consistently present in patients with depression. While many of the symptoms of the HDRS can be linked to frontal lobe function, there are many symptoms, including appetite, weight control, sleep, retardation, and even anxiety that can be related to brainstem function. The GDS items are much more clearly related to expressed feelings, but symptoms less clearly related to the frontal lobes develop, particularly no longer feeling full of energy, and the brainstem is the brain structure which regulates the energy of the body. See Fig. 25.1.

The most commonly prescribed medications for depression—antidepressants—primarily act on the neurotransmitters serotonin, norepinephrine, or both. The earliest antidepressants were mono-amine-oxidase inhibitors (MAOIs), which prevented oxidation of serotonin and norepinephrine and increased their effects at brain synapses. Later tri-cyclic antidepressant medications inhibit the reup-

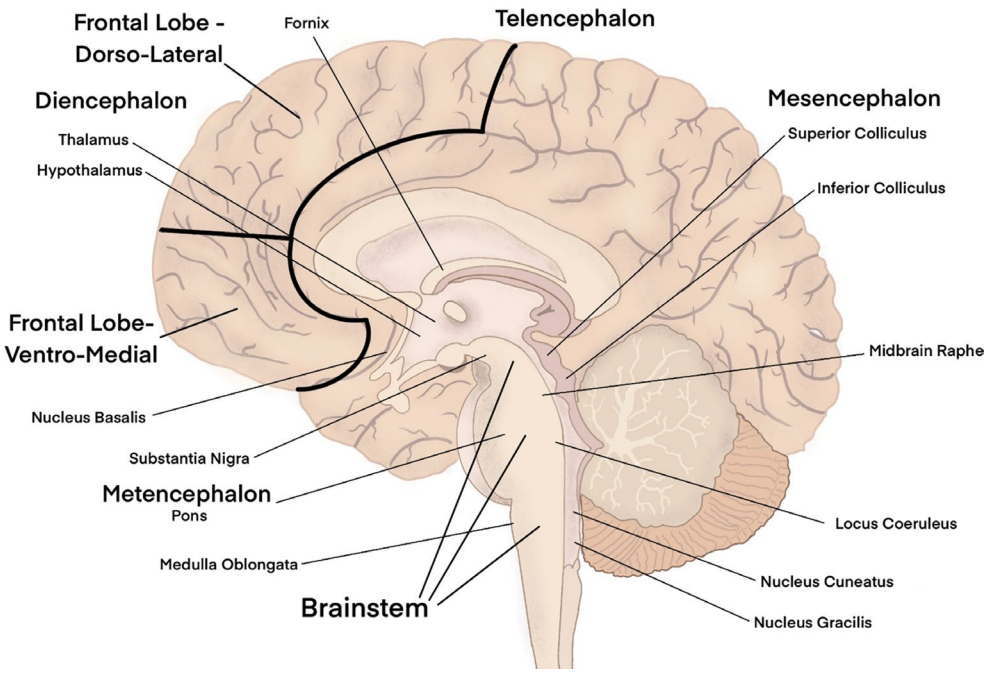

Fig. 25.1 Schematic representation of the human brain showing components of the brainstem and cerebral cortex

take of serotonin and norepinephrine to different degrees though with frequent side effects, mostly anti-cholinergic.[5] The more recent selective-reuptake inhibitors also increase the amount of serotonin (SSRIs) or norepinephrine (SNRIs) in synapses, though without the anti-cholinergic side effects. The relevant issue is that the cell bodies of the serotonin and norepinephrine systems are located in the brainstem—specifically, many serotonin neuronal cell bodies reside in the midbrain raphe nuclei, while norepinephrine neuronal cell bodies are situated in the midbrain locus coeruleus. See Fig. 25.1. Neurons from both of these groups have axons that project widely and diffusely throughout the cerebral neocortex, not just the frontal lobes [15, 16].

For understanding how the norepinephrine and serotonin neurons relate to depression, it is central to understand what their roles are in brain function. Serotonin neurons from the midbrain raphe nuclei are involved in the management of several vegetative functions, including energy management, appetite, temperature control,[6] and phases of sleep [18], as well as playing a role in mood regulation and sexual behavior. Of particular interest, the serotonin neurons have a major role in classical conditioning,[7] a fundamental learning mechanism in the brain and a major component of neuroplasticity [19]. A relevant sidenote is that serotonin neurons typically fire at a rate of approximately 1 to 5 times per second during wakefulness. While bursts of higher activity may occur in response to specific stimuli or environmental conditions, their firing rate decreases during slow-wave sleep and ceases altogether during REM sleep [20]. LSD toxicity causes a similar slowing and decreases of the firing of serotonin neurons [21], suggesting that serotonin neurons have a role in controlling thought processes and their encoding into memory.

Alternatively, norepinephrine neurons from the locus coeruleus have roles in regulating arousal, alertness, attention, cognitive function, and stress responses. In particular, the locus coeruleus has a role in generating anxiety. The locus coeruleus norepinephrine neurons also play a role in operant conditioning and reward-related learning [22], thus another important aspect of neuroplasticity.

A related consideration is the link between depression, apathy, and Alzheimer's disease (AD). Depression and apathy [23, 24] are both common in very early stages of AD. The earliest changes in AD are losses of brainstem norepinephrine neurons of the locus coeruleus [25–30] followed by the cortically projecting serotonin neurons of the midbrain raphe [31–34]. Both of these neurotransmitter systems project diffusely from the brainstem to the cerebral cortex, though therapies targeting these neurotransmitters have not been shown to have benefit in AD [35]. Since these are the same neuron groups related to depression, their demise may be the cause of depression frequently seen in early AD. There are still other considerations such as that losing one's memory and the onset of dementia are just depressing. However, given that AD is fundamentally an attack on neuroplasticity [36–38], this link supports the important consideration that impairment of neuroplasticity, learning, and memory are critical concerns for understanding, preventing, and treating depression.

Accordingly, both serotonin and norepinephrine significantly influence cerebral cortex activity, neuroplasticity, and the encoding of new information into memory. Given that these neurotransmitters—closely associated with depression—also play critical roles in neuroplasticity, psychotherapy may similarly support recovery by fostering the encoding of new insights and adaptive strategies for living. This neuroanatomical association thus provides a compelling basis for the therapeutic value of psychotherapy in treating depression.

Since it is then clear that two major brainstem nuclei are involved in depression, it is necessary to understand how these systems play a broader role in the brainstem, and how the brainstem functions with respect to overall brain activity [39]. The brainstem is the component of the brain which manages all vegetative functions, including the whole sleep–wake cycle, energy/fatigue, respirations, appetite, body temperature, and pain modulation, and through control of the autonomic nervous system, cardiovascular status and gastrointestinal and bowel activity. And all of these functions may be considered to be "energy management activities," and thus the brainstem controls the body and the rest of the brain to acquire and apportion energy resources. In this role, the brainstem can then be seen as managing the cerebral cortex, including overall activity (as it clearly does during sleep). Brainstem disruption is also seen in Gulf War Illness (GWI), particularly with regard to autonomic dysregulation, chronic pain intensity, and increased sleep difficulties [40], which are associated loss of brainstem volume and reduced integrity in brainstem-subcortical tracts [41].

[5]Anti-cholinergic symptoms that arise from blocking the acetylcholine neurotransmitter include peripheral and central effects [14]. Common central effects may include headaches, reduced cognitive functions, impaired memory, behavioral disturbances and anxiety. At higher doses confusion and agitation may occur. Peripheral symptoms may include such conditions as arrhythmias, flushing, constipation, urinary retention and dryness.

[6]Note about serotonin and temperature, unpublished observation made by J. Wesson Ashford in the laboratory of Michel Jouvet and Jacques Mouret (University of Lyon, France) in 1971: the drugs 6-chlorotryptophan and 6-fluoro-tryptophan, short acting serotonin synthesis inhibitors (provided by Patrick McGeer, University of British Columbia), were injected intraperitoneally in rats [17]. Within 30 min their body temperature dropped by 2 degrees centigrade, then their temperature returned to normal within 4 h. When the injection was repeated 2–5 days later, the rats dropped their body temperature to ambient within an hour and did not recover, the rats dying 2–3 days later.

[7]Classical conditioning associates two stimuli to produce an automatic response. Operant conditioning associates a behavior with its consequence such as a reward or punishment to influence future behaviors.

The roof of the brainstem, the tectum (dorsal component), serves as a sentinel to detect relevant environmental events. The sensory sentinels of the tectum include the nuclei of Burdock and Gall (gracilis and cuneatus), which detect somatosensory stimuli; the auditory sentinel, the inferior colliculi; and the visual sentinel, the superior colliculi. See Fig. 25.1. The tectum is the initial manager of incoming information and is the first brain region to detect any tactile, auditory, or visual stimulus.

When a notable environmental stimulus is detected, the *reticular activating system (RAS)*[8] of the anterior brainstem is activated as well as the relevant thalamic relay nuclei, which in turn activate the cerebral cortex. When environmental stimuli are deemed novel or significant by the cerebrum (including regions such as the hippocampus and amygdala), the brainstem is engaged. It then sends projections back to the cerebrum, instructing relevant neurons to encode the new information via mechanisms such as the P300 evoked potential[9] [44–47]. In this way, the brainstem contributes to the regulation of awareness and consciousness. As noted above, many brainstem functions are mildly to severely disrupted in individuals with depression.

A related issue is post-traumatic stress disorder (PTSD), frequently accompanied by depression, which can be understood as a learned hyper-alert state, pointing to an important role of the tectum. When a notable environmental stimulus is detected, the RAS is activated as well as the relevant thalamic relay nuclei. However, the serotonin and norepinephrine systems are also activated. Importantly, certain antidepressant agents have been recommended for the treatment of PTSD—such as the SSRI sertraline and the atypical antidepressant trazodone—both of which modulate serotonin and norepinephrine systems [48, 49]. Also, the antihypertensive medication prazosin, which affects norepinephrine, has been recommended for the nightmares associated with PTSD [50, 51]. And PTSD can also be associated with neocortical damage related to the frontal lobes and connections back to the brainstem [52]. So, PTSD can also be understood as involving brainstem function or dysfunction.

Returning to the frontal lobe, it is important to consider the role of the *basal ganglia*, which generate movement in coordination with the motor cortex. The nucleus accumbens, at the rostral end of the basal ganglia, coordinates thought signals from the pre-frontal cortex. And the basal ganglia and nucleus accumbens are both managed by dopamine neuron projections from the brainstem, from the substantia nigra (see Fig. 25.1) and adjacent medial dopaminergic nuclei. Dopamine is involved both in the generating and pacing of movements and thoughts. Dopamine also has a role in reward-linked neuroplasticity and behavior, and unfortunately in addictive behavior as well [53]. These dopamine systems are involved in Parkinson's disease and schizophrenia. However, the dopaminergic medications used to treat these conditions, though speeding (e.g., stimulants, dopaminergic agonists, amphetamines) or slowing (e.g., neuroleptics) behavior and thought, are not particularly beneficial for treating mood disorders including depression.

Summary

Given the perspective of considering both frontal lobe and brainstem roles in depression, there needs to be more extensive understanding of the role of the brainstem, particularly the serotonin and norepinephrine projections to the cerebrum. Considering that both of these neurotransmitters are involved in neuroplasticity and depression, the issue to understand is that the brainstem is using these neurotransmitters to activate the frontal lobes to learn and retain information that is relevant for the energy management of the organism. If the brainstem is not set correctly, the thoughts encoded in the frontal lobes could be negative and lead to depression. Alternatively, an opposite brainstem activation of frontal lobe patterns could lead to manic behavior and explain manic-depressive illness. Of course, a tragic direction is perception that coping with the environment is hopeless, and suicidal ideation can lead to a self-perpetuating negative perception with a mortal consequence.

This perspective of brainstem function in affective disorder does lead to some very important considerations for prevention and management of depression. In addition to the interventions mentioned above, other preventive measures and interventions can be considered. Cultural exposure, music, art, exercise, sleep, and specific activities, including yoga and meditation [54], can help teach control of the brainstem and stabilization of mood, thus preventing depression. Psychotherapy and medications could be more effective if they are provided and prescribed with this focus on control of the brainstem. Further, appropriate encouragement to consider the positive aspects of life and caution to avoid thoughts of self-harm can help the frontal lobes to guide the direction from the brainstem to maintain a stable mood.

[8]The reticular activating system (RAS) is located in the most anterior segment of the brainstem [42]. The RAS coordinates sleep-wake cycles, attention, arousal, ability to focus and muscle tone. The RAS is composed of four main groups of nuclei. These are the locus coeruleus, raphe nuclei, posterior tuberomammillary hypothalamus, and pedunculopontine tegmentum. Each of these areas have characteristic neuropeptides that they release.

[9]The P300 wave is a positive deflection on an electroencephalogram that occurs about 300 msecs after a stimulus [43, 44]. The P300 is considered to be the results of cognitive processes including decision making and attention in response to unexpected or novel stimuli, but generated by cholinergic projections from the brainstem, Nucleus Basalis of Meynert (See Fig. 25.1) to the cerebral cortex.

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