

Differentiation of Primary Emotions through Neuromodulators: Review of Literature

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ABSTRACT

Emotional mental disorders are a leading cause of disabilities worldwide. Despite the obvious importance of emotion for human existence, controversy still abounds over the definition of emotion, the number of emotions that exist, whether different emotions have different physiological signatures. In this paper, we review papers about the emotional functions of neuromodulators: dopamine (DA), norepinephrine (NE), serotonin (5-HT) and acetyl choline (ACh), and propose that they act as the primary neural basis for 5 primary emotions (joy, anger/fear, sadness and missing). DA is a rewarding signal for salient stimuli such as food, sex and other needs. 5-HT has been related to depression for decades, it might be a marker for dislike/disgusting things. NE is the substrate for surprise, whose release induces “fight or flight” behaviors, or fear and anger emotions. Even though anger and fear are common emotions, there are no previous papers differentiating them or probing into their relationships. Here we found that fear and anger usually come hand in hand with fear followed by anger. And we give an equation to

describe their relationships: The total amount of Surprise/stress = fear + anger. This equation fits in both duration and tension. Finally we introduced ACh emotions, which are opposite to NE induced stressful emotions. These emotions include “missing and wanting”, “calm/tame”, affectionate, submissive, et al. The significance of ACh emotions lies in the treatment for aggressive, impulsive behaviors, or phobia and manic disorders. In all, there might be 5 basic emotions (joy, anger/fear, sadness and missing).

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Key words: Neuromodulators; Basic emotions; Serotonin; Dopamine; Norepinephrine

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INTRODUCTION

Emotional mental disorders are a leading cause of disabilities worldwide. Despite the obvious importance of emotion for human existence, scientists concerned with human nature have not been able to reach a consensus about what emotion is^[1]. Controversy still abounds over the definition of emotion, the number of emotions that exist, whether different emotions have different physiological signatures^[1-4]. Although there has been no shortage of psychological research on these topics, the findings have not resolved many of the issues. Information about the representation of emotions in the brain may shed light on the nature of emotional processes^[1]. Like color, people will never imagine that there are only three primary colors, if not for the physiological proof of three different kinds of conic cells in the eye, but emotion seems much more complicated.

Studies of the neural basis of emotion have a long history, and are

still an active field of experimental and theoretical research. Most of the work focuses on identifying neural structures responsible for the experience of particular emotions. This kind of research culminated around mid-century in the limbic system theory of emotion. The neural anatomical basis of emotion helped us find important structures involved in primary emotions, but the structure for emotions is usually mixed and widespread in the brain, which suggests an alternative approach: neuromodulators. With the development of drugs for the affective disorders, catecholamine was shown to be the substrate for emotion ever since the 50s-60s in last century^[5]. Even though many years have passed, the effects of catecholamine in treating affective diseases are still quite mixed. For example, antidepressant drugs affect almost all the catecholamine neuromodulators and are used for almost all affective diseases such as anxiety, phobia, depression *et al.* There is a need to improve the conceptualization and classification of the emotional states and the involvement of the neuromodulators. Here we review papers about their differences in modulating emotions, and propose that these three monoamine neuromodulators together with ACh underlie the 5 primary emotions of human (DA-pleasant, 5-HT-unpleasant, NE-surprise/anger-fear, ACh-missing).

DOPAMINE (DA) – PLEASANT MARKER

DA has been linked to rewarding processes in the brain since 1980, when Wise first proposed the hedonic hypothesis of DA^[6,7], who proposed that DA is a signal of stimulus salience, providing feeling of enjoyment. DA is a rewarding signal for salient stimuli such as food, sex and other needs, which are excited by reward seeking behaviors. The reward depends on the needs of subjects. Human needs were classified by Maslow (1943) as the hierarchy of needs, from physiological needs to social needs. The physiological needs are required for human survival; they are so primitive in evolution that they responded just automatically, and they were used as unconditioned rewarding stimuli in Pavlovian experiments. Social needs include love, trust, esteem, pride and self-actualization *etc.*, which depends upon human appraisal.

Many pharmacological and behavioral studies on intracranial self-stimulation established the important role of the medial prefrontal DA system in positively motivated behavior^[8]. We don't need to review them here, for the rewarding role of DA has been well documented in many aspects. For example, drug addictions are involved in the reward system by affecting DA release and reuptake. Imaging studies revealed that drug-naive individuals show enhanced DA levels in the striatum upon exposure to psycho-stimulants such as cocaine and amphetamine; in contrast, decreased striatum DA responses were reported in detoxified cocaine abusers^[9,10]. Furthermore, individuals with a history of abuse of alcohol, cocaine, heroin, or methamphetamine display lower levels of DA receptor binding compared to non-abusers^[11]. Together, these studies suggest an involvement of DA neurotransmission in the acute and long-term effects of abused drugs^[12].

Over the past several decades, extensive studies have refined the function of DA, and theories concerning the role of midbrain DA on behavior have also changed dramatically^[12,13]. For example, empirical evidence revealed that global DA depletion does not impair hedonic (liking) response to primary reward such as the preference for sucrose over water. These observations have led to a formulation that the contribution of DA includes an effect on motivated behavior toward desired goals. Mesolimbic DA is also involved in aversively motivated behaviors. Medial hypothalamic stimulation, which has

been considered to cause a primary aversive state, cause significant decrease in extracellular DA^[14]. However, when rats can lever-press to escape the stimulation, NAc DA increased instead. This is similar to findings from Cabib^[15], that when animals were allowed to control the painful shock experience, NAc DA metabolites increased.

The most interesting study about DA is prediction error. Prediction error was proposed by Schultz *et al.*^[16], who discriminate role of DA in reward and prediction. Their connection derives from a wide variety of conditioning experiments. They proposed that the function of DA is a signal of salience of stimulus, for example, DA neurons are activated when animals touch a small morsel of apple or receive a small quantity of fruit juice to the mouth. These phased activations do not, however, discriminate between these different types of rewarding stimuli. Aversive stimuli like air puffs to the hand or drops of saline to the mouth do not cause these same transient activations. This unconditioned reaction can be connected to some neutral stimuli. For example, if presentation of a light is consistently followed by food, a rat will learn that the light predicts the future arrival of food. Only the light with food will induce DA release. The prediction-based explanation is that the light fully predicts the food that arrives. Surprisingly, once the stimulus-reward association is learned, reward delivery no longer elicits an increase in the activity of DA neurons as it is fully expected^[16]. It appears therefore that learning is driven by deviations or "errors" between the predicted time and amount of rewards. So Schultz *et al.* proposed that DA encodes expectations about external stimuli or reward, especially when it is uncertain or deviation or error (prediction error)^[16].

SEROTONIN (5-HT) – UNPLEASANT MARKER

5-HT has been related to depression for decades mostly because of the antidepressant drugs, and till now, the mostly prescribed drugs for depression are drugs that alter 5-HT levels. Even though 5-HT functions as a neurotransmitter in the nervous system, it is mostly released in the gut (about 90%), where enterochromaffin cells release 5-HT in response to noxious substance in the food. 5-HT makes the gut move faster, causing vomiting or diarrhea. Plant seeds with 5-HT exploit this reaction to speed the passage of seeds through the digestive tract. Animals such as wasps and scorpion sting can induce pain, for 5-HT presents in their venom. So 5-HT give objects a negative/disliked marker. Even in phylogenetically distant animals such as the mollusk, 5-HT release is involved in the regulation of avoidance behavior^[17]. Drugs which block 5-HT (5-HT_{2c} receptors) make the body unable to shut off appetite, and are associated with increased weight gain^[18]. It is really the case that people with low 5-HT showed more aggressive behavior, don't care about the negative (punishment) results, they even commit suicide. In 1976, Asberg and Traskman-Bendz identified a subgroup of depressed subjects with low cerebrospinal fluid (CSF) concentrations of 5-HIAA who had a history of serious suicide attempts^[19,20]. And thereafter, the correlation between low CSF 5-HIAA concentrations and increased risk for suicide has become one of the most reproducible findings in biological psychiatry, with over 20 studies finding low CSF 5-HIAA concentrations in populations that attempt suicide^[21,22]. Some other studies have suggested that the deficits in 5-HT functioning within the frontal cortex may underlie the other behavior disturbance, such as impaired impulse control, increased incidence of violent episodes^[23,24]. Some studies even suggested that low 5-HIAA (5-HT metabolite) in CSF is a marker for the predisposition to a wide array of psychopathological problems, such as impulse control, suicide, impulsive fire setting, or frequent violent criminal behavior, even

alcohol intake and dependence^[25].

5-HT in the central nervous system (CNS) mostly produced by neurons in raphe nuclei, and released into extracellular space between neurons in almost every part of the CNS, such as medial prefrontal cortex, amygdala, hippocampus, and is involved in appetite, sleep, mood, emotion^[26]. These functions have been revised in the past years. For example, it was thought that 5-HT induced sleep, one of the main arguments related to the insomnia following the destruction of midbrain raphe nuclei in the cat^[27,28]. But it is currently accepted that 5-HT functions predominantly to promote wakefulness and to inhibit REM sleep^[29], for the activity of serotonergic neurons of the dorsal raphe nuclei decreases from waking through slow wave sleep to REM sleep. Only under some circumstance it contribute to the increase in sleep propensity^[29]. So the function of 5-HT might act as a tranquilizer, and many studies support this. For example, tryptophan, which is easily converted to 5-HT in the body, is used as a tranquilizer; and it has been proved that 5-HT is involved in the biology of torpor and hibernation and it inhibits mitochondrial respiration.

Abundant evidence points to a decrease of the serotonergic system in anxiety, phobias, panic attacks and post-traumatic stress and depression disorders based on effects of treatments that enhance 5-HT, and the most popular kind of antidepressant is said to increase the action of 5-HT in the brain, however, it has been difficult to establish a primary role for 5-HT deficiency in these diseases^[30]. Even though the company called these drugs antidepressant, actually they are good for aggressive or anxiety behaviors instead of depression. Actually these drugs affect all the catecholamine (DA, NE and 5-HT). For example, the first generation of antidepressants: the monoamine oxidase inhibitor has similar effect on all catecholamine neuromodulators. The drug companies are finding more specific drugs, the third generation of antidepressants: the 5-HT specific reuptake inhibitors. While it is true that these newer drugs increase the actions of 5-HT, it is hard to find their effects on depression. On the contrary, selective 5-HT reuptake inhibitors have many depression-like side effects, such as apathy, nausea/vomiting, drowsiness, weight loss or diminished libido, even a higher risk of suicidal behavior in children. These drugs' improvement of depressive symptoms, sometimes better than placebo, might be the result of increased social interaction subsequent to a reduction in fear and avoidance^[31]. Injecting 5-HT never reduced depression, sometimes NE or DA does. Injecting 5-HT, or increasing its activity, can cause sedation, helplessness. Learned helplessness, a behavioral depression caused by exposure to inescapable stress, is considered to be an animal model of human depressive disorder. Cortical 5-HTergic excess is causally related to the development of learned helplessness^[32], and learned helplessness patients have high level of 5-HT. If increasing 5-HT is not the cure, then maybe decreasing 5-HT will be the cure. Indeed, chemicals that antagonize 5-HT do seem to function as antidepressants^[33]. It has been found that L-tryptophan depresses while levodopa intensifies emotional reactivity, the former lowering the level of endogenous 5-HT. And it was also found that lack of 5-HT enhances the emotional reactivity to learned fear memories^[34]. So the major benefit of the 5-HT drug is alleviated anxiety and improved sleep. So the term antidepressants is not correct, actually it acts as a tranquilizer. It never relieved depression, actually it induces more depression.

Genetic proofs also support this point. Pet1 is specifically expressed in the 5-HT neurons and directly activates the transcription of genes implicated in the serotonergic machinery. Compared to WT and Pet +/- littermates, Pet -/- mice has an 80% reduction in 5-HT

tissue levels, with no significant changes in the levels of DA^[35]. These mice showed normal ambulatory activity in a novel arena; however, they explored more in the aversive areas, which suggests lacking of dislike marker due to low 5-HT. Additionally, these mice showed increased levels of aggression as measured by the resident-intruder assay^[35]. The hydroxylation of tryptophan into 5-hydroxy-tryptophan is the rate-limiting step in the synthesis of 5-HT. Two isoforms of the enzyme tryptophan hydroxylase, Tph1 and Tph2 are responsible for catalyzing this reaction. Tph2 is exclusively expressed in the 5-HT neurons of the raphe nuclei. Genetic deletion of Tph2 was obtained in several groups. The depressive-like behavior of the Tph2 -/- mice was evaluated. Savelieva and colleagues^[36] found that these mice spent less time immobile in the test suggestive of an antidepressant phenotype.

Another example is the vesicular monoamine transporter (Vmat) 2, which transports monoamines into the synaptic vesicle. The homozygote Vmat2 -/- induced a major depletion of all monoamines and die within a few days after birth^[37]. In contrast, heterozygote Vmat2 +/- mice, have 34% decrease in brain 5-HT, are viable and showed normal growth rate and behavior. These animals also showed significant reduction in level of DA 42% and NE, 23%. Interestingly, they showed pronounced depressive-like phenotype characterized by increased immobility^[38]. In contrast, no anxiety phenotype was detected in a large battery of tests. To overcome the lack of specificity, a conditional knockout mouse was created by crossing Sert mice with Cmat2, allowing for the deletion of the Vmat2 gene specifically in 5-HT neurons^[39]. No depression like phenotype was observed; instead they showed less latency to reach out the food pellet in a NSF test, suggesting an anxiolytic-like phenotype. Overall, both pharmacological and genetic studies reviewed above prove that 5-HT is an aversive marker, which induces emotional depression.

NOREPINEPHRINE (NE)– SURPRISE MARKER

DA and 5-HT give the value of the objects around us according to whether they fit our needs or if they are dangerous to us. But everything in the world, whether it is positive or negative, occurs in anticipated ways (expected) or unanticipated ways (surprisingly). If it happens as anticipated, people feel calm; instead if it happened surprisingly, the first reaction of people would be scared and angry. For example, the door was knocked very loudly, while you were focusing on your reading. The first reaction is scared and then angry about why it was knocking so loudly. After opening the door, you can decide if it is happy (if it is what you wanted) or sad (if it is not what you wanted) (refer to figure1). So fear and anger are not due to likeness or dislikeness of things themselves, instead they are due to unexpected ways these things happen. Let us take one example from Izard's paper^[40], when Rafe was hit from the back by a wheel chair, the first reaction of him was scared and angry, and showed angry expression and clenched fist. But after he turned back to see Rebecca, a person with hemiplegia whose wheelchair had gone out of control and cause her to crash into Rafe. Rafe's understanding changed his anger to sadness and sympathy.

The substrate for both fear and anger is NE. In the periphery autonomous nervous system, NE acts as a sympathetic neurotransmitter, together with hypothalamic-pituitary-adrenal (HPA), they act as stress hormones, which underlie "fight-or-flight" responses, directly increasing heart rate, triggering the release of glucose, and increasing blood flow to skeletal muscles. In the CNS, the NE system is considered to play an important role in attention, sleep/wakefulness, emotion and central responses to

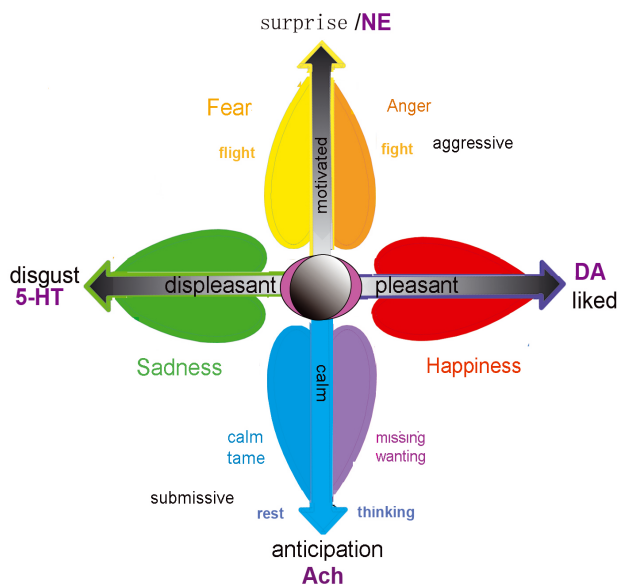


Figure 1 Emotions are due to catecholamine (DA, NE and 5-HT) and ACh. DA is a pleasant marker, 5-HT is an unpleasant marker. NE is a surprise marker, while ACh is a marker for anticipation. NE is well known for fight (anger) or flight (fear) behaviors. Fear and anger are twin emotions, which usually come together hand-in-hand with fear followed by anger, but they never happen at the same time in a same person. The total surprise = fear + anger. Therefore, it is usually the more scared, the less angry; and vice versa. ACh is the cognitive part of emotion, which gives the subject a quiet anticipated emotion, such as calm, tame, affectionate, missing and wanting, nostalgia, et al., which can be called “ACh related emotions”. The figure is Modified from our previous paper in *Mens Sana Monographs* (2015 in press).

stress. It might also be involved in anxiety disorders, especially in panic/fear disorders^[41]. NE is released from the locus coeruleus at stressful events to keep the brain alert to the unexpected stimuli (and inhibits irrelevant stimuli), which has been described as increasing the “signal to noise” of the afferents^[42]. The locus coeruleus (LC) is the largest NE nucleus in the brain and projects axons to almost all brain regions. LC is a pure NE nucleus, comprising approximately 1500 cells on each side of the brain stem in rats. Many studies have been conducted in LC to show its implication in sleep, attention and alertness, anxiety and stress response^[43-45]. Robust activation of the LC has been reported after stressful stimuli in cats: an increase in firing of LC neurons was observed following exposure to noxious air puff stimuli or visual threat^[46]. Electrical stimulation of the LC resulted in particular behaviors that were observed in fearful or threatening situations in the wild^[47]. LC sends projection to many brain areas, such as amygdala. It is now recognized that the amygdala plays a prominent role in stress elicited fear and anxiety^[48]. Electrical stimulation of the amygdala promotes stress-like behavioral and autonomous reactions, whereas ablation of Amygdala showed a marked increase of tameness, loss of motivation and decrease of fear response to aversive stimuli and a more rapid extinction of conditioned avoidance responses acquired preoperatively^[49,50]. However there are too many papers about NE, it is impossible to review them here. Here we will talk a little more about the relationship between anger and fear.

It is well known that NE release induces fight (anger) or flight (fear), which is an early evolutionary adaptation to allow better coping with dangerous and unexpected situations. For example, when a deer meets a lion, NE is released in both brains, but the reaction of the deer is flight (fear), while the reaction of a lion is fight (anger). So fear and anger are twin emotions coming from

the same neuromodulator NE, and they always come together at a stress. But they also exclude each other in that they never occur at the same time in the same subject, usually fear first and anger next. For example, when an aggressive driver cut in front of you, you first reaction is scared (fear), and next you will feel angry after and only if fear is gone. So fear is the scariness from the unexpected coming of unpleasant/dangerous things or unexpected loss of adored things. Anger is the blaming of the reasons for the unexpected things after fear is gone. So both fear and anger derive from the surprising ways things occur; if things occur just as anticipated, people will not feel scared or angry. Fear and anger are twin emotions; they always come together with fear followed by anger. We give the equation below, which fits in both duration and tension.

The total amount of Stress = fear (duration, tension) + anger (duration, tension).

If fear is stronger, anger would be relatively less for certain amount of stress; for example, when people feel highly scared at strong dangerous things, such as tornado, there is no time left for anger. On the contrary, when the fear is less, anger should dominate, such as betray by a lover; or when your kids did not listen to you and result in failure of a test. So it seems that fear is facing dangerous /disliked things, while anger is for liked things; this is correct at the poles of liked or disliked things. If fear duration is similar to anger duration, they are mixed together. For example, after class begins, the teacher tells you unexpectedly there will be test, you will be very nervous: your first reaction will be scared, next you will be angry. Not only the total amount of surprise will be less, the distribution of mixed feelings will change too, and result in fear or anger dominating, if things happened the second time or many times again. The same example: if the teacher always gives you this kind of unexpected tests, your fear will dwindle, and your anger will dominate. The typical example is that when two cocks first meet, mixed feelings of fear and anger arise in both of them. Then they will start to fight, and the results will be that one wins with the other one fails and runs away. They don't need to fight anymore the next time they meet, the failed one would run away with fear, and succeeded one would threaten with anger.

It is well documented that NE and DA are usually released together to induce aggressive behaviors (anger); and they have come to be recognized as playing an important role in attention and focus, which are the most activated state of emotion. On the contrary, the interaction between NE and 5-HT to make the fear emotions is much less documented. A considerable amount of research has focused on the finding of low 5-HT metabolite levels in abnormal aggression, but the mechanism is not clear. It is easy to explain using our equation shown above. At low levels of 5-HT, people cannot feel the scary results of their behavior; therefore they show very high anger at surprising things, which would induce impulsive behaviors, violent or aggressive behavior, or even suicide. Serotonergic neurons in Raphe nuclei project to key fear-related amygdala^[51], and these serotonergic inputs play a functional role the amygdala. Loud noise increases midbrain tryptophan hydroxylase activity^[52,53], but it is blocked by a lesion of the central amygdala^[54]. Within the circuits of fear, it has been proposed that central seotonergic activity plays a crucial role by enhancing fear through the raphe nuclei-amygdala pathway^[51]. Serotonergic cells in raphe nuclei firing activity rise with restraint and dog confrontation^[55,56]. And 5-HT levels rise during inescapable shock treatment but not during escapable shocks^[57], when DA is released as we stated before. This indicated the antagonist role of DA with 5-HT in emotions. Izard also noticed that the uncertainty regarding whether a stimulus will predict threat or reward, the need

to pay more attention to a stimulus of importance, or an urgency to engage in active coping are inborn to almost all needed or disliked things^[58]. Of note, the safety need in Maslow's hierarchy of need is overlapping with the vertical axis (surprise) of our model (Figure 1).

ACETYLCHOLINE (ACH) – ANTICIPATION MARKER

There are considerable evidences suggesting that monoamine (including DA, NA and 5-HT) in emotion. So far, it might be enough to propose 3 basic emotional neuromodulators in the brain to form 4 primary emotions (joy, sadness, fear and anger), like 3 basic colors. So it might be redundant to involve one additional neuromodulator ACh in emotion. Indeed, there are few reports about cholinergic involvement in emotion. In the periphery nervous system, ACh acts as a parasympathetic neurotransmitter, and it is responsible for stimulation of “rest and digest” activities that occur when the body is at rest: including sexual arousal, salivation, tears, urination, digestion and defecation, which is compensatory to the NE. In the CNS, ACh might act as “rest and thinking”, it is the neuromodulator in the brain that can boost cognitive function and its uptake inhibitors have been used for Alzheimer's disease. So its function is well known in learning/reinforcement, or to form the association between unconditioned stimulus with neutral stimulus in Pavlovian conditioning. ACh might be the cognitive part of emotion, and the only cognitive part in Izard's emotional theory. Even though using cognitive strategies is a good way to regulate the expectation of reward^[59], cognition is not an emotion in itself. Plutchik was the first to include anticipation in primary emotion list. Here we still want to propose another batch of emotions, which were omitted by many psychologists before: “missing and wanting”, which was found when we tried to look for the opposite of anger and fear. Actually the same question was already mentioned at the start of the last section: “Everything in the world, whether it is positive or negative, occurs in ways anticipated (expected) or not anticipated (surprisingly). If it happens anticipated, people feel calm; instead if it happened surprisingly, the first reaction of people would be scared and angry.”

What is the opposite of anger? It is hard to find a proper English word for it. Darwin used the related words, “aggressive-submissive” in his famous book about emotions more than 100 years ago^[60]. While probing into the angry emotion, he found that even bees get angry. He described dogs at anger as retracting upper lips, exposing teeth for biting. And in a similar fashion, dogs stand erect, hairs on its back upright to appear large, thus threatening. On the contrary, the dog slinks, with back down and close to the ground to show affectionate or submissive. Therefore Darwin invokes the principles of antithesis. He even extended it to human by showing a stance of an aggressive man as compared to a helpless man shrugging. So the opposite emotion for anger should be affectionate, and opposite emotion for fear might be “missing/wanting”. These related emotions include/ not limited to: calm, affectionate, tame, submissive, pensiveness, and nostalgia, and ACh underlies these emotions by inhibiting the excitation of cortex^[61,62]. The significance of ACh related emotion lies in that they can help people relax from the stressful events. For example, nostalgia music (not sad music) can make people calm down. Furthermore, long term stressful events usually lead to back pain, because of long time back stance, while slink-like activity help relax. Although ACh related emotions are not all positive, such as apprehension and worrying which also belong to this group, the benefit of ACh related emotions is that they are not so motivated to affect the body and spirits, especially for the highly motivated

people, who are very easily to burst into angry even for very small unexpected things, such as the baby not listening to him. So these emotions are the long time pursuit of many religions.

Actually, it has long been suggested for cholinergic involvement in the depression since 1972^[63]. At the time when the hypothesis was first published, the primary evidence was that a number of cholinesterase inhibitors have been shown to induce depression and to exhibit anergic effects^[64], presumably by increasing central acetylcholine levels^[65]. For example, physostigmine, a centrally acting cholinesterase inhibitor, was shown to decrease manic symptoms and increase depressed reaction^[65]. Later on, many studies provided information that largely supported the hypothesis^[64,66,67]. The theory was further supported by animal studies showing that mice bred specifically for sensitivity to cholinergic agents demonstrated depression-like behaviors^[68]. Other studies found that learned helplessness and swim stress, widely used preclinical models of depression, could induced sensitivity to cholinergic agents^[69]. In addition, the effects of the monoamine depletory, reserpine, the mood depressing effects of which have been used to support the monoamine hypothesis of depression, are remarkably similar to those of the cholinesterase inhibitors. Overlapping symptoms include apathy, lassitude, slowed down thinking, psychomotor retardation, lack of interest, fatigue, lethargy, nightmares, and depression^[65]. In addition, reserpine has been reported to have central cholinergic properties^[70]. Thus the reserpine induced effect might be due to a combination of monoamine depletion and cholinergic activation, shifting NE-ACh balance to a cholinergic dominance^[63].

There are a lot of reports about the interaction between ACh with catecholamine. For example, the contradiction of NE and ACh in the affective disorder in the CNS was reflected in their synaptic wire in amygdala^[71]: ACh carries the influence of the amygdala to other brain structures, NE inhibits the activity of ACh^[72]. Through these synaptic wires, the amygdala filters its incoming sensory streams of information, looking for those ‘dangerous’ stimulus features which would require the organism to engage in certain species-specific instincts, such as freezing or starting^[73]. Similarly, the inhibition of ACh on DA is also involved in the predication error experiments. As we know, ACh is involved in the conditioned learning, after learning, light will not induce DA release, because ACh dominates and inhibits DA release. Similarly, DA release during feeding signals food reward, the increase in ACh in NAc has a role in the onset of satiation^[74]. This increase in ACh is attenuated with sham feeding where food drained from a gastric fistula after ingestion. Thus the food-induced DA release goes unopposed by ACh. Hoebel and colleagues^[75] suggested that the DA and ACh balance in the NAc may affect motivation, while DA enables a person to start moving, which ACh acts as a control to prevent over-responding and facilitate stopping, this interaction between DA and ACh is well documented in Parkinson's diseases.

The interaction between ACh with 5-HT has also been reported. Selective 5-HT reuptake inhibitor fluoxetine has demonstrated the ability to alleviate behavioral depression in the forced swim test, one of the potential mechanisms is to suppress cholinergic activities in the nucleus accumbens^[76]. Tobacco smoking also supports the relationship between ACh and depression. The depression rates are much higher in smokers, smokers with a history of major depression have a harder time quitting smoking, and patients with depression are at a risk for developing a major depression episode. Smoker also have lower levels of monoamine oxidase A^[77]. Many patients with depression fail to derive sufficient benefits from available treatment options, and with up to a third never reaching remission despite

multiple trials of appropriate treatment. Novel antidepressant agents, and drugs targeting ACh receptors appear to hold promise^[78].

CONCLUSIONS

Ekman devised a list of 5 basic emotions: anger, disgust, fear, happiness, sadness and surprise^[79], which are similar to our model. Robert Plutchik proposed 8 primary emotions: anger, fear, sadness, disgust, surprise, anticipation, trust and joy, and arranged them in a color wheel. He was the first to put anticipation as emotion. The earliest dimensional study of emotion came from Wundt (1897), who identified three dimensions of emotion as pleasant-unpleasant, tension-relaxation, and excitation-calm. Actually his dimension is very similar to our model, except that we put the last two dimensions which are actually overlapping into one dimension. James Russell's proposed two dimensions for emotions: hedonic (pleasure-displeasure) and arousal (rest-activated), which is similar to our model here^[80]. Combined, our two-dimensions model (Figure 1) derived from neuromodulators are very similar to the previous emotional theories. In conclusion, we in this paper propose 4 different kinds of neuromodulators that are the substrates of emotion, which can be made up of 5 kinds of primary emotions: pleasant, unpleasant, (fear and anger), and wanting.

Even though there are many standards for primary emotions, the most important is that they should exclude each other, which means that they should not occur at the same time. Like we talked before, anger and fear never happen in at the same time in a same person, so it is with happiness and sadness. It might also be right with calm and wanting. The second rule is that they should be able to make all of the emotions, like the 7 colors in rainbows. Let us end our paper with an example of the emotional changes in everyday life (Figure 2): life is normally calm, everything is as expected; then something unexpected happens, people first feel scared (fear) and then blame (anger) the reasons for the unexpectancy after fear is gone; then people feel happy or sad depending on whether the thing happened fits for their needs or not. Finally, the thing goes away, and people calm down from the happiness, or feel missing and wanting for the lost thing.



Figure 2 life is normally calm, everything is as expected; then something unexpected happens, people first feel scared (fear) and then blame (anger) the reasons for the unexpectancy after fear is gone; then people feel happy or sad depending on whether the thing happened fits for their needs or not. Finally, the thing passes away, and people calm down from the happiness, or feel missing and wanting for the lost thing.

CONFLICT OF INTERESTS

The Author has no conflicts of interest to declare.

REFERENCES

- 1 LeDoux JE. Emotion: clues from the brain. *Annual review of psychology*. 1995;46:209-35.
- 2 Ortony A, Turner TJ. What's basic about basic emotions? *Psychol Rev*. 1990;97(3):315-31.
- 3 Izard CE. Basic emotions, relations among emotions, and emotion-cognition relations. *Psychol Rev*. 1992;99(3):561-5.
- 4 Ekman P. Are there basic emotions? *Psychol Rev*. 1992;99(3):550-3.
- 5 Schildkraut JJ, Kety SS. Biogenic amines and emotion. *Science*. 1967;156(771):21-37.
- 6 Bozarth MA, Wise RA. Electrolytic microinfusion transducer system: an alternative method of intracranial drug application. *Journal of neuroscience methods*. 1980;2(3):273-5.
- 7 Bozarth MA, Gerber GJ, Wise RA. Intracranial self-stimulation as a technique to study the reward properties of drugs of abuse. *Pharmacology, biochemistry, and behavior*. 1980;13 Suppl 1:245-7.
- 8 Mora F, Ferrer JM. Neurotransmitters, pathways and circuits as the neural substrates of self-stimulation of the prefrontal cortex: facts and speculations. *Behavioural brain research*. 1986;22(2):127-40.
- 9 Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, et al. Relationship between subjective effects of cocaine and DA transporter occupancy. *Nature*. 1997;386(6627):827-30.
- 10 Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R, Chen AD., Dewey SL., Pappas N. Decreased striatal DArgic responsiveness in detoxified cocaine-dependent subjects. *Nature*. 1997;386(6627):830-3.
- 11 Volkow ND, Wang GJ, Fowler JS. Imaging studies of cocaine in the human brain and studies of the cocaine addict. *Annals of the New York Academy of Sciences*. 1997;820:41-54; discussion -5.
- 12 Willuhn I, Wanat MJ, Clark JJ, Phillips PE. DA signaling in the nucleus accumbens of animals self-administering drugs of abuse. *Current topics in behavioral neuroscience*. 2010;3:29-71.
- 13 Redgrave P, Prescott TJ, Gurney K. Is the short-latency DA response too short to signal reward error? *Trends Neurosci*. 1999;22(4):146-51.
- 14 Rada PV, Mark GP, Hoebel BG. DA release in the nucleus accumbens by hypothalamic stimulation-escape behavior. *Brain research*. 1998;782(1-2):228-34.
- 15 Cabib S, Puglisi-Allegra S. Opposite responses of mesolimbic DA system to controllable and uncontrollable aversive experiences. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1994;14(5 Pt 2):3333-40.
- 16 Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275(5306):1593-9.
- 17 Inoue T, Inokuma Y, Watanabe S, Kirino Y. *In vitro* study of odor-evoked behavior in a terrestrial mollusk. *Journal of neurophysiology*. 2004;91(1):372-81.
- 18 Wheeler DC, Morgan R, Thomas DM, Seed M, Rees A, Moore RH. Factors influencing plasma lipid profiles including lipoprotein (a) concentrations in renal transplant recipients. *Transpl Int*. 1996;9(3):221-6.
- 19 Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. "5-HT depression"--a biochemical subgroup within the affective disorders? *Science*. 1976;191(4226):478-80.
- 20 Asberg M, Traskman L, Thoren P. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Archives of general psychiatry*. 1976;33(10):1193-7.
- 21 Banki CM, Arato M. Amine metabolites, neuroendocrine findings, and personality dimensions as correlates of suicidal behavior. *Psychiatry research*. 1983;10(4):253-61.

22. Asberg M, Eriksson B, Martensson B, Traskman-Bendz L, Wagner A. Therapeutic effects of 5-HT uptake inhibitors in depression. *The Journal of clinical psychiatry*. 1986;47 Suppl:23-35.
23. Miller LA. Impulsivity, risk-taking, and the ability to synthesize fragmented information after frontal lobectomy. *Neuropsychologia*. 1992;30(1):69-79.
24. Higley JD, Mehlman PT, Poland RE, Taub DM, Vickers J, Suomi SJ, Linnoila M. CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. *Biological psychiatry*. 1996;40(11):1067-82.
25. Virkkunen M, Nuutila A, Goodwin FK, Linnoila M. Cerebrospinal fluid monoamine metabolite levels in male arsonists. *Archives of general psychiatry*. 1987;44(3):241-7.
26. Pakalnis A, Splaingard M, Splaingard D, Kring D, Colvin A. 5-HT effects on sleep and emotional disorders in adolescent migraine. *Headache*. 2009;49(10):1486-92.
27. Juvancz P. The effect of raphe lesion on sleep in the rat. *Brain research*. 1980;194(2):371-6.
28. Pujol JF, Sordet F, Petitjean F, Germain D, Jouvet M. [Insomnia and cerebral metabolism of 5-HT in cats: study of *in vitro* synthesis and release of 5-HT 18 hours after destruction of the raphe nuclei]. *Brain research*. 1972;39(1):137-49.
29. Monti JM. 5-HT control of sleep-wake behavior. *Sleep medicine reviews*. 2011;15(4):269-81.
30. Fernandez SP, Gaspar P. Investigating anxiety and depressive-like phenotypes in genetic mouse models of 5-HT depletion. *Neuropharmacology*. 2012;62(1):144-54.
31. Dempsey JP, Randall PK, Thomas SE, Book SW, Carrigan MH. Treatment of social anxiety with paroxetine: mediation of changes in anxiety and depression symptoms. *Compr Psychiatry*. 2009;50(2):135-41.
32. Petty F, Kramer G, Wilson L, Jordan S. In vivo 5-HT release and learned helplessness. *Psychiatry research*. 1994;52(3):285-93.
33. Martin P, Gozlan H, Puech AJ. 5-HT₃ receptor antagonists reverse helpless behaviour in rats. *European journal of pharmacology*. 1992;212(1):73-8.
34. Dai JX, Han HL, Tian M, Cao J, Xiu JB, Song NN, Huang Y, Xu TL, Ding YQ, Xu L. Enhanced contextual fear memory in central 5-HT-deficient mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2008;105(33):11981-6.
35. Hendricks TJ, Fyodorov DV, Wegman LJ, Lelutiu NB, Pehek EA, Yamamoto B, Silver J, Weeber EJ, Sweatt JD., Deneris ES. Pet-1 ETS gene plays a critical role in 5-HT neuron development and is required for normal anxiety-like and aggressive behavior. *Neuron*. 2003;37(2):233-47.
36. Savelieva KV, Zhao S, Pogorelov VM, Rajan I, Yang Q, Cullinan E, Lanthorn TH. Genetic disruption of both tryptophan hydroxylase genes dramatically reduces 5-HT and affects behavior in models sensitive to antidepressants. *PloS one*. 2008;3(10):e3301.
37. Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, Schwartz DA, Krishnan KR, Caron MG. Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. *Neuron*. 2005;45(1):11-6.
38. Fukui M, Rodriguiz RM, Zhou J, Jiang SX, Phillips LE, Caron MG, Wetsel WC. Vmat2 heterozygous mutant mice display a depressive-like phenotype. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2007;27(39):10520-9.
39. Narboux-Neme N, Sagne C, Doly S, Diaz SL, Martin CB, Angegard G, Martres MP, Giros B, Hamon M, Langumey L, Gaspar P, Mongeau R. Severe 5-HT depletion after conditional deletion of the vesicular monoamine transporter 2 gene in 5-HT neurons: neural and behavioral consequences. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011;36(12):2538-50.
40. Izard CE. Four systems for emotion activation: cognitive and non-cognitive processes. *Psychol Rev*. 1993;100(1):68-90.
41. Itoi K, Sugimoto N. The brainstem noradrenergic systems in stress, anxiety and depression. *Journal of neuroendocrinology*. 2010;22(5):355-61.
42. Morilak DA, Barrera G, Echevarria DJ, Garcia AS, Hernandez A, Ma S, Petre CO. Role of brain NE in the behavioral response to stress. *Progress in neuro-psychopharmacology & biological psychiatry*. 2005;29(8):1214-24.
43. Bremner JD, Krystal JH, Southwick SM, Charney DS. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse*. 1996;23(1):39-51.
44. Bremner JD, Krystal JH, Southwick SM, Charney DS. Noradrenergic mechanisms in stress and anxiety: I. Preclinical studies. *Synapse*. 1996;23(1):28-38.
45. Itoi K. Ablation of the central noradrenergic neurons for unraveling their roles in stress and anxiety. *Annals of the New York Academy of Sciences*. 2008;1129:47-54.
46. Rasmussen K, Morilak DA, Jacobs BL. Single unit activity of locus coeruleus neurons in the freely moving cat. I. During naturalistic behaviors and in response to simple and complex stimuli. *Brain research*. 1986;371(2):324-34.
47. Redmond DE, Jr., Huang YH, Snyder DR, Maas JW. Behavioral effects of stimulation of the nucleus locus coeruleus in the stump-tailed monkey *Macaca arctoides*. *Brain research*. 1976;116(3):502-10.
48. LeDoux J. Fear and the brain: where have we been, and where are we going? *Biological psychiatry*. 1998;44(12):1229-38.
49. Gallagher M, Kapp BS, Musty RE, Driscoll PA. Memory formation: evidence for a specific neurochemical system in the amygdala. *Science*. 1977;198(4315):423-5.
50. Weiskrantz L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *Journal of comparative and physiological psychology*. 1956;49(4):381-91.
51. Graeff FG, Silveira MC, Nogueira RL, Audi EA, Oliveira RM. Role of the amygdala and periaqueductal gray in anxiety and panic. *Behavioural brain research*. 1993;58(1-2):123-31.
52. Boadle-Biber MC, Corley KC, Graves L, Phan TH, Rosecrans J. Increase in the activity of tryptophan hydroxylase from cortex and midbrain of male Fischer 344 rats in response to acute or repeated sound stress. *Brain research*. 1989;482(2):306-16.
53. Azmitia EC, Liao B, Chen YS. Increase of tryptophan hydroxylase enzyme protein by dexamethasone in adrenalectomized rat midbrain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1993;13(12):5041-55.
54. Singh VB, Onaivi ES, Phan TH, Boadle-Biber MC. The increases in rat cortical and midbrain tryptophan hydroxylase activity in response to acute or repeated sound stress are blocked by bilateral lesions to the central nucleus of the amygdala. *Brain research*. 1990;530(1):49-53.
55. Jacobs BL. 5-HT and behavior: emphasis on motor control. *The Journal of clinical psychiatry*. 1991;52 Suppl:17-23.
56. Jacobs BL, Fornal CA. Activity of brain serotonergic neurons in the behaving animal. *Pharmacol Rev*. 1991;43(4):563-78.
57. Maswood S, Barter JE, Watkins LR, Maier SF. Exposure to inescapable but not escapable shock increases extracellular levels of 5-HT in the dorsal raphe nucleus of the rat. *Brain research*. 1998;783(1):115-20.
58. Izard CE. Emotion theory and research: highlights, unanswered questions, and emerging issues. *Annual review of psychology*. 2009;60:1-25.
59. Delgado MR, Gillis MM, Phelps EA. Regulating the expectation of reward via cognitive strategies. *Nature neuroscience*. 2008;11(8):880-1.
60. Ekman P. Emotions inside out. 130 Years after Darwin's "The Expression of the Emotions in Man and Animal". *Annals of the New York Academy of Sciences*. 2003;1000:1-6.
61. Eggermann E, Feldmeyer D. Cholinergic filtering in the recurrent excitatory microcircuit of cortical layer 4. *Proceedings of the National Academy of Sciences of the United States of America*.

- 2009;106(28):11753-8.
62. Gullledge AT, Park SB, Kawaguchi Y, Stuart GJ. Heterogeneity of phasic cholinergic signaling in neocortical neurons. *Journal of neurophysiology*. 2007;97(3):2215-29.
 63. Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet*. 1972;2(7778):632-5.
 64. Janowsky DS. Serendipity Strikes Again: Scopolamine as an Antidepressant Agent in Bipolar Depressed Patients. *Current psychiatry reports*. 2011.
 65. Janowsky DS, el-Yousef MK, Davis JM. Acetylcholine and depression. *Psychosomatic medicine*. 1974;36(3):248-57.
 66. Mearns J, Dunn J, Lees-Haley PR. Psychological effects of organophosphate pesticides: a review and call for research by psychologists. *Journal of clinical psychology*. 1994;50(2):286-94.
 67. Houlihan WJ, Kelly L, Pankuch J, Koletar J, Brand L, Janowsky A, et al. Mazindol analogues as potential inhibitors of the cocaine binding site at the DA transporter. *J Med Chem*. 2002;45(19):4097-109.
 68. Overstreet DH. The Flinders sensitive line rats: a genetic animal model of depression. *Neuroscience and biobehavioral reviews*. 1993;17(1):51-68.
 69. Dilsaver SC, Alessi NE. Chronic inescapable footshock produces cholinergic system supersensitivity. *Biological psychiatry*. 1987;22(7):914-8.
 70. Mobley PL, Sulser F. Adrenal steroids affect the NE-sensitive adenylyl cyclase system in the rat limbic forebrain. *European journal of pharmacology*. 1980;65(2-3):321-2.
 71. McGaugh JL, Cahill L. Interaction of neuromodulatory systems in modulating memory storage. *Behavioural brain research*. 1997;83(1-2):31-8.
 72. Packard MG, Cahill L, McGaugh JL. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proceedings of the National Academy of Sciences of the United States of America*. 1994;91(18):8477-81.
 73. Samson RD, Frank MJ, Fellous JM. Computational models of reinforcement learning: the role of DA as a reward signal. *Cogn Neurodyn*. 2010;4(2):91-105.
 74. Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens DA repeatedly and eliminates the acetylcholine satiety response. *Neuroscience*. 2006;139(3):813-20.
 75. Hoebel BG, Avena NM, Rada P. Accumbens DA-acetylcholine balance in approach and avoidance. *Curr Opin Pharmacol*. 2007;7(6):617-27.
 76. Chau DT, Rada PV, Kim K, Kosloff RA, Hoebel BG. Fluoxetine alleviates behavioral depression while decreasing acetylcholine release in the nucleus accumbens shell. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011;36(8):1729-37.
 77. Dani JA, Harris RA. Nicotine addiction and comorbidity with alcohol abuse and mental illness. *Nature neuroscience*. 2005;8(11):1465-70.
 78. Philip NS, Carpenter LL, Tyrka AR, Price LH. Nicotinic acetylcholine receptors and depression: a review of the preclinical and clinical literature. *Psychopharmacology*. 2010;212(1):1-12.
 79. Ekman P, Friesen WV. Nonverbal leakage and clues to deception. *Psychiatry*. 1969;32(1):88-106.
 80. Russell JA. Core affect and the psychological construction of emotion. *Psychol Rev*. 2003;110(1):145-72.

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