

Chapter 22

Anxiety-Mood Spectrum Syndromes: Anxiety, Panic, Phobias, ASD, PTSD, Borderline Syndrome, Dependent and Avoidant Personalities, Social Phobia, Bipolarity and Mania, Depression – Neurotic and Syndromic, Adjustment Disorders

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22.1 Gene × Meme Interaction, Evolutionary Adaptation, and Syndromes

Anxiety is ubiquitous and is a natural function of the brain structure, conserved and evolved over time in animals to be aware of danger situations. The limbic system, particularly the amygdala, hippocampus, and the cingulate gyrus, is involved in anxiety and depression (see Chapters 1 and 2). Like a smoke detector, the generation of anxiety allows an animal to prepare for fight or flight, conferring survival and thus reproductive advantage. Sad expression and withdrawal behavior in depression draw attention and support from others and thus may confer survival value.

We examined at some length in Chapters 1 and 2 how stress may affect certain genes, which may in turn affect the morphology and function of brain structures such as the connection between the amygdala and the cingulate gyrus. Anxiety is the experience of stress within the brain – how the sensory input is processed within the brain as a danger signal. When a sensory input, which may be either physical (e.g., cold weather) or memetic (e.g., words), enters the sensory cortex, it is presented to the amygdala, to the hippocampus, and to the association cortex where the sensory input is compared with memory (existing memes), then an interpretation is made as to whether it is dangerous or not, and this information is fed back to the amygdala. Many sensations turn out to be not very dangerous, and the feedback will tune down the amygdala in most persons. In individuals with the short allele of the serotonin transporter promoter gene (5-HTTLPR), especially in those who had been exposed to abuse as a child, there is a reduction in this feedback loop back to amygdala. Thus, such individuals tend to have heightened and more frequent anxiety responses to stress in adult life and eventually an increased risk of depression and suicidal behavior (Caspi et al., 2003; Pezawas et al., 2005; Ribases et al., 2008; Stein et al., 2008). It appears that repeated and unabated activation of the anxiety-fear circuit eventually results in depression.

Abuse in childhood represents not only physical stress from trauma, but also the infusion of memes into the immature brain. The memes associated with childhood abuse are exactly the kinds of memes that are associated with fear, anxiety, and depression – “The world is a dangerous and hostile place” “I am not worthwhile” “I deserve to be punished,” etc. Stress in adult life, with infusion of similar memes, may result in an unchecked proliferation of anxiety and depressive memes.

In rhesus monkeys, animals heterozygous for the *s* allele were shown to exhibit exaggerated stress responses only in already stressful situations, such as being in a new cage, while in their home cages, they exhibited similar responses as the *ll* allele monkeys (Kalin et al., 2008).

Recent studies have shown that fear conditioning and extinction involve two different sets of neurons in the amygdala with connections to the medial prefrontal cortex and the hippocampus (Herry et al., 2008). The fear neurons received input from the hippocampus and projected to the medial prefrontal cortex, while the extinction neurons had bidirectional connections to medial prefrontal cortex. During extinction of fear response, the extinction neurons were active even when the fear neurons were not. In effect, extinction occurs through the creation of memory, i.e., a meme. The introduction of a meme could thus extinguish fear.

22.1.1 Anxiety

Anxiety is identifiable through the transmission of memes indicating its presence, which may be in words, facial expression, or behavior. It may be experienced as pure emotion, a subjective sense of anxiety which is not expressed, or it may be feigned or mimicked, as in playacting. Even when anxiety is not communicated, the

pure experience may replicate inside the brain as a meme, eventually building up pressure to be expressed.

While anxiety is usually experienced as a negative emotion, it is necessary and desirable as a warning signal of an impending danger (both external and internal, which may be a result of a memetic conflict). As anxiety involves arousal and attention, it facilitates performance in moderate amounts. When anxiety is excessive, however, there is a decline of performance, sometimes to the point of paralysis or extreme purposeless agitation.

Locus ceruleus, the nucleus of a majority of noradrenergic neurons in the brain, plays an important role in anxiety. Activation of the locus ceruleus is an important aspect of the physiologic activation associated with anxiety. This response may be explosive and if unchecked, results in the panic syndrome. Panic may be precipitated by a memetic stimulus, such as a thought or perception of an open space in an agoraphobic patient.

Phobias represent severe anxiety and fear associated with memes and memetic stimuli.

22.1.2 Panic Syndrome and Agoraphobia

In panic syndrome, there is unexpected and repeated episodes of intense fear accompanied by physical symptoms that may include chest pain, heart palpitations, shortness of breath, dizziness, or abdominal distress. The symptoms usually last minutes, peaking in about 10 min, though sometimes longer. This may be accompanied in about a third of cases by agoraphobia, the fear of public or unfamiliar places, or even going out of the house lest a panic attack might occur. Various genes have been identified that might contribute to anxiety proneness in general and panic syndrome and agoraphobia in particular (Domschke et al., 2008a, b; Hettema et al., 2008; Strug et al., 2008). It appears that panic syndrome with agoraphobia may have a stronger genetic component.

Panic syndrome clearly represents a severe and episodic dysregulation of the fear-anxiety apparatus, probably determined by an unstable regulatory mechanism. Memetic stimulus such as being in an unfamiliar place might provide the initial ignition of anxiety that results in a full blown panic attack.

22.1.3 Specific Phobias

Phobias to specific objects, such as acrophobia, misophobia, arachnophobia, and ailurophobia probably represent conditioned anxiety to memetic stimuli. The phobic object may be symbolic of a meme that one fears, such as a feared person. Phobic memes are common in most cultures and some may be even inherent, such as the fear of spiders and snakes. Others, such as the fear of germs and contamination (misophobia) are results of modern civilization.

Phobic symptoms are more likely to develop in individuals with genetic predisposition for anxiety, and who also had exposure to the phobic memes. Most phobic objects can be avoided and thus not a source of great distress, but when a person is unexpectedly exposed to a phobic object, panic may ensue. Such exposure may be traumatic enough to leave lasting consequences.

22.1.4 Acute Stress and Posttraumatic Stress Syndromes

These represent the effects of overwhelming stress on the brain, i.e., overwhelming infusion or activation of stress memes that take over the function of the brain. The stress reaction involves the activation of the hypothalamo-pituitary-adrenocortical axis and massive production of glucocorticoids which are neurotoxic to the hippocampus, and may result in a smaller volume and difficulty in processing memory (see Chapter 2).

With PTSD, there may be a permanent damage to the meme-processing ability of the brain, setting the stage for a labile equilibrium among conflicting memes and susceptibility to be overwhelmed with new incoming memes or an inability to process new and useful memes. The stress memes that overwhelmed the brain are likely to reside in the brain and proliferate at every opportunity. Note that strong emotions may enhance long-term potentiation and thus memory formation through dopaminergic and serotonergic mechanisms (“flashbulb memory”; see Chapter 9).

Persons who have no memory of a traumatic event in 24 h were shown to be less likely to develop PTSD in 6 months than those who had memories of the trauma (Gil et al., 2005). This finding supports the notion that the ability to inhibit the traumatic meme proliferation (memory) prevents PTSD.

Once PTSD has been established, reservoirs of traumatic memes may proliferate unpredictably and uncontrollably as in flashbacks and nightmares. EMDR (eye movement desensitization and reprocessing therapy) might be effective as it simulates the saccadic eye movements of the REM (rapid eye movement) sleep during which traumatic memes may be processed in the cortex (Stickgold, 2002).

22.1.5 Borderline Syndrome and Traits

Characterized by emotional instability, stormy relationships, and tendency for dissociation, this syndrome overlaps considerably with the symptoms and neurophysiology of PTSD and depression, and may indeed represent the sequelae of childhood traumas interacting with genetic vulnerability (Hunt, 2007; Minzenberg et al., 2008). Nightmares and dream anxiety are quite common in borderline syndrome and may represent intense replication of trauma memes as in PTSD (Semiz et al., 2008).

Borderline syndrome patients often have identity diffusion, or a fragmented sense of self (Brenner, 1996; Charry, 1983; Fuchs, 2007; Jorgensen, 2006). This may

represent a failure to develop harmonious relationships among several competing selfplexes (the memes that constitute the sense of self, see Chapter 12). Thus, there may be no consistent selfplex that presides over other selfplexes and use them as the occasion demands, and the contradictory selfplexes may alternate or shift unpredictably instigated by otherwise insignificant stress memes. Depending on which selfplex is dominant at the moment, the individual may feel different emotions and exhibit different behavioral traits.

22.1.6 Dependent Personality Traits and Syndrome

This is characterized by degrees of psychological dependence on others for decision making and submissive and clinging behavior and a lack of initiative.

Everyone has some dependency needs – in fact, all mammals are dependent on their mothers in the early stages of life. There are, however, genetic polymorphisms that may predispose an individual to various personality traits including extraversion, novelty seeking, withdrawal from angry faces, tendency for drug use (Han et al., 2008; Luo et al., 2008; Perlis et al., 2008). As in borderline personality, there may be specific gene × meme interactions in the development of dependent personality traits and syndrome.

Early memetic environment that discouraged independence and fostered dependence would strongly contribute to the development of dependent personality. This would be particularly so if dependence was expected because of the gender, race, or social class of the child, and there were numerous memetic models (identification figures) for this.

22.1.7 Avoidant Personality Traits and Syndrome, Social Phobia

Avoidant persons show pervasive social inhibition, feelings of inadequacy, extreme sensitivity to negative evaluation and avoidance of social interaction. They often consider themselves to be socially inept, and avoid social interactions for fear of being rejected. They often consider themselves to be loners and feel alienated. In Social Phobia, there is excessive anxiety in social situations for fear of being humiliated or ridiculed. Such persons may show physiologic signs of anxiety such as blushing and sweating, which may further cause embarrassment and anxiety. Avoidant personality may be a more pervasive type of social phobia (Chambless et al., 2008). Like any other anxiety conditions, these traits develop over development through interaction between genetic disposition and memes introduced from the environment. Repeated exposure in childhood to critical memes in social situations, or the stress of having to repeatedly adapt to new and strange environments in an anxiety-prone person would set the stage for social phobia and avoidant personality.

22.1.8 Bipolarity and Mania

Bipolar disorder in current terminology means one or more episodes of abnormally elevated mood, either hypomania or the more severe form, mania. Hypomania or mania often occurs in persons who also have episodes of depression, thus the original term, bipolar. There may also be mixed episodes of both depression and mania/hypomania. These episodes are usually separated by periods of euthymia, but in some individuals, depression and mania may rapidly alternate. During manic states, the person may be very speeded up, with rapid thoughts, pressured speech, and the mood may be irritable rather than euphoric, sometimes with grandiose delusions and hallucinations.

There is considerable overlap between borderline personality and bipolar disorder (Hunt, 2007; Smith et al., 2004). Seventeen percent of first degree relatives of borderline personality had bipolar disorder according to one study (Akiskal, 1981). The rate of bipolar disorder among first degree relatives of unipolar depression was 3.5% (Andreasen et al., 1987).

Affective instability may be seen to be an underlying mechanism for both (Mackinnon and Pies, 2006). The mechanism of switch between depression and mania is unclear. In one study, 9 of 11 patients with bipolar depression switched to an elevated mood state with the administration of *S*-adenosyl methionine (SAM), indicating the involvement of dopamine and serotonin (Carney et al., 1989).

While mania may be considered to be a dysregulation of mood, it has also been proposed that mania may represent a dysfunction of *reentry* described by Edelman (see Chapter 9), the process of ongoing parallel and recursive signaling between separate neuronal groups along parallel reciprocal fibers that link these groups anatomically. According to this view, reentry is speeded up through some biochemical mechanism, resulting in rapid recursive signaling and thought (Mellerup and Kristensen, 2004). As reentry is the process through which memes are consolidated and replicate, there would be a rapid proliferation of memes under those conditions. The kinds of memes that would proliferate would depend on the mood state, which is elevated in manic states. Thus, there is proliferation of euphoric, high self-esteem, and grandiose memes, at times to the point of delusions and hallucinations when a psychotic process is activated when the manic state reaches a threshold.

22.1.9 Depression – Neurotic and Major Depressive Syndrome

How do you know a person is depressed? By simply looking at a person, then, by talking with the person. Depression is perhaps one of the states that illustrates the meme as something imitable. We know how to look depressed and feel depressed, and when we imitate someone's depressed expression, we feel depressed. This empathy, feeling what another feels by imitation, is in fact the first mode of communication between a preverbal child and caregiver and involves the activation

of the mirror neurons, prefrontal cortex, and the limbic system through the insula (Carr et al., 2003; Lenzi et al., 2008).

The verbal communication of a depressed person is, of course, full of depressive memes and represents a state of unchecked proliferation of such memes. In other words, the neurobiology of depression permits explosive replication of depressive memes. It is important, however, to recognize that in very severe depression, there may be sufficient psychomotor retardation such that the depressive memes are predominantly nonverbal.

Common memes replicated in depressive states are sad, crying, helpless, hopeless, pessimistic, self-reproach, self-punitive, uncaring, apathetic, self-destructive, and suicidal memes.

With severe depression or depressive syndrome, there is often physiologic signs such as insomnia, fatigue, anhedonia, and anorexia. Anhedonia is also associated with a dampening of feedback information, such as reward for an action. This is associated with functional changes in the brain, such as activation of ventral striatum that indicates a reward stimulus (Steele et al., 2007). There may also be psychotic symptoms, such as depressive delusions and hallucinations.

Sadness is often a consequence of an event about which one had felt anxious – inability to master a threat may result in sadness and helplessness and may trigger the depressive syndrome in vulnerable individuals. Depression may occur purely from memetic processes, such as the recognition of an inability to meet the demands of a memplex (ego ideal) (Busch et al., 2004).

Depressed mood, cognition, and behavior are memes that can be imitated and feigned, and serve a communicative purpose. They draw attention to the helplessness of the individual and may elicit support and protection by others. Depressed memes may also represent submissiveness, as displayed by some animals toward a higher ranking one, thus avoiding confrontation and harm. “Learned helplessness” to unavoidable danger situations may protect the organism from futile expenditure of energy and effort. Such “learning,” however, may be maladaptive as the situation may have changed, and there may indeed be ways of mastering the current situation. There is evidence that the experience of learned helplessness may lead to specific activation of the amygdala and the mammillary bodies (Schneider et al., 1996; Seligman, 1972).

Depression may vary in severity from sad affect to *depressive neurosis* to major depressive syndrome. Sad affect is generally associated with an identifiable loss or an anniversary of a loss and is temporary. Depressive neurosis represents a depressive trait – a tendency to experience mild to moderate depressed mood with minor stresses. They may have a pessimistic outlook, and may feel helpless in warding off depressogenic stresses.

In *major depression*, which often arises in persons with depressive neurosis, there are several categories of symptoms and signs – (1) affective (sad, blue, apathetic, crying), (2) cognitive (pessimistic, helpless, hopeless, low self-esteem, self-reproach, guilt, suicidal ideation and plans), (3) neurovegetative and physiologic (anhedonia, insomnia, hypersomnia, psychomotor agitation/retardation, constipation, fatigue, vague pains and discomfort), (4) Behavioral (self neglect,

neglect of hygiene, social withdrawal, substance use/abuse, suicidal behavior). Once major depressive syndrome develops, it usually has an autonomous course lasting on the average 6–12 months without specific treatment and suicide is a serious risk. Major depressive syndrome is a final common pathway brain dysfunction requiring coordinated psychiatric treatment.

22.1.10 Adjustment Disorders

In a sense, all psychiatric syndromes may be considered to be adjustment disorders, but the term is generally reserved for relatively mild and transient symptoms of distress to stressful situations that do not reach the threshold for diagnosing a more serious and persistent conditions such as neurosis or major psychiatric syndromes (e.g., major depression, psychosis).

In adjustment disorders, the symptoms, while distressing, is usually within the boundaries of normality and the autonomous course of a final common pathway syndromes has not been triggered.

Adjustment disorders may be characterized with prominent anxiety and/or depressed mood and/or behavioral problems including acting out, substance use, which may be a maladaptive way of coping with the stress.

There is a proliferation of stress and distress memes in adjustment disorders which may threaten to trigger a proliferation of depressive and/or psychotic memes if these are already present in the brain in relatively large quantities. The stress memes may also induce certain physiologic symptoms such as insomnia and other manifestations of anxiety.

22.2 Treatment

22.2.1 Prevention

There has been little genetic evolution in humans during the eyeblink of time between the stone age and the modern age, though the memes have evolved at an exponential rate. It is no wonder, then, that the genetic machinery of our brain is often mismatched for the memetic onslaught through our perceptual apparatus. Thus, brains well adapted to generate anxiety at the slightest sensation indicating the presence of a predatory animal may find itself generating anxiety signals at various sensations arising from memetic (e.g., images, voice, words) and physical (e.g., speeding vehicles, being in tall buildings) stimuli that are commonplace and benign.

The anxiety-prone genes may have been adaptive in the stone age, but may cause vulnerability to anxiety in modern age. Identification of children with highly threat-sensitive genes and providing them with training on stress management and coping skills may prevent future development of symptoms and syndromes.

22.2.2 Mild Symptoms (Problems of Living and Adjustment Reactions)

Mild anxiety and depressive symptoms may arise as a function of the individual vulnerability interacting with perceived stress. Intervention should be geared toward reduction of perceived stress through reframing if the perception of danger is excessive, or through more effective coping. Broad-spectrum meme-oriented therapy, such as relaxation, meditation, and massage therapy may be particularly useful (Chapter 17), as well as certain specific meme-oriented therapies (Chapter 18). Enhancing coping ability and thus reducing helpless feelings may be particularly useful for mild depressive symptoms.

22.2.3 Neurosis

Neurosis indicates the presence of a pattern of behavior and emotional arousal that is distressing and that is often the patient's own making. Such patients are often self-defeating and pessimistic. Neurosis may be truly memetic, i.e., learned (imitated) way of living patterned after a parent or surrogate, or arise out of repeated adjustment reactions with failure to cope.

Specific meme-oriented therapies should be used for neurosis, augmented with broad-spectrum therapies and medications as needed. The medications may be antianxiety agents when the patients find themselves in an excessively anxiety-provoking situation, even if it is of their own making, or antidepressants or hypnotics as the occasion demands.

Therapy for neurosis should be geared toward the memes that constitute the pattern of behavior and emotional arousal by modifying and replacing them with more effective memes and thus creating a healthier selfplex.

22.2.4 Major Syndromes

Major syndromes of the fear–anxiety–depression spectrum syndromes include panic syndrome, phobias, acute stress disorder (ASD), posttraumatic stress disorder (PTSD), borderline syndrome, mania, and major depressive syndrome.

Gene-oriented treatment should be ideally geared to turning off the expressed genes that may cause the dysfunction of the brain structures. This may be possible through drugs that might be developed for specific genes or choice of drugs in a pharmacogenetically informed way. For example, SSRIs may be more effective for specific genomic groups, while alpha II agonists such as clonidine might be more effective for others whose locus ceruleus may be hypersensitive.

Current gene-oriented therapy, unfortunately, remains at the level of trial and error of drugs that have been shown to be effective for a significant but less than satisfactory percentage of patients with overlapping symptoms and that are associated

with often highly undesirable and dangerous side effects. They include antidepressants (tricyclics, SSRIs), serotonergic-noradrenergic drugs (SNRIs, mirtazapine), mood stabilizers (lithium, anticonvulsants, antipsychotics), and benzodiazepines. All of these drugs except lithium (which is used more specifically for bipolar and recurrent depression) have been used for any of the above syndromes largely on a trial and error basis.

There is clearly a need to develop more specific gene- and genome-oriented drugs. Gene-oriented therapy is not confined to pharmacotherapy. As has been shown in rhesus monkeys (Suomi, 2003, 2005), good nurturance can reverse the adverse effects of genes such as the short allele of 5-HTTLPR. Long-term psychotherapy and/or nurturing environment in adulthood may also affect genes.

General meme-oriented therapy for anxiety and depression would include all broad-spectrum therapies outlined in Chapter 17. Meme-oriented therapy includes all of the specific therapies discussed in Chapter 18. Specific therapies such as cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) for anxiety and depression should be used, as well as dialectical behavioral therapy (DBT) for borderline syndrome.

Memetically, anxiety symptoms may represent a tension among existing memes in the brain or between an incoming meme and existing memes. Specific techniques could be developed to examine recently introduced memes and their relationship to existing ones, so as to achieve a reconciliation if a conflict is found. Note that the newly introduced meme may have arrived unconsciously or semiconsciously, sometimes as a part of a complex meme such as a song or other works of art. Resident memes that may tend to generate anxiety easily, such as rigid and punitive moral codes, may be reexamined and reprocessed rationally if they are identified.

When anxiety remains unabated, or the stressful situation is perceived to be hopeless, hopeless and helpless memes replicate and predominate and depressive syndrome ensues. Depressive syndrome may also be the result of new infusion of depressive memes or the replication of existing depressive memes because of a change in the brain environment (e.g., cytokines associated with a viral infection) or triggered by incoming depressive memes.

Specific antianxiety and/or antidepressive memes could be infused through words (e.g., mantra, self-suggestion), song, visual imagery, or physical activity (e.g., flexing and relaxing muscles).

Combined gene- and meme-oriented therapy may be used. For example, desensitization to an anxiety-provoking meme may be conducted through exposure after medication with an anxiolytic drug. Antidepressive memes could be infused after medication with a stimulant drug. In ASD and PTSD, neuroprotective drugs should be used as well as treating the proliferation of unintegrated trauma memes through broad-spectrum therapies as well as specific meme-oriented therapies that may include reexperiencing trauma with beta blockade or controlled exposure therapy.

Virtual reality therapy can be used effectively to treat situational anxieties including social anxiety and phobias through desensitization. Avatars may also be used to introduce new memes, such as mastery of fear and assertiveness in social

situations. An avatar is a virtual image of oneself, and there is nothing more effective than watching and imitating oneself actually doing the things one wished one could do. Avatars could show the patient how he/she can interact with people confidently, become physically fit, and enjoy life. A new selfplex could be built.

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