Basic Foundations of Diagnosis, Psychiatric Diagnosis, and Final Common Pathway Syndromes

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7.1 Diagnosis: The Basics

The word *diagnosis* derives from the Greek prefix *dia*, meaning *across*, *apart,* or *through*, and the Greek word *gnosis*, meaning *knowing*. Diagnosis, a thorough (through and through) knowing of the patient's illness, including knowing it apart from other possibilities (differential diagnosis), is the essential first step in all medical intervention including psychiatric consultation.

When a psychiatric consultation is requested from our non-psychiatric colleagues, one or more medical diagnoses are probably at least suspected or being evaluated. The psychiatric consultant is then expected to consider possible psychiatric diagnoses and to integrate an understanding of the patient from the psychiatric, medical, and psychosocial dimensions in making a recommendation.

7.1.1 DSM—Historical

The standard reference in making a psychiatric diagnosis is the Diagnostic and Statistical Manual (DSM) of Mental Disorders, published by the American Psychiatric Association (APA), now in its fifth edition (APA 2013). The APA published a predecessor to a DSM in 1844, which was a statistical classification of institutionalized mental patients. The first official DSM, published in 1952, was based on Adolf Meyer's psychobiology, a model that prominently posited the interaction between constitution, personality, and environment (Meyer and Winters 1950). Psychiatric disorders were considered to be "reactions" of the personality while adapting to environmental demands.

Both DSM I and DSM II (published in 1968) were based on the then prevailing etiologic theory—psychodynamics. DSM III, published in 1980, was a frank admission of the inadequacy of the psychodynamic model as it attempted to redefine psychiatric diagnoses as research questions rather than coherent entities. By adopting an "atheoretical" model, it dropped the psychodynamic view of etiology and the notion of neurosis, that there is a continuum of psychiatric problems or conflicts between the normal and the psychiatrically ill. It adopted, to a large measure, the "research criteria for psychiatric diagnosis" that was designed to choose "pure cultures" of major psychiatric disorders for genetic research (Feighner et al. 1972). DSM III and its direct successor, DSM IV (1994), classified major psychiatric syndromes into mutually exclusive categories (e.g., schizophrenia vs. schizoaffective disorder), presumably based on the notion of different genetic underpinnings. Though it claimed to be atheoretical, it thus implicitly adopted a biological/genetic model of psychiatric syndromes. Another outstanding feature of DSM III and IV was the multiaxial system of diagnosis—Axis I: Major Psychiatric Syndromes, Axis II: Personality Disorders and Developmental Disorders, Axis III: Medical Diseases, Axis IV: Stressors, Axis V: Global level of functioning (scale of 0–100). This system explicitly made the important declaration that psychiatric syndromes and medical diseases coexist in a patient, and made important contributions in avoiding the "either physical or all in the head" notion of a symptom.

DSM III and IV have helped foster psychiatric research by defining reliable populations for study. This fortuitously coincided with the rapid development in molecular biology and genetics, psychopharmacology, neuroimaging, and the completion of the Human Genome Project. If we can define a "pure culture" of a genetic syndrome, we were now in a position to understand its genetic underpinnings.

The multiaxial system of DSM III and IV, in addition to recognizing the coexistence of medical and psychiatric conditions, had also pioneered the notion that diagnosis is more than the listing of diseases and includes the personality aspect of the patient, as well as the role of stress and the level of functioning. It was an attempt to diagnose the *patient*, not merely the disease.

On the negative side, the problems included: confusion concerning the categories and criteria for diagnosis, confusion concerning the distinction between Axis I and Axis II, and confusion concerning the nature and function of multiaxial diagnosis (Leigh 2009).

As DSM III/IV were based on research diagnostic criteria (Feighner et al. 1972) and was designed to obtain a "pure culture" for biologic research, the diagnoses were categorical and mutually exclusive, even though many psychiatric syndromes represent extremes of gradations of symptoms, many of which overlap and coexist. This overlap is not surprising, as the same susceptibility genes may have different phenotypic expressions depending on early experience and stress (See Final Common Pathways, below). Furthermore, there is a continuum of experiences and moods from normality to repeated distress, not quite reaching the criteria for the disorders of frank major psychiatric syndromes. Especially in consultation-liaison settings, patients often experience anxiety and depression associated with both medical conditions and the stress of hospitalization. The term *disorder*, adopted since DSM-III, is also problematic as it is a vague and pejorative term not commonly used in medicine. "Syndrome" is a better designation widely used in medicine, which term may be substituted for "disorder."

7.1.2 DSM-5

DSM-5, published in 2013, attempts to address some of the problems in DSM III/IV. DSM-5 dropped the multiaxial system of DSM III/IV, so that psychiatric diagnoses (both major syndromes and personality disorders) may be listed side by side, together with relevant medical diagnosis/conditions. Stressors (formerly Axis IV) and global level of functioning (formerly Axis V) are no longer part of the diagnosis but may be specified using non-DSM classifications such as certain codes and scales such as ICD and WHO Disability Assessment Schedule. DSM-5 adopts a dimensional approach to psychiatric diagnosis (i.e., gradations between health and disorder), and psychiatric diagnoses are not mutually exclusive. Thus, a patient may develop a mild depressive episode, then develop at a later time a psychotic disorder, and may also have a diagnosis of borderline personality disorder.

DSM-5 adopts a developmental and life span approach, as well as an internalizing/externalizing distinction in the ordering of chapters as follows:

Neurodevelopmental disorders
Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Depressive disorders
Anxiety disorders
Obsessive-compulsive and related disorders
Trauma and stressor-related disorders
Dissociative disorders
Somatic symptom and related disorders
Feeding and eating disorders
Elimination disorders
Sleep–wake disorders
Sexual dysfunctions
Gender dysphoria
Disruptive, impulse-control, and conduct disorders
Substance-related and addictive disorders
Neurocognitive disorders (in which there is delirium and major and minor neurocognitive disorders due to Alzheimer's disease, etc.)
Personality disorders
Paraphilic disorders
Other mental disorders
Medication-induced movement disorders and other adverse effects of medication
Other conditions that may be a focus of clinical attention

The adoption of the Arabian numerals instead of the Roman numerals indicates the readiness for revisions to DSM-5 without having to wait 20 years for a new edition, e.g., DSM-5.1, DSM-5.2.

In our CL Service, we do a formal differential diagnosis for any salient symptom or behavior, such as depression or overdose. For example, for depression, the large differential diagnostic categories are:

Secondary Contributing factors:
  Medical Disease (e.g., hypothyroidism)
  Substances
    Prescribed (e.g., steroids)
    Recreational (e.g., cocaine)

Primary Psychiatric Disorder
- Depressive disorders
- Bipolar and related disorders
- Schizophrenia spectrum and other psychotic disorders
- Trauma and stress-related disorders (including PTSD and Adjustment disorder)
- Neurocognitive disorders (delirium and dementias)
- Others (e.g., gender dysphoria)

Once psychiatric diagnoses are made, we also indicate certain important considerations as example below:

Psychiatric Diagnoses: Major depressive disorder, moderate, with anxious distress, contributed by methamphetamine use; Schizophrenia by history, Borderline personality disorder by history, methamphetamine withdrawal

Relevant Medical Diagnoses: anemia, diabetes mellitus

Stresses: childhood abuse, recent divorce

Assets: boyfriend, brother

Formulation: Patient with genetic predisposition for depression and substance use (both parents had both), early childhood physical abuse and ensuing depression was self-treated with methamphetamine causing further mood instability and was unable to develop sufficient coping skills as she dropped out of school in 11th grade. Recent stress of divorce caused heavy use of methamphetamine which caused both depression and neglect of adequate nutrition, which, in turn, may have caused anemia, further contributing to pt's current fatigue and depression.

7.1.3 Levels of Diagnosis

Thorough knowledge of a patient's illness involves knowing (1) the patient as a person, who has a personal history that determined his or her way of perceiving the self and the outer world, and habitual ways of coping; (2) the illness, which is a result of the interaction between the patient and the effects of disease, for example, pain, discomfort, anxiety, and its treatment, including drugs, procedures, and laboratory tests; and (3) the patient in interaction with the social and physical environment, including the health care personnel, family, and the hospital setting.

Thus one has to also consider, in addition to the patient's illness, who the patient is, what the support systems are, and the nature of the biologic problems that may affect the patient's physical and psychological condition.

Historically, medical diagnosis evolved from the naming of symptoms (e.g., fever), to a syndromic diagnosis based on a cluster of symptoms and signs that might indicate a common pathology (e.g., grippe: influenza; dropsy: glomerulonephritis, and congestive heart failure, a term still in use), to the current etiologic diagnosis that relies heavily on laboratory findings. Etiologic diagnosis is based on the biologic abnormality that is a necessary condition for the development of the syndrome.

Psychiatric diagnosis, on the other hand, has not yet evolved beyond the syndromic stage, and with a few exceptions, is based on clusters of symptoms and signs.

7.2 Psychiatric Syndromes

7.2.1 Characteristics of Psychiatric Syndromes: Extremes of Adaptive Normal Traits

Most major psychiatric illnesses are chronic conditions and tend to run in families. This seems to indicate that heredity plays an important role. Yet most psychiatric syndromes consist of symptoms that represent extremes of normal human experiences, such as anxiety, depression, and euphoria. These emotions clearly have evolutionarily adaptive value. Imagine a person who congenitally lacks anxiety, sadness, or pleasure. Survival itself from early childhood, let alone socialization and procreation (and therefore empathy), would be seriously in doubt for such a person!

Many psychiatric conditions are precipitated or exacerbated by stressful events. Once a psychiatric syndrome develops, it often has a course of its own, and is not easily reversible without psychiatric intervention. Taken together, these

characteristics indicate that (1) many of the genes that confer susceptibility for psychiatric syndromes probably also subserve normal emotional and cognitive functions, and (2) psychological stress and early environment are important in the eventual precipitation of the illness.

A genetic model that might explain this is the *cliff-edged fitness* model (Nesse 2004), in which fitness increases as a trait (or its alleles) increases, and then at a certain point it crashes. An example might be one's ability to be sensitive to others' feelings in social interactions, until it reaches the point of sensing the least amounts of rejection or hostility, leading to anxiety and depression. Some individuals with a very low anxiety threshold might have the equivalent of a highly sensitive smoke-detector alarm that would be a nuisance in normal neighborhoods but might be lifesaving in a fire-prone environment. Some individuals may have inherited such sensitivity genes, which at one time had a great evolutionary advantage. Another example might be the ability to think about and understand others' needs and motivations, until it reaches the level where every word or act of another person attains great significance and ulterior motives—that is, paranoia. There is a continuum of emotional and cognitive experiences from normality to abnormality, with repeated abnormal experiences not quite reaching the diagnostic criteria for major syndromes. The subsyndromal personality traits, such as neuroticism (Eysenck 1990), may predispose an individual to a major syndrome under stress (see below—Sect. 7.2.5).

Many putative genes that code for vulnerability for psychiatric syndromes are evolutionarily conserved and serve adaptive functions. This explains why schizophrenia, which is associated with low fertility rates in the afflicted, has not become extinct.

Certain genes that endow vulnerability to anxiety, e.g., the short allele of the serotonin transporter promoter gene, may confer sensitivity to the "smoke detector" of anxiety activation (Nesse 2001) and have been evolutionarily adaptive when humans dwelled in caves in fear of predatory animals. In the modern world, however, such sensitivity to anxiety would be dysfunctional for the individual, and thus be considered a psychiatric syndrome.

7.2.2 Brain Areas and Circuits in Normal Emotions and Cognition

There are important brain structures and circuits involved in emotions and cognition, the dysfunctions of which may underlie psychiatric symptoms and syndromes. The Web site http://www.thebrain.mcgill.ca/flash/index_i.html has excellent diagrams to use in following the descriptions below.

7.2.2.1 Mood, Emotions, Pleasure, and Sadness

How do we experience mood and emotions? Activations of certain areas of the brain seem to be associated with the subjective experience of emotions and are responsible for the patterns of behavioral/muscular activations we call emotional expression, and for the autonomic and endocrine arousal that accompany emotions (Figs. 7.1 and 7.2). The emotion of pleasure and reward seems associated with the dopaminergic activation of a circuitous pathway, first involving a descending medial forebrain bundle component and then involving the ascending mesolimbic ventral tegmental pathway (Bozarth 1987; Wise and Bozarth 1984), eventually activating the dopaminergic nucleus accumbens. The septum, the amygdala, the ventromedial prefrontal cortex, and certain parts of the thalamus also participate in the circuit.

The ventromedial prefrontal cortex, with its extensive connections with the limbic system, may link the conscious to the unconscious and ascribe meaning to perceptions by associating them with a meaningful whole. The ventral tegmental pathway can also be activated by various substances including alcohol, amphetamines, exogenous and endogenous opiates, barbiturates, caffeine, marijuana, and nicotine.

All of these pleasure centers are interconnected and innervate the hypothalamus, particularly the lateral and ventromedial nuclei. The hypothalamus then activates the ventral tegmental area, as well as the autonomic and endocrine functions through the pituitary gland.

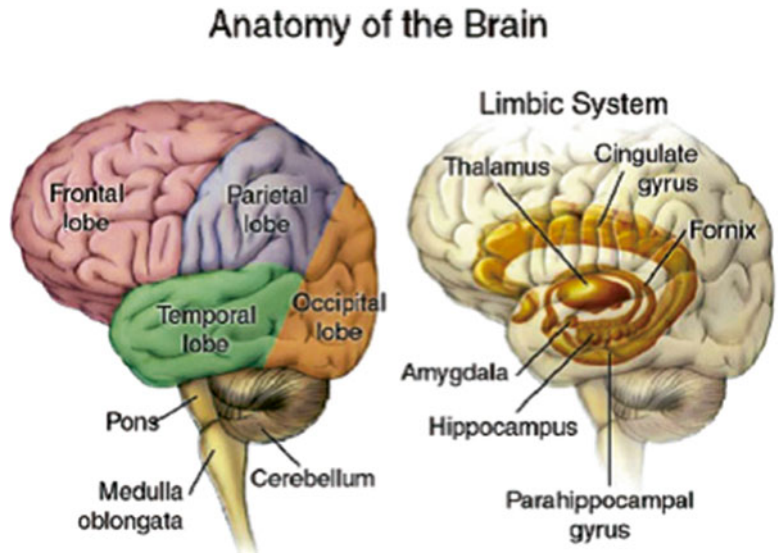

Fig. 7.1 Anatomy of the brain (From http://www.stanford.edu/group/hopes/basics/braintut/ab5.html, with permission from The Huntington's Disease Outreach Project for Education at Stanford.)

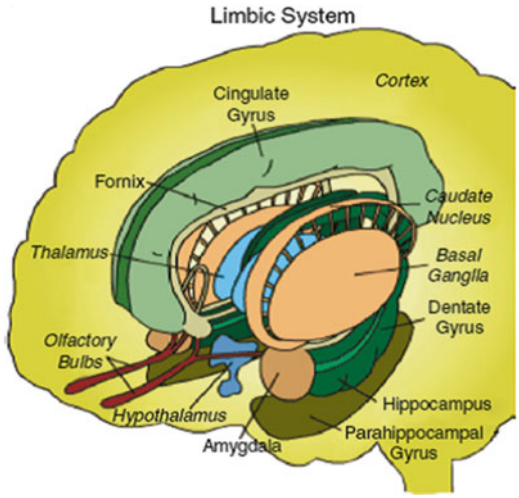

Fig. 7.2 Limbic system. (From http://www.stanford.edu/group/hopes/basics/braintut/ab5.html, with permission from HOPES.)

Aversive stimuli that provoke fight or flight responses activate the brain's punishment circuit [the periventricular system (PVS)] to cope with unpleasant situations. This circuit includes the hypothalamus, the thalamus, and the central gray substance surrounding the aqueduct of Sylvius. Some secondary centers of this circuit are found in the amygdala and the hippocampus. The cholinergic punishment circuit stimulates the secretion of adrenocorticotropic hormone (ACTH) as well as the adrenal medulla and sympathetic outflow; ACTH in turn stimulates the adrenal cortex to release adrenocortical hormones. Stimulation of the punishment circuit can inhibit the pleasure circuit; thus fear and punishment can drive out pleasure.

The behavioral inhibition system (BIS), associated with the septohippocampal system, the amygdala, and the basal nuclei, receives inputs from the prefrontal cortex and transmits its outputs via the noradrenergic neurons of the locus ceruleus and the serotonergic fibers of the medial raphe nuclei. Serotonin may also play a major role in this system. The BIS is activated when both fight and flight seem impossible and the only remaining behavioral option is to submit passively.

When a sensory stimulus is perceived by the cortex to indicate a danger, it is routed first to the thalamus. From there, the information is sent out over two parallel pathways: the thalamo-amygdala pathway (the "short route") and the thalamo-cortico-amygdala pathway (the "long route"). The short route quickly activates the central nucleus of the amygdala. Then the information that has been processed by the cortex through the long route reaches the amygdala and modifies

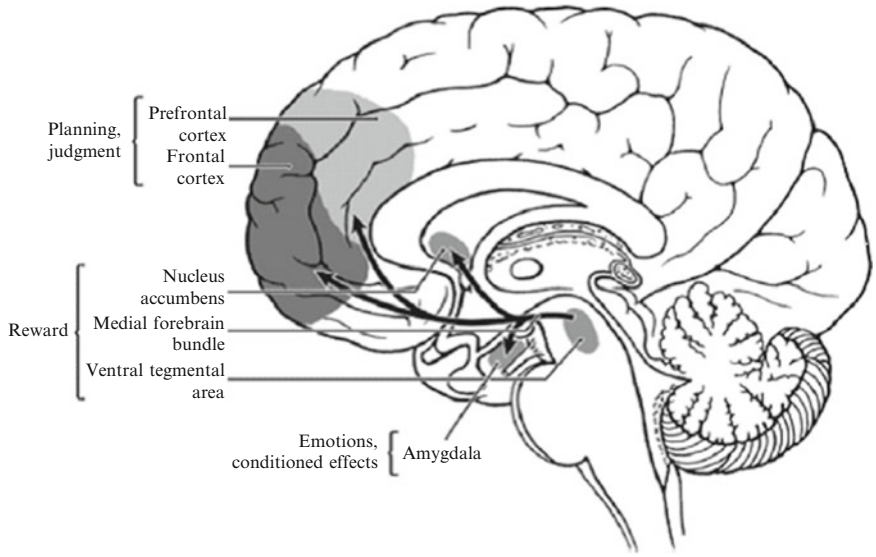

Fig. 7.3 Schematic diagram of the human brain that highlights some of the main brain areas and neurotransmitter pathways implicated in reward processes. ("Addiction and the brain: the role of neurotransmitters in the cause and treatment of drug dependence"—Reprinted from, *CMAJ* 20-Mar-01;164(6), Page(s) 817–821 by permission of the publisher. ©2001 Canadian Medical Association.)

its response dependent on the cortical evaluation of the threat. This cortical evaluation involves the following steps: (1) The various modalities of the perceived object are processed by the primary sensory cortex. Then the unimodal associative cortex provides the amygdala with a representation of the object. (2) The polymodal associative cortex conceptualizes the object and transmits the information to the amygdala. (3) This elaborated representation of the object is then compared with the contents of explicit memory available through the hippocampus, which also communicates closely with the amygdala.

The hippocampus is also involved in the encoding of the context associated with a fearful experience, i.e., memory. The amygdala conveys the gratifying or aversive nature of the experience through connections to the nucleus accumbens, the ventral striatum, the septum, the hypothalamus, the nuclei of the brainstem, and the orbitofrontal, cingulate, piriform, and other parts of the cortex. The combination of stimuli from the amygdala with working memory in the dorsolateral prefrontal cortex may constitute the experience of emotion. The basal ganglia have close connections with the amygdala and are involved with the voluntary expression of emotions. The amygdala has outputs to the nuclei of the sympathetic nervous system in the brainstem and the hypothalamus, controlling the pituitary gland and the endocrine system.

The anterior cingulate gyrus of the frontal lobe seems to be important in emotions and cognition. The subgenual anterior cingulate, together with the rostral cingulate, is considered to be the emotional sector of the anterior cingulate gyrus and it subserves autonomic arousal, reward mechanisms, and emotions, particularly anxiety and sadness in close coupling with the amygdala (Grady and Keightley 2002; Pezawas et al. 2005).

The dorsal portion of the anterior cingulate, called the cognitive cingulate, is involved with error monitoring and selecting among competing responses. Orbitofrontal cortex plays an important role in decision making in the context of emotional situations. Ventrolateral prefrontal cortex, together with the subgenual cingulate, plays a role in responding to reward contingencies (Fig. 7.3).

7.2.2.2 Memory and Cognition

The dorsolateral prefrontal cortex seems to play an important role in reasoning. It stores the memories

needed for doing tasks (working memory). The concept of working memory posits that a limited-capacity system temporarily stores information and thereby supports human thought processes. One prevalent model of working memory consists of three components: a central executive, a verbal storage system ("phonological loop"), and a visual storage system ("visuospatial sketchpad") (Baddeley 2003). It has been proposed that the phonological loop evolved to facilitate the acquisition of language. Visuospatial working memory predicts success in fields such as architecture and engineering. The phonological loop is associated with the left temporoparietal region and activates the Wernicke's and Broca's areas. The visuospatial working memory is an associated analogous area in the right hemisphere and the visual cortex. The central executive, including the reasoning and decision-making function, is probably associated with the frontal lobes.

Declarative memory, that is, the memory of facts and events, seems to be a function of the hippocampus and its connections with the cortex. The hippocampus seems to connect various memory traces in the sensory and association cortices into discrete "episodes" that also include emotion-associated inputs from the limbic system. The hippocampus seems to enable us to "play a scene back" by reactivating this particular activity pattern in the various regions of the cortex. The hippocampus plays an essential role in the consolidation of short-term memory into long-term memory, which may represent various cortical regions activated during an event becoming so strongly linked with one another that they would no longer need the hippocampus to act as their link. Thus, information that has been encoded in long-term memory no longer requires the intervention of the hippocampus. This is the case in particular for general knowledge (semantic memory), which is associated with the activation of the frontal and temporal cortices. The activity in the temporal lobe may correspond to the activation of the fact in question, while the activity in the frontal cortex may correspond to its reaching consciousness. Spatial memory, unlike semantic or episodic memory, appears to be confined to the right hippocampus. Procedural memory, such as how to walk or ride a bike, seems to be stored in motor areas, cerebellum, amygdala, and the basal ganglia, particularly the striatum (Barnes et al. 2005).

7.2.3 Neurotransmitters and Brain-Derived Neurotrophic Factor (BDNF)

7.2.3.1 Neurotransmitters

Nerve transmission occurs when neurotransmitters bind to specific receptors in the postsynaptic neuron. In addition to potentially causing an action potential, neurotransmitters play a modulating role in the excitability of the neuron depending on specific receptor activation. Many chemicals serve the role of neurotransmitters, including acetylcholine, biogenic amines (dopamine, norepinephrine, serotonin, and histamine), amino acids [γ-aminobutyric acid (GABA), glycine, glutamate, aspartate], and neuropeptides (corticotropin-releasing hormone, corticotropin, ACTH, endorphins, substance P, somatostatin, bradykinin, vasopressin, angiotensin II).

There are two types of neurotransmitter receptors: ligand-gated receptors and G-protein-linked receptors. Stimulation of a ligand-gated receptor enables a channel in the receptor to open and permits the influx of chloride and potassium ions into the cell. The positive or negative charges that enter the cell either excite or inhibit the neuron. Ligands for these receptors include excitatory neurotransmitters, such as glutamate and aspartate. Binding of these ligands to the receptor produces an excitatory postsynaptic potential (EPSP). Binding of inhibitory neurotransmitter ligands, such as GABA and glycine, produces an inhibitory postsynaptic potential (IPSP). These ligand-gated receptors are also known as ionotropic or fast receptors.

G-protein-linked receptors are indirectly linked to ion channels through a second messenger system involving G proteins and adenylate cyclase. These receptors modulate the actions of the excitatory and inhibitory neurotransmitters such as glutamate and glycine. G-protein—linked receptors are known as metabotropic or slow receptors and examples

include GABA-B, glutamate, dopamine (D_1 and D_2), and the 5-hydroxytryptamine (5-HT) receptors 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C}.

Several different neurotransmitters can be released from a single nerve terminal, including neuropeptides and biogenic amines. Neuropeptides can act as co-transmitters or primary neurotransmitters. As co-transmitters, they bind to specific presynaptic or postsynaptic receptors to alter the responsiveness of the neuronal membrane to the action of other neurotransmitters, such as norepinephrine and serotonin.

Glutamate is a pivotal amino acid in the brain. It is derived from α-ketoglutarate, which is one of the intermediates in the Krebs cycle. Glutamatergic neurons are extensively distributed in the brain, comprising more than 50 % of the neurons. Glutamate is an excitatory neurotransmitter. There are four types of glutamate receptors: the NMDA (*N*-methyl-D-aspartate) receptor, the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor, the kainate receptor, and the metabotropic receptor. The NMDA receptor is regulated by at least five binding sites, that is, those for (1) glutamate, (2) glycine, (3) magnesium, and (4) zinc, and a site that binds to (5) phencyclidine (PCP). The NMDA receptors have a capacity for long-term potentiation (LTP), an activity-dependent increase in synaptic efficiency that is crucial for learning and memory. The NMDA receptors are most densely concentrated in the cerebral cortex, especially the hippocampus, the frontal lobes, the amygdala, and the basal ganglia.

Excess glutamate has been shown to be neurotoxic, and an inability to remove glutamate by glial cells, thus eventually resulting in a hypofunction of the glutamatergic neurons, may underlie the cognitive deficits in schizophrenia as well as in certain dementias.

Nitric oxide may be synthesized and released when the NMDA receptor is stimulated by glutamate, enhancing neurotransmitter release from adjacent synapses and playing a role in LTP. Granule cells of the dentate gyrus of the hippocampus are rich in nitric oxide synthetase.

γ-Aminobutyric acid (GABA) is derived from glutamate and is distributed extensively throughout the brain, playing an inhibitory role. Following its release, GABA can be taken up by the neurons or by astrocytes. There are two basic GABA receptors, GABA-A and GABA-B. Stimulation of the GABA-A receptor increases the permeability to chloride ion, resulting in a hyperpolarization of the neuron or inhibition. The GABA-A receptor has three basic binding sites: for GABA, for benzodiazepine, and for barbiturates. The GABA-B receptor is a G-protein-related receptor that increases the efflux of K^+ from the cell, causing hyperpolarization. The principal effect of GABA-B agonism is muscle relaxation.

Dopaminergic neurons are widely distributed throughout the brain in three pathways: the nigrostriatal, the mesocorticolimbic, and the tuberohypophysial. There are two primary dopamine receptor types, D_1 and D_2, both of which act through G proteins. D_2 receptors often function as autoreceptors, providing negative feedback.

The mesolimbic and mesocortical dopaminergic systems play an important role in motivation, by attaching cognition of incentive to stimuli. Cocaine increases dopaminergic activity in the mesolimbic areas by inhibiting dopamine reuptake in the ventral tegmental area and the nucleus accumbens. Amphetamine seems more generalized in its action, not only by inhibiting reuptake but also by releasing dopamine from most brain regions. Both cocaine and amphetamine produce feelings of psychological energy and arousal, and cause diminished appetite and sleep. Both cocaine and amphetamine can cause visual and tactile hallucinations and paranoia.

Perception of time intervals may be mediated by dopaminergic spiny neurons located in the striatum of the basal ganglia. Marijuana slows subjective time by lowering the amount of dopamine available, whereas cocaine and methamphetamine accelerates the sense of time by increasing dopamine availability.

Dopaminergic neurons are important in pleasure and reward systems as well as in regulation of movement. They are also important in sustaining attention and concentration.

Overstimulation of D_2 receptors in the mesolimbic and mesocortical systems may result in psychotic symptoms, as D_2 agonists such as

amphetamines can cause them and antagonists like haloperidol can reverse them. An overstimulation of striatal D_2 receptors and an understimulation of cortical D_1 receptors have been postulated for schizophrenia.

There is a significant relationship between dopamine and GABA neurons. In general, GABA acts to reduce the firing of the dopaminergic neurons in the tegmentum and substantia nigra. It forms the basis for benzodiazepine augmentation in the treatment of psychosis. In addition, benzodiazepines may be helpful in cases where there is an overactivity of dopamine in the motor striatum such as Huntington's chorea or tardive dyskinesia. The feedback inhibition from the GABA neurons of the globus pallidus and putamen to the dopaminergic neurons of the substantia nigra is an important modulating force on the activity of the dopamine neurons.

The natural brain amine phenylethylamine (PEA), which is also found in chocolate, has been associated with sexual attraction and emotional infatuation. Phenylethylamine concentrations are high in the nucleus accumbens and the frontal and cingulate cortices. Levels spike during orgasm and ovulation. Phenylethylamine is very similar to amphetamine in chemical structure and likewise may act by causing dopamine release, but endorphin release may also be a significant effect.

Histamine is synthesized in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project diffusely to most cerebral areas including the suprachiasmatic nucleus (SCN) and have been implicated in regulating circadian rhythms, ACTH secretion, cardiovascular control, thermoregulation, food intake, and memory formation. Outside of the central nervous system (CNS), histamine is stored in mast cells, whose release causes the allergic reaction. There are three types of histamine receptors: H_1 receptors, which are widely distributed in the body; H_2 receptors, which are distributed in the stomach and the heart; and H_3 CNS autoreceptors. There is close interaction between histamine and serotonin, as both are concerned with circadian rhythms and feeding behavior, and in the CNS there is a stimulatory effect of endogenous serotonin on histamine release.

Serotonin is synthesized from the amino acid, L-tryptophan, which readily crosses the blood–brain barrier unlike serotonin itself. Most L-tryptophan that crosses the blood–brain barrier becomes serotonin. Meals high in branch-chained amino acids and L-tryptophan or in carbohydrates increase insulin secretion, which facilitates the transport of the branch-chained amino acids into muscle cells, thereby reducing the competition for L-tryptophan for the large neutral amino acid transporter that will transport it across the blood–brain barrier. This increase in serotonin often results in drowsiness. The pineal body has the richest concentration of serotonin in the brain, but the pineal serotonin is used for synthesis of melatonin rather than as a neurotransmitter. Serotonin neurotransmitter neurons are located in the raphe nuclei. The caudal nucleus projects largely to the medulla and spinal cord for the regulation of pain perception. The rostral nucleus projects extensively to the limbic system and the cerebral cortex. In the limbic system, the serotonergic receptors are co-localized with norepinephrine receptors, and serotonin and norepinephrine may work in conjunction in the regulation of arousal. At least 15 subtypes of serotonin receptors have been identified.

The suprachiasmatic nucleus (SCN) of the hypothalamus regulates the mammalian circadian clock. It is richly innervated by serotonergic input from the dorsal raphe nucleus. When light is present, the release of melatonin by the SCN is inhibited. Serotonin also seems to inhibit the responsiveness of the SCN to light.

Serotonin plays an important role in sleep, satiety, and mood. Serotonergic hypofunction in certain areas may underlie depression, aggression, and impulsive behavior.

About 95 % of serotonin in the body is outside of the CNS, mainly in the intestines. There are seven families of serotonin receptors, among which 5-HT_1 and 5-HT_2 receptors are mostly in the brain, and 5-HT_3 and 5-HT_4 receptors are mostly in the gut.

When stretch receptors on the gut wall are stimulated, serotonin, which enhances peristalsis, is released. Vagus nerve stimulates serotonin release in the gut. Current antidepressants that

block reuptake of serotonin at synapses (SSRIs) often have gastrointestinal side effects.

Serotonin syndrome is a potentially life-threatening adverse reaction to drugs that increase serotonin levels in CNS and the body. Signs of excess serotonin range from tremor and diarrhea in mild cases to akathisia, clonus, delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. Patients usually manifest mydriasis, hyperactive bowel sounds, and diaphoresis, and show flushing or normal skin color. Creatine phosphokinase (CPK) is usually normal. Serotonin syndrome usually develops rapidly following the ingestion of drug, often in an overdose or drug interaction (e.g., a serotonin reuptake blocker with a monoamine oxidase inhibitor). Management of the syndrome involves the removal of the precipitating drugs, supportive care, control of agitation, prescribing serotonin antagonists (e.g., cyproheptadine), the control of autonomic instability, and the control of hyperthermia. Benzodiazepines are helpful for muscular rigidity and agitation. Olanzapine and chlorpromazine parenterally may also be helpful (Boyer and Shannon 2005; also go to http://www.benbest.com/science/anatmind/anatmd10.html).

Norepinephrine (noradrenaline)-containing neurons arise mainly from the locus ceruleus in the pons. They project extensively to the cortex, hippocampus, thalamus, and midbrain. Norepinephrine tends to increase the level of excitatory activity within the brain, and seems to be particularly involved in attention, arousal, and anxiety. Norepinephrine is the neurotransmitter of the sympathetic nervous system, and its activation, as in anxiety, has major effects on heart rate and blood pressure. There are benzodiazepine receptors in the locus ceruleus, as well as opiate receptors and α_2-autoreceptors, that all reduce its firing. The beta-blocker propranolol also has been used to treat anxiety. By blocking the adrenergic inputs to the amygdala, beta-blockers may inhibit the formation of traumatic memories. Cortisol stimulation of the locus ceruleus due to chronic stress exacerbates norepinephrine stimulation of the amygdala.

Acetylcholine is abundant in the interpeduncular nucleus located near the substantia nigra, and all the interneurons in the striatum and the nucleus accumbens are cholinergic. The septum provides cholinergic fibers to the septal hippocampal tract. The primary cholinergic input to the cerebral cortex comes from the basal nucleus of Meynert, which also innervates the basolateral amygdala, the basal ganglia, and the reticular nucleus of the thalamus. Cholinergic transmission is important in cognition and sleep, and is the main neurotransmitter in the parasympathetic nervous system as well as in muscles. There are two types of cholinergic receptors: fast-acting nicotinic receptors and slow-acting muscarinic receptors. The presynaptic parasympathetic fibers and fibers innervating the voluntary muscular system are nicotinic, which are antagonized by curare. Atropine, which blocks the muscarinic receptors, can cause memory loss, and there seems to be a deficiency of muscarinic cholinergic transmission in patients with Alzheimer's disease. Postganglionic parasympathetic fibers are also muscarinic.

Oxytocin is a nonapeptide released from the paraventricular nucleus of the hypothalamus through the posterior pituitary. It is a central mediator of pro-social behavior. Oxytocin is also released during stress and is an important modulator of anxiety and fear response (McCarthy et al. 1996).

7.2.3.2 Significance of Neurotransmitters in Psychiatry

Functional changes in neurotransmitters have been implicated in many psychiatric syndromes. Most antidepressant drugs enhance the functional availability of biogenic amines (dopamine, serotonin, norepinephrine) in the synapse either through reuptake blockade, blocking degradation, or direct agonistic action. Most antipsychotic drugs, particularly the first generation antipsychotics block the dopamine D2 receptors in the brain. Benzodiazepines, the principal anti-anxiety drugs, are GABA agonists.

7.2.3.3 Brain Derived Neurotrophic Factor (BDNF)

BDNF is a protein secreted in many cells by the endoplastic reticulum. It is encoded in BDNF

gene, and it acts on neurons of the CNS and the peripheral nervous system, helping to support the survival of existing neurons and enhancing neurogenesis and the growth and differentiation of new neurons and synapses (Acheson et al. 1995; Huang and Reichardt 2001). BDNF is widely distributed—in the kidneys, retina, and motor neurons as well as in the brain. In the brain, it is particularly active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking. BDNF plays an essential role in long-term potentiation (LTP) and the formation of long-term memory (Bekinschtein et al. 2007, 2008a, b, 2013, 2014; Yamada and Nabeshima 2003).

BDNF binds to at least two receptors, TrkB (pronounced "Track B") and the LNGFR (for *low-affinity nerve growth factor receptor*, also known as p75) (Patapoutian and Reichardt 2001; Reichardt 2006). It may also modulate the activity of various neurotransmitter receptors, including the Alpha-7 nicotinic receptor (Fernandes et al. 2008).

There is evidence that BDNF expression is decreased in patients with depression or schizophrenia and that BDNF levels may predict the outcome of antidepressant treatment (Tadic et al. 2011; Thompson Ray et al. 2011).

In fact, most antidepressant drugs and electroconvulsive therapy eventually increase BDNF levels (Haghighi et al. 2013; Okamoto et al. 2008; Ryan et al. 2013; Sen et al. 2008). Exercise and caffeine also increase BDNF levels (Adlard et al. 2005; Costa et al. 2008a, b; Cotman and Berchtold 2002).

Traditional antidepressants require many weeks before therapeutic effects occur.

Ketamine intravenous administration in subanesthetic doses has been shown to result in rapid antidepressant response in a matter of hours in treatment resistant depressed patients. Ketamine is an NMDA receptor antagonist and participates in the regulation of glutamatergic transmission. There is robust evidence that the glial cells, astrocyte and satellite oligodendrocyte populations are reduced in prefrontal cortex and other cortical regions in postmortem tissue from individuals who had suffered from major depression and bipolar disorder and ketamine has been shown to be effective in both types of depression.

The glial loss in depression may reflect the convergence of many features of stress response in animal models, including immunologic attack on glial integrity due to elevated brain cytokine and cortisol levels, increased oxidative stress, and reduced levels of free radical scavengers including glutathione, and stress-induced glutamate release. Glial loss has a number of downstream consequences that may lead to the pathophysiology of major depression. Glial loss, produced by specific glial toxins, produces biochemical and behavioral signs of depression in animal models (Banasr et al. 2010; Sanacora and Banasr 2013). Because glia are centrally involved in glutamate inactivation, glial loss may elevate glutamate levels in both synaptic and extrasynaptic spaces. Overstimulation of presynaptic receptors has been shown to depress glutamate neurotransmission and compromise synaptic connectivity, consistent with the association of elevated anterior cingulate glutamate levels and reduced cingulate functional connectivity in major depression (Horn et al. 2010). A consequence of elevated extrasynaptic glutamate levels is overstimulation of extrasynaptic NMDA receptors. Overstimulation of these receptors has a number of downstream consequences including a reduction in BDNF levels, culminating in dendritic regression and activation of apoptosis. Thus, glial deficits in depression may contribute to abnormalities in cortical functional connectivity by compromising structural connectivity and dysregulating glutamate synaptic transmission. (Horn et al. 2010; Kavalali and Monteggia 2012; Krystal et al. 2013; Liu et al. 2013, 2012).

Thus, ketamine and other glutamatergic drugs might target rapid BDNF enhancement, which may result in rapid antidepressant action as well as cognitive enhancement (Krystal et al. 2013; Salvadore and Singh 2013).

There is a recent intriguing report indicating an increase in the methylation status (i.e., inactivation) of the BDNF gene in borderline personality disorder patients who had childhood abuse history, and that responders to dialectical behavioral therapy showed an eventual decrease in the

BDNF methylation, while non-responders showed an increase in methylation (Perroud et al. 2013). Thus, the epigenetic changes of the BDNF gene through the experience of childhood abuse may be reversed through psychotherapy in adulthood.

7.2.4 The Brain in Psychiatric Syndromes

7.2.4.1 Prefrontal Cortex

In the prefrontal cortex, the ventromedial cortex seems affected by both depression and mania. It is located on either side of the center line separating the two hemispheres and is closely involved with the pleasure circuit. It also seems to be involved in switching from one kind of affect to another. The ventromedial cortex has extensive connections with the limbic system (Fellows and Farah 2003). The volume of the ventromedial cortex is decreased in chronic depressives, mostly owing to a decrease in the number of glial cells.

There seems to be a hyperactivity of the rostral and subgenual cingulate (Area 25) in depression, and hyperactivity of the rostral cingulate may be a predictor of the response to antidepressant therapy. Recently, a number of studies indicate that there is impairment of the connectivity and function of subcallosal anterior cingulate in major depression, PTSD, as well as anorexia nervosa, and deep brain stimulation of the area may be effective in a variety of conditions. (Davey et al. 2012; Grady and Keightley 2002; Holtzheimer et al. 2012; Lane et al. 2013; Lipsman et al. 2013; Pizzagalli et al. 2001; Siegle et al. 2012; Tripp et al. 2012). Anterior cingulate and amygdalar activation has been shown to predict the response to cognitive behavioural therapy in PTSD (Bryant et al. 2008), and CBT for depression has been shown to change the activity of anterior cingulate and medial prefrontal cortex (Yoshimura et al. 2014).

The dorsolateral prefrontal cortex (DLPFC) is involved in executive functions and working memory, which are particularly disturbed in schizophrenia. In schizophrenia, there is cortical thinning within the cingulate, occipital, and frontopolar cortices, and a reduction in overall brain volume. Functional imaging studies show a reduction in neuronal density and activity in the prefrontal cortex and hippocampus in schizophrenia (Jann, 2004).

7.2.4.2 Locus Ceruleus

The locus ceruleus, which supplies a majority of noradrenergic neurons in the brain, plays an important role in anxiety and in activating physiologic and behavioral arousal.

7.2.4.3 Basal Ganglia

The basal ganglia, including the caudate and substantia nigra and thalamus, show hyperactivity in obsessive-compulsive disorder (OCD), and dopaminergic corticostriato-thalamic circuit dysfunction has been postulated for this disorder (Graybiel et al. 2000). Provocation of OCD symptoms is associated with an increase in cerebral blood flow in the orbitofrontal cortex, anterior cingulate cortex, striatum, and thalamus (Lagemann et al. 2012; McGuire et al. 1994; Rauch et al. 1994). Hypofunction of serotonergic neurons arising from the rostral raphe nucleus may result in a lack of inhibitory effect on the putative OCD pathway. Successful treatment with pharmacotherapy or cognitive-behavioral therapy has resulted in reversal of some of the brain activation (Carey et al. 2004; Figee et al. 2013; Schwartz et al. 1996).

7.2.4.4 The Limbic System and the Amygdala

Intimately involved in all things emotional, the limbic system, and particularly the amygdala, is dysregulated in psychiatric syndromes. Functional imaging studies show an increase in activation of the limbic structures, including the amygdala, hippocampus, and adjacent temporal cortex, in anxiety states including phobia. As described below, a dysfunction of the circuit that connects the amygdala to the anterior cingulate gyrus may underlie anxiety and depressive syndromes.

7.2.5 Final Common Pathways: Genes, Memes (Memory), Stress, Brain Function, and Psychiatric Syndromes

The net result of activations of various parts of the brain manifests itself in the efferent pathways of behavior (motoric), in the hypothalamic–pituitary–adrenal axis (autonomic and endocrine), and in intracranial subjective cognitive and emotional experiences. When these manifestations are dysfunctional or disordered, a psychiatric syndrome results.

We are at the threshold of understanding the genetic mechanisms of emotions and psychosis, and of understanding how some of the genes might be turned on or off by experiential, environmental, and developmental factors(i.e., epigenetics) and how such experiential factors affect brain structures and function, resulting in normal emotions/behavior or a psychiatric syndrome.

As far as psychiatric diagnosis goes, the current state of affairs concerning genes can be summarized as follows: for each diagnostic category, there are many susceptibility genes, and a single gene or a few genes may code for the susceptibility for many different disorders.

7.2.5.1 Serotonin Transporter Gene, Depression, Anxiety, and Neuroticism

An example of a single gene that codes for the vulnerability to multiple psychiatric (and medical) conditions is the serotonin transporter gene *(SERT)* and its promoter region polymorphism (5-HTTLPR). *SERT* is highly evolutionarily conserved, and regulates the entire serotoninergic system and its receptors. DNA screenings of patients with autism, attention-deficit hyperactivity disorder, bipolar disorder, and Tourette's syndrome have detected signals in the chromosome 17q region where *SERT* is located (Murphy et al. 2004a) .

The 5-HTTLPR polymorphism consists of short (s) and long (l) alleles, and the presence of the short allele tends to reduce the effectiveness and efficiency of *SERT* .

A variable number of tandem repeats in the serotonin (5-HT) transporter gene linked polymorphic region (5-HTTLPR), located at the SLC6A4 locus on chromosome 17 (17q11.1–17q12) influences the transcriptional activity and subsequent availability of serotonin [see National Center for Biotechnology Information (NCBI) map Web site for 5HTTLPR gene at http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?taxid=9606&chr=17&MAPS=morbid,genec,ugHs,genes,pheno%5B24579425.12:27953447.37%5D-r&query=uid(7812322,5968)&QSTR=SLC6A4.] The 5-HTTLPR short allele "s" has reduced transcriptional efficiency compared with the long allele, and individuals carrying the "s" allele tend to show increased anxiety responses and seem to show an increased risk of depression (Lotrich and Pollock, 2004). The short-allele carriers show reduced gray matter in limbic regions critical for processing of negative emotion, particularly the perigenual cingulate and amygdala.

Functional magnetic resonance imaging (MRI) studies of fearful stimuli show a tightly coupled feedback circuit between the amygdala and the cingulate, implicated in the extinction of negative affect. Short-allele carriers showed relative uncoupling of this circuit, and the magnitude of coupling inversely predicted almost 30 % of variation in temperamental anxiety (Pezawas et al. 2005). Pezawas et al. (2005) showed that the short-allele carriers show reduced gray matter in limbic regions critical for the processing of negative emotions, particularly the subgenual cingulate and amygdala. They also show increased amygdala activation to fearful stimuli (Beevers et al. 2011; Bertolino et al. 2005; Hariri et al. 2002) . Thus, this gene seems to increase the sensitivity of the affected individual's brain to negative affect and anxiety (Caspi et al. 2010; Sugden et al. 2010; Uher et al. 2011)

The short-allele carriers have also been reported to have an increased risk for irritable bowel syndrome (Yeo et al. 2004) and migraine (Gonda et al. 2007). 5-HTTLPR short-allele carriers with neuroticism have been found to be more likely to smoke, especially to reduce negative mood and to feel stimulated, and have the most difficulty in quitting smoking (Hu et al. 2000; Lerman et al. 2000). On the other hand, the long allele has been reported to be associated

with increased cardiovascular disease and reactivity (Brummett et al. 2011).

A dietary deficiency in the serotonin precursor, tryptophan, has been shown to induce depression in healthy women with the 5-HTTLPR s/s, regardless of their family history of depression, while those with l/l were resistant to depression regardless of family history of depression (Neumeister 2003; Neumeister et al. 2006)

Caspi et al. have shown, in an elegant longitudinal study, that stress during the previous 2 years in adulthood and maltreatment in childhood interacted with the 5-HTTLPR status. Individuals with 2 copies of the short allele who also had the stressors had greatest amount of depressive symptoms and suicidality than heterozygous individuals, and those with only the long alleles had the least amount of depression(Caspi et al. 2002; Caspi et al. 2003; Enoch 2006; Machado et al. 2006; Stein et al. 2008).

Thus, the 5-HTTLPR short allele, in conjunction with childhood stress, may confer an individual with a trait of responding to later stress with increased anxiety, neuroticism, and subclinical depression (Gonda et al. 2005), which, in turn, may predispose the individual for later major depression, suicidality, bulimia (Ribases et al. 2008) and psychophysiologic disorders.

Studies in monkeys have shown that the anxiety-enhancing effect of the short allele is mitigated with good mothering in infancy (Barr et al. 2004; Suomi 2003, 2005).

5-HTTLPR may also determine the response to drugs. Depressed individuals with the short allele were found to respond better to antidepressants that are both serotonergic and noradrenergic (i.e., mirtazapine), rather than serotonin specific reuptake blockers. On the other hand, individuals with the long allele may have more side effects with exactly those drugs that are more effective for those with the short allele (Murphy et al. 2004b) . This is an elegant example of genetic polymorphism and resulting brain structural variations interacting with stress and producing susceptibility to anxiety and depression, and influencing the treatment choice.

There is evidence that 5HTTLPR polymorphisms may have differential effects on ethnicity, gender, and age. For example, females with the short allele may be more susceptible to depression (Beaver et al. 2012), and Caucasians with the short allele may be more susceptible to depression (van Ijzendoorn et al. 2012). The short allele interacted with environmental factors in the self esteem of adolescents (Jonassaint et al. 2012).

Why does a single gene code for so many traits, both adaptive and maladaptive, and vulnerabilities? One simple answer may be that the gene codes for one or more basic evolutionarily adaptive predispositions that, in combination with other factors, may determine the development and severity of a psychiatric syndrome. There is also the effect of other genes that may interact with the gene in question (epistasis) (Goenjian et al. 2012; Thaler et al. 2013).

When we look at the list of conditions affected by 5HTTLPR polymorphism, it seems clear that there is a continuum, from anxiety to adaptive/maladaptive behavior to phobia to major depression, and/or to physical symptoms (Fig. 7.4).

7.2.5.2 Monoamine Oxidase Gene

Similar interactions have also been reported with functional polymorphism in the gene encoding the monoamine oxidase A *(MAOA),* located on the X chromosome Xp11.4-11.3 (for maps of genes, go to http://www.ncbi.nlm.nih.gov/projects/mapview/). It encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine (NE), serotonin (5-HT), and dopamine (DA), and renders them inactive. Genetic deficiencies in MAOA activity have been associated with aggression in mice and humans. Maltreated males with the low-MAOA activity genotype were more likely than non-maltreated males with this genotype to develop conduct disorder in adolescence and be convicted of violent crimes in adulthood. In contrast, among males with high MAOA activity, maltreatment did not confer significant risk for either conduct disorder or violent conviction (Caspi et al. 2002).

7.2.5.3 Stress and the Aging Process

Stress affects the aging process directly at the cellular level. Perceived stress and chronicity of stress was significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length—known determinants of

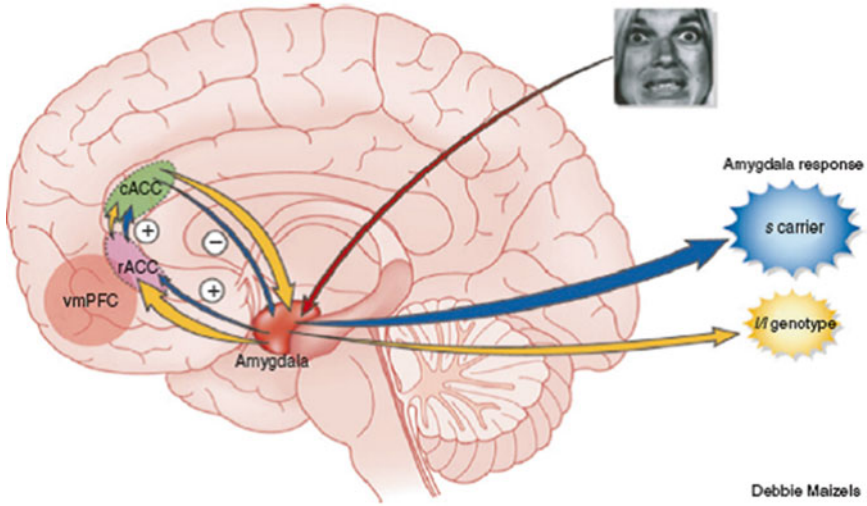

Fig. 7.4 Serotonin transporter promoter polymorphism (5-HTTLPR s/s) and emotional hypersensitivity to negative stimuli. Differences in processing of emotional stimuli between *s* allele carriers (*darker arrows*) and homozygous *l* allele carriers (*light arrows*). Negative emotional stimuli are evaluated by the amygdala (*arrow* from eyes) after preliminary analysis in the ventral visual pathway (not shown). Carriers of the *s* allele have markedly reduced positive functional coupling between the rostral anterior cingulate (rACC; lower oval) and the amygdala, which results in a net decrease in inhibitory feedback from the caudal anterior cingulate (cACC; *upper oval*), via connections between rACC and cACC (*short upward arrows*). Brain volume was also substantially reduced in *s* allele carriers in the rACC and, to a lesser extent, the cACC and amygdala. The consequence of these genotype-based alterations is an emotional hyperresponsivity to negative affective stimuli in *s* allele carriers (*large dark cloud*) compared with individuals lacking this allele (*small lighter cloud*), which may be related to an increased risk of developing depression. As found in a previous study, functional coupling between the vmPFC (*light circle*) and the amygdala was also increased in *s* allele carriers. (From Hamann, 2005. Reprinted by permission from Macmillan Publishers, Ltd: Nat Neurosci, copyright 2005.)

cell senescence and longevity. Telomeres are DNA–protein complexes that cap chromosomal ends, promoting chromosomal stability. When cells divide, the telomere is not completely replicated, leading to telomere shortening with every replication. In one study, women who had highest levels of perceived stress had telomeres that were, on the average, at least a decade older than women with lowest stress levels (Epel et al. 2004).

7.3 Final Common Pathway Model

7.3.1 The Role of Memory and Memes

Since the elegant demonstration by Caspi and colleagues of gene–environment interaction (Caspi et al. 2002, 2003; Risch et al. 2009), other studies including a meta-analysis (Risch et al. 2009) failed to support the interaction. There is, however, abundant evidence that early experiences affect gene expression in the brain, affecting both morphology and physiology (Caspi et al. 2010; Eley et al. 2004; Sugden et al. 2010; Uher et al. 2011). These data suggest that external environment does not directly interact with genes, but rather an individual's experience of the environment, i.e., memories of past experience interact with perception, forming new information that interact with genes in the brain. Such information resides in the brain as reinforced neural clusters, and their activity causes epigenetic changes of vulnerability genes.

In the course of evolution, the brain evolved as a specialized organ dedicated to processing memory, both learned and intrinsic (DNA), which in turn facilitated learning, survival, reproduction, and further enlargement of the brain. Learning through trial and error created memories that facilitated individual and species

survival, and resulted in building bigger brains, but the memories themselves died with the organism until the brain developed imitation as a learning tool. With imitation, which is robustly in evidence in primates and in songbirds, learned behavior (memory) could be transferred from one brain to other brains in the form of memes. "Meme" is a term coined by the evolutionary biologist Richard Dawkins in his book, *The Selfish Gene,* (Dawkins 1976, 2006), which I use here to denote any portable memory, i.e., information (Leigh 2010, 2012a, b). Chimpanzees could observe a bright chimpanzee cracking a nut with a stone, and this information could spread, but only to a limited degree. First, they had to be in visual contact with the bright chimpanzee, and second, the bright chimpanzee must engage in the behavior for the meme (how to crack a nut) to spread, and this presupposes that there are nuts and stones around. If chimpanzees had language, one who observed the behavior could describe it even when there were no nuts and stones, and such a meme could spread much faster and wider. Such was the case with humans.

With the development of written word, memes found an abode outside of brains. Now they could reside in patterns of indentations in clay or stone, or ink on paper, and eventually as electronic signals in magnetic tapes and optical media. Now, more memes reside outside of human brains than inside them, in printed form in libraries and homes, in electronic media, and in digital form in computers, CDs and DVDs, and in the cloud. The acquisition of language by *Homo sapiens* was instrumental in memes' attaining dominance over genes for the first time on planet earth. In fact, memes in the form of moral codes have suppressed gene-derived sexual drive in many cultures, and memes in the form of scientific knowledge provides humans with the ability to control gene propagation.

7.3.2 Neural Memes and Evolution of Memes in the Brain

How exactly does a meme reside in the brain? Kandel described a sequence of events in long-term memory formation in Aplysia. With repeated stimulus of a neuron, a sequence of chemical reactions causes gene activation in the nucleus of the neuron, resulting in release of messenger RNA in a dormant form. Further stimulation of the neuron causes a prion-like protein, CPEB (Cytoplasmic Polyadenylation Element-Binding Protein), which is present in all synapses, to become activated (to an infectious form), which in turn activates dormant messenger RNA, which in turn makes protein to form a new synapse. The prion-like infectious form of CPEB infects adjacent CPEB, and thus perpetuates itself and the protein synthesis, maintaining and reenforcing the new synaptic connection (Kandel 2006).

In higher organisms, the stimulus that reaches a neuron resulting in this series of events is itself modified in several interneurons which have their own connections, i.e., stimulus (perception) is modified by existing memory (memes). Furthermore, neurons are capable of generating impulses without external stimulus, which may stimulate and reinforce connected neural clusters. Memories thus formed and residing in reinforced neural connections are the basis of memes. A reinforced neural cluster may be represented as a binary neural code (Lin et al. 2006; Yang et al. 2007). In this sense, memory in the brain may be similar to memory encoded in the hard drive of a computer. How does memory become portable and thus a meme?

Originally, Dawkins pointed out that through imitation, memes are replicated in the brains of the imitators. As the replications are not always exact, memes undergo Darwinian natural selection and evolution by being copied inexactly by different brains. How about the memes within an individual's brain?

Edelman described Darwinian natural selection of certain clusters of reinforced neurons in the brain in somatic time (Edelman 1987). Neuronal groups may be reinforced by signals from other similarly firing neuronal groups (forming memes) and thus gain survival advantage.

This may be particularly important during adolescence, when neuronal pruning occurs. We are born with approximately 100 billion neurons

which are whittled down by about 50 % before adulthood (Pfefferbaum et al. 1994). Neurons with stronger synaptic connections survive while those with weaker connections are pruned (Chechik et al. 1999; Low and Cheng 2006; Osan et al. 2011). One might say that neurons thrive on memes.

When a competing meme becomes dominant, neural clusters underlying it are enhanced, i.e., better fed, with more synapses. Such enhanced connections may be of nurturance or stress memes as in childhood abuse (Cisler et al. 2013). Thus, some memes will become dominant with repeated exposure and rehearsal and proliferate, i.e., recruit other neuronal groups; others will become dormant, not forming new connections or recruiting others. The process resulting in new parallel connections may be seen to be a process of replication of the meme, a prion-like replication by contact through synaptic and/or dendritic connection. This is not to imply that one neuron serves only one meme. In fact, a neuron has many connections and may be a component of a number of different memes and mimetic connections.

Meme replication in the brain, therefore, does not involve reproducing new neurons, but rather occurs through recombination of component memes in existing neuronal groups. Such replication may occur through meme-processing mechanisms such as cognition, often stimulated by the entry of new memes into the brain.

The brain, in my view, is more like the Internet than a computer, with redundant storage and constantly changing connections and storage, in which memes are constantly created, propagated, combined, disintegrated, mutated, and evolved. Like the Internet, there are many interconnected processing centers that execute these functions. Some of these functions may involve a threshold number of processing units and reach consciousness, others functions occur without reaching consciousness. Just like information on the internet, some memes stay dormant and others become activated and spread.

Cognition is the brain's activity of processing memes. This may involve comparing new memes with existing ones, juggling existing memes to make way for new memes, rearranging memes by combining or breaking down memes and reassembling them. When memes combine to form memeplexes, i.e., neural clusters forming a meme develop strong connections to another, these memes may become synergistic and powerful.

Most of our memes are unconscious, and have migrated into our brains through auditory (verbal and sound), visual (books, images), and other senses. In fact, the unconscious may be likened to a meme pool where memes generated from our genes, as well as memes that have invaded our brains, percolate vying to surface.

Many of our memes are mutually supportive and coherent; others are in conflict with each other. Some may be frankly toxic, e.g., "Die for me (the meme may be a god, a cause, a clan); Kill for me."

Some memes, such as clichés, jingles, rhythms, and melodies propagate particularly well because they are adaptive memeplexes, i.e., the rhythm or melody is coupled with words that by themselves may not be as catchy. Earworms, melodies that keep on recurring in the head to the annoyance of the individual, are an example.

Gene-based life has evolved over some 3.7 billion years to the present splendor and diversity. The rapid increase in memes parallels the rapid increase in brain size that began in earnest some 2.5 million years ago when *homo habilis ("handyman")* began to use stone tools (Blackmore 1999). *Homo sapiens* emerged some 200,000 years ago, and in this eye-blink of geologic time, memes have built cultures, language, ethics, religions, ideologies, art, and science that have all evolved in a Darwinian fashion.

7.3.3 Memeplexes, Development, and Psychopathology

Why are our brains full of thoughts? According to Blackmore, the answer lies in the fact that memes are replicators, and the thoughts we have are expert replicators that survived Darwinian selection (Blackmore 1999). While most of the memes in our brains come from outside of the brains, some memes are created or cobbled

together in new combinations within our brains in the form of new memeplexes. Our brain is full of memes and memeplexes that we have acquired over time.

Some examples of memeplexes include: "I am intelligent," "good," "evil," "health," "God," "Devil," "socialism," "psychiatry," etc. Memeplexes may be complexes of ideas, sounds, and other perceptual memories, e.g., songs, scenes, posters, jingles.

A person is the net result of gene x meme x environment interaction that we call development. Except in rare cases where the environment interacts directly with genes as with environmental toxins and climate, genes interact with memes in the brain, which may have been absorbed directly from the environment as information, or may have been induced through experiential learning. Some newly introduced memes may conflict with existing memes in the brain, and may either die or become dormant (unconscious). Others may combine with existing dormant memes and activate them.

While the aggregate of these memes and memeplexes constitute our personalities, some such acquired memes are pathogens, and in interaction with genes and other "host factors" may cause mental illness. Treating such an infection may require the equivalents of either a pathogen-specific antibody or a broad-spectrum antibiotic therapy.

Prevention may also be possible through appropriate immunization.

7.3.4 Gene x Meme x Environment Interaction in the Pathogenesis of Mental Illness

Genes may create an environment in the brain that is more hospitable to certain types of memes than others. For example, in the presence of the short allele of the serotonin transporter promoter gene (5HTTLPR), the amygdala tends to be more sensitive to threatening stimuli (memes) (Caspi et al. 2010; Sugden et al. 2010). In spite of the gene, if the child experiences abundant nurturance, the gene may be turned off. On the other hand, if the child is mistreated, the brain will respond with increased fear, anxiety, and helplessness, generating corresponding memes, which are likely to epigenetically activate the vulnerability gene. Such a brain would be more susceptible to infection by depressive memes and memeplexes coming from social interactions, learning, and even the media. A stressful event in adulthood may then infuse the brain with a massive dose of depressive memes. Thus, a brain that is already inhabited with a large number of depressive memes (most of which may be unconscious) may be overwhelmed by addition of new infection resulting in a depressive syndrome, a state of total control by the depressive memes (Figs. 7.5 and 7.6).

In drug-induced depression, the drug attenuates the brain's ability to suppress already resident depressive memes which then multiply as well as making the brain to be more accepting of new depressive memes.

Similar models may be constructed for bipolar disorder, paranoia and delusions, obsessive-compulsive disorder, anxiety disorder, PTSD, etc. (Leigh 2012a).

Figure 7.4 may thus be reset, according to this model, as Fig. 7.7.

7.3.5 Psychiatric Syndromes as Final Common Pathway Phenomena

The final common pathway model of psychiatric syndromes may be described as follows: Genes adapted to serve various normal emotional and cognitive functions have natural variations. Some such genes may confer susceptibility to exaggerated reactions to stress, particularly if coupled with childhood stress. The final common pathway leading to pathology would be a functional cliff-edge change in the functional status of brain regions, such as a decoupled feedback loop.

Final common pathway syndromes are phenomenologic diagnoses with potentially multiple etiologies and contributing factors. Once having made the syndromic or phenomenologic diagnosis, it is important to elucidate the potential

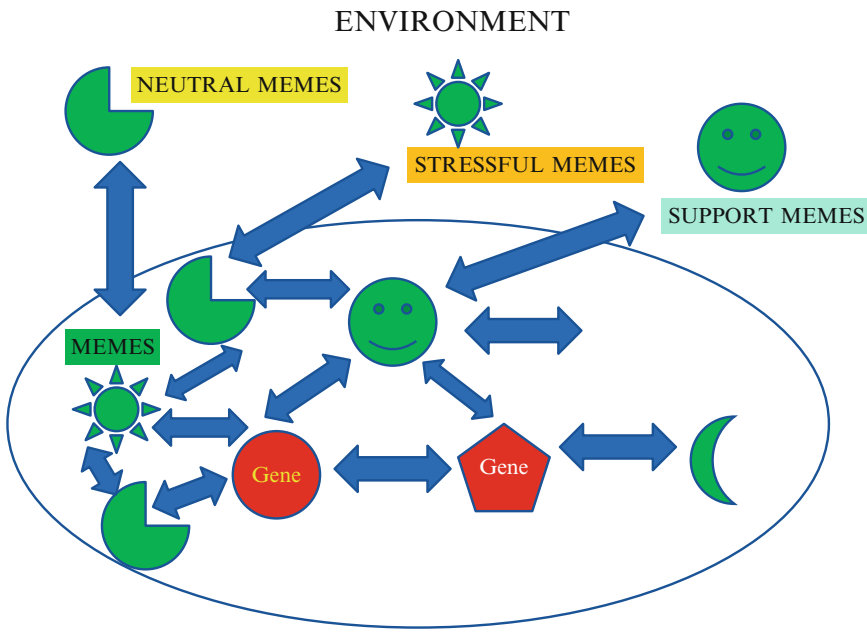

Fig. 7.5 Memes, genes, and environment

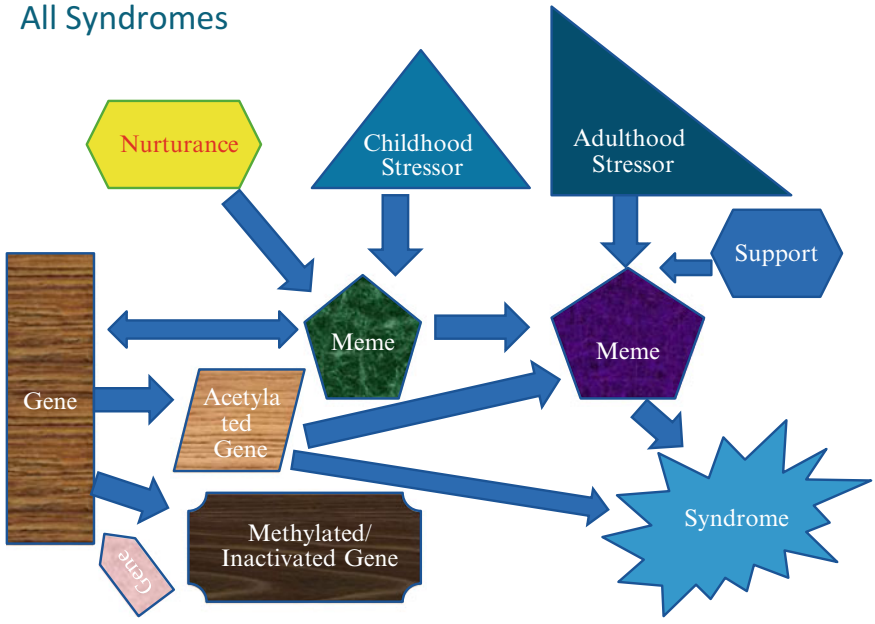

Fig. 7.6 Gene–meme–environment interaction in all syndromes

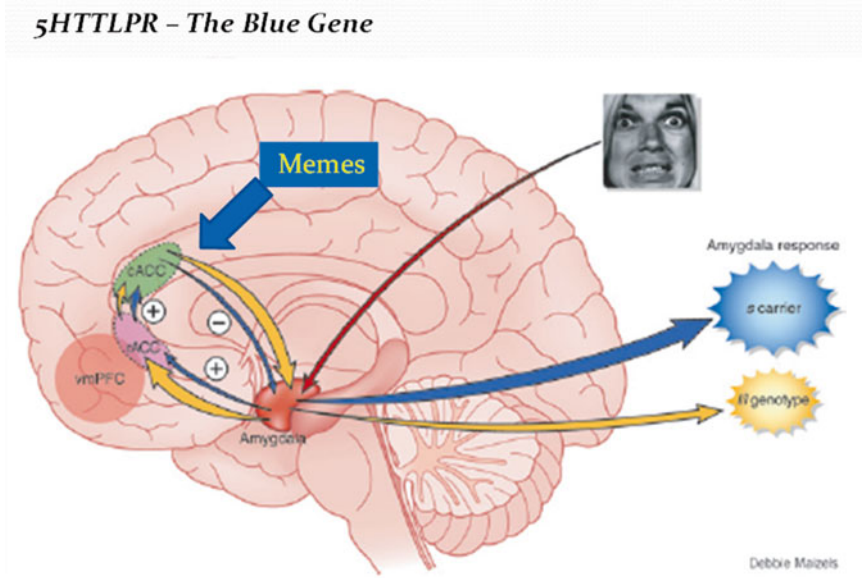

Fig. 7.7 Gene x Meme Interaction. Memes, consisting of memories and learned information including coping mechanisms and trauma-induced threat sensitivity, affect the processing of perception, modulating amygdalar response.

etiologic and contributing factors as well as the protective and mitigating factors such as social support and coping skills (Figs. 7.8 and 7.9).

7.3.6 Evaluation of Final Common Pathway Psychiatric Syndromes

As most psychiatric syndromes represent a final common pathway change in the specific areas of brain function, it is crucial to evaluate the various paths that may contribute to the syndrome. In general, the following factors should be considered in a systematic evaluation:

1. Susceptibility genes: As a direct assessment of the susceptibility genes is not yet a practical diagnostic tool in psychiatry, taking a careful family history for psychiatric syndromes/symptoms is helpful. If family members responded to a particular medication, that medication should be seriously considered for the patient.
2. Onset: A careful inquiry concerning onset of the psychiatric symptom helps differentiate between an ongoing chronic psychiatric illness (that might also be exacerbated by the stress of a nonpsychiatric illness or hospitalization) and a psychiatric condition directly secondary to a medical illness, medications, or medical disability.
3. Secondary psychiatric syndromes: This step entails recognition of, or ruling out, a medical illness, a prescribed medication, or a

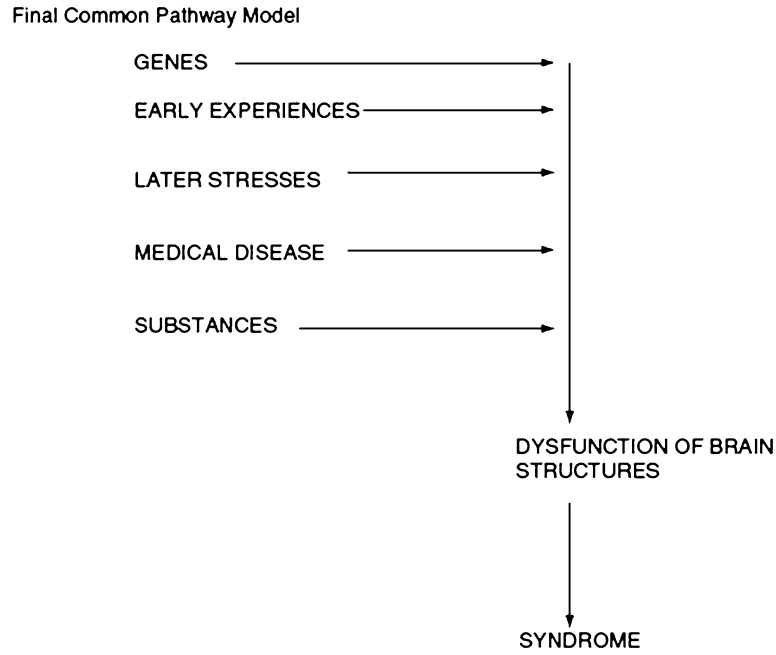

Fig. 7.8 Final common pathway model

recreational drug contributing significantly to the psychiatric symptoms. Many medical illnesses and conditions cause psychiatric syndromes directly, particularly endocrine/metabolic disorders, infections, neoplasms, CNS diseases, and cardiovascular diseases. The mechanism by which nonpsychiatric illnesses cause psychiatric syndromes varies, from direct endocrine effect, paraneoplastic syndrome, to direct tissue destruction in a CNS disease. Prescribed medications and recreational drugs often cause psychiatric complications that range from delirium, to anxiety, to depression, to psychosis (Table 7.1).

4. Primary psychiatric syndrome: Consideration of the above three parameters will enable the consultant to decide whether the psychiatric syndrome is predominantly secondary or primary. Primary psychiatric syndromes are the final common pathway syndromes resulting from interactions of genetics, early experience, environment, and stress rather than due to an identifiable nonpsychiatric illness, a prescribed medication, or a recreational drug. An example of secondary psychiatric syndrome would be major depression secondary to pancreatic cancer. The consultant may also diagnose a combination of both primary and secondary psychiatric syndrome, for example, schizophrenia, with visual hallucinations and confusion secondary to delirium caused by morphine.

   In making a primary psychiatric disorder diagnosis, the clinician should refer to the DSM, published by the American Psychiatric Press, for diagnostic criteria and coding. Alternatively, the International Classification of Diseases (ICD-10), published by the World Health Organization (http://www3.who.int/icd/vol1htm2003/fr-icd.htm), may be used.
5. Role of stress: Stress has impact on the pathogenesis of psychiatric final common pathway syndromes in several ways—by increasing the individual's susceptibility, by precipitating the onset of the syndrome, and by precipitating a recurrence or contributing to exacerbation of the syndromes.

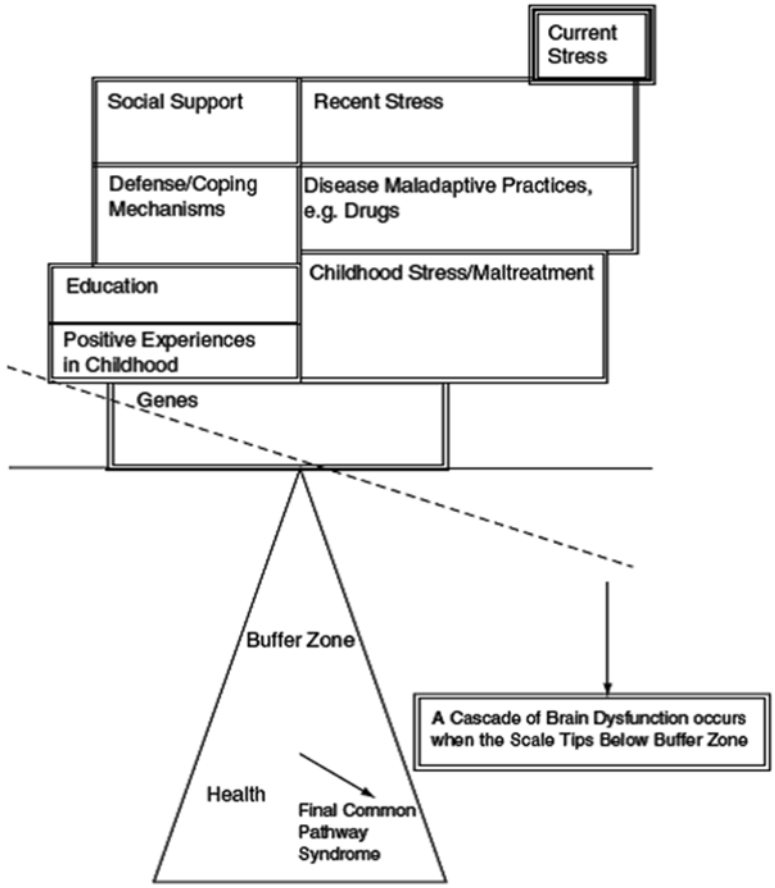

Fig. 7.9 A model of the final common pathway syndrome. An imbalance between salutary and pathogenic factors results in a cliff-edge cascade of brain dysfunction

7.3.7 Management of Final Common Pathway Syndromes: How to Change the Brain with Psychotherapy and Pharmacotherapy

Multiple interacting paths, some sequential, others parallel, may lead to a final common pathway syndrome. The treatment and management of such a syndrome may also follow multiple interacting sequential or parallel paths. For example, the depressive syndrome may be treated with a selective serotonin reuptake inhibitor (SSRI), such as fluoxetine; a serotonin and norepinephrine reuptake inhibitor (SNRI), such as duloxetine; or electroconvulsive therapy, in conjunction with either cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT). All of these treatments may be done after an environmental change (admission to a psychiatric unit). The susceptibility for depression in some individuals with 5-HTLPR short allele may be attenuated if maltreatment in childhood was prevented, protective memes are introduced through education and coping skills training, and eventually, by genetic engineering to modify the pathogenic aspects of the genome.

Judicious use of treatment modalities in biologic, psychological, and social/environmental dimensions is indicated in managing final common pathway syndromes. Protecting an acutely suicidal patient through hospitalization may be the first priority, followed by psychoeducation (both of patient and family) and antidepressant

Table 7.1 Identifiable factors causing secondary psychiatric syndromes/symptoms

A. Medical disease/condition
1. Endocrine/metabolic disturbances
a. Pituitary gland: Sheehan's syndrome, pituitary adenoma
b. Thyroid gland: thyrotoxicosis, Hashimoto's disease, hypothyroidism, cretinism
c. Adrenal cortex: Cushing's disease/syndrome, Addison's disease
d. Parathyroid gland and hypercalcemia/hypocalcemia
e. Insulin and hypoglycemia, diabetes mellitus
f. Gonadal hormones: Turner's syndrome, Klinefelter's syndrome, polycystic ovaries (Stein–Leventhal)
g. Electrolyte imbalance
h. Wilson's disease
2. Deficiency diseases
a. Malnutrition/iron deficiency
b. Vitamin deficiencies
Thiamine: Wernicke–Korsakoff syndrome
Niacin: pellagra
B_{12}: macrocytic anemia, combined degeneration
Folate: macrocytic anemia
3. Infections
a. HIV/AIDS: encephalitis, delirium, dementia
b. Syphilis: general paralysis
c. Viral encephalitis/post-viral syndromes
d. Other infections, e.g., coccidioidomycosis, tuberculosis
4. Immunologic
a. Systemic lupus erythematosus
b. Iatrogenic immune suppression (e.g., in transplant)
B. Substances
1. Prescribed medicines: most prescription drugs can cause mood changes and psychosis; steroids and opiates are particularly common causes
2. Recreational drugs: narcotics, stimulants (amphetamines, cocaine, etc.), phencyclidine (PCP), d-lysergic acid (LSD), peyote, etc
C. Environmental
Sensory deprivation and/or overload (as in intensive care units), extremes of temperatures, altitude, carbon monoxide, environmental toxins

drug therapy as well as psychotherapy. Brain function imaging studies show that both drug therapy and psychotherapy affect the functional status of the brain when successful.

In depression, with successful treatment with CBT or IPT, patients exhibited decreased activity in dorsal frontal regions and increased activity in ventral frontal and subcortical regions (notably including limbic and paralimbic structures). Of note is that the brain changes seen with psychotherapy of depression, unlike those in OCD or phobias, are different from those seen with successful treatment with medications, which results in an increase in prefrontal cortex metabolism and a decrease in the activity in the posterior cingulate and in the subgenual cingulate, and may represent different mechanisms of recovery from depression (Goldapple et al. 2004; Roffman et al. 2005).

Long-term psychotherapy has been shown to reduce the increased activation of left anterior hippocampus/amygdala, subgenual cingulate, and medial prefrontal cortex. This reduction was associated with improvement in depressiveness specifically, and in the medial prefrontal cortex with symptom improvement more generally (Buchheim et al. 2012). Deep brain stimulation of the subgenual anterior cingulate (Area 25) has been used successfully in treatment refractory depression (Holtzheimer et al. 2012; Lozano et al. 2012).

In OCD, behavioral therapy reduces the metabolism in the caudate nucleus. Both fluoxetine and psychotherapy seem to uncouple dysfunctional corticostriato-thalamic circuitry. Deep brain stimulation for nucleus accumbens has been used successfully in treatment refractory OCD patients as they exhibit excessive connectivity between nucleus accumbens and prefrontal cortex (Figee et al. 2013; Ooms et al. 2013).

In phobias, patients have significant activation in the parahippocampal gyrus and right dorsolateral prefrontal cortex as compared to normals. With successful CBT utilizing exposure therapy, patients demonstrated significantly less activation in both the parahippocampal gyrus and right dorsolateral prefrontal cortex (DLPFC), and

increased activation in the right ventral prefrontal cortex (PFC) (Paquette et al. 2003). The abatement of the parahippocampal gyrus response may be due to a dampening of contextual memory believed to be mediated by this structure. A shift of activity to the ventral PFC could prompt downregulation of limbic activity, dampening the fear reaction.

In social phobia, CBT that targeted the anxiety associated with public speaking demonstrated a significant reduction of activity in the limbic system including the amygdala. Psychotherapy and pharmacotherapy seem to have differential effects in phobia. Citalopram, an SSRI, reduced the activity of ventral prefrontal cortex in phobics, while CBT caused no change. Patients receiving CBT showed decreased CBF in the periaqueductal gray area, which has been associated with defense behaviors. Citalopram reduced the blood flow to the thalamus, potentially reflecting reductions in sensory input to the amygdala (Charney and Deutch 1996).

In schizophrenia, the functional hypofrontality has been partially reduced with second-generation antipsychotic drugs (see Chap. 19), and the limbic overactivation of D2 neurons are reduced with antipsychotics in general.

In considering psychotherapies, broad-spectrum meme directed therapies should be considered. These therapies are geared to generalized reduction in meme proliferation that is often seen in psychiatric syndromes. Such broad spectrum meme-directed therapies would include mindfulness training, general relaxation therapy, music and dance therapy, etc. (Leigh 2010)

In the final common pathway model, the therapeutic intervention may be directed at any and all of the specific pathways leading to the syndrome, including genetic, epigenetic, memetic, and environmental factors.

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