

## Review

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# Neuromodulation, Emotional Feelings and Affective Disorders

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## ABSTRACT

*Affective disorders such as anxiety, phobia and depression are a leading cause of disabilities worldwide. Monoamine neuromodulators are used to treat most of them, with variable degrees of efficacy. Here, we review and interpret experimental findings about the relation of neuromodulation and emotional feelings, in pursuit of two goals: (a) to improve the conceptualisation of affective/emotional states, and (b) to develop a descriptive model of basic emotional feelings related to the actions of neuromodulators. In this model, we hypothesize that specific neuromodulators are effective for basic emotions. The model can be helpful for mental health professionals to better understand the affective dynamics of persons and the actions of neuromodulators - and respective psychoactive drugs - on this dynamics.*

**Key Words:** *Affective Disorders; Emotions; Feelings; Monoamines; Neuromodulators*

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## Introduction

Scientists concerned with human health have not been able to reach a consensus about the aetiology and treatment of affective disorders, and whether they have different physiological markers (Bos *et al.*, 2013<sup>[8]</sup>; Gruber *et al.*, 2011<sup>[36]</sup>; Lipp *et al.*, 2014<sup>[61]</sup>; Terry *et al.*, 2013<sup>[100]</sup>). Looking for an advance in this field of research and therapy, we discuss the scientific approach to affective disorders and their putative brain correlates. First, we discuss conceptual issues and the usage of tools as the 'conceptual space' framework (Gardenfors, 2000<sup>[32]</sup>). Second, we discuss the physical-biological structure (transmitters, modulators, receptors) experimentally related to the phenomena. Third, we discuss the possibility of an integrative model of four basic emotional feelings and related neuromodulators involved in affective disorders.

A clarification between neurotransmission and neuromodulation would be in order before we proceed further. Regarding the neurobiological terminology used here, and how we understand it, transmission of sensory and endogenous information in the thalamo-cortical system is primarily dependent on Glutamate (Glu), an excitatory transmitter present in the whole brain, and is balanced by inhibitory transmitter gamma-aminobutyric acid (GABA). The use of Glu in psychiatry, for the treatment of schizophrenia, is very recent. Inhibitory psychoactive drugs, in contrast, are widely used for anxiety disorders.

On the one hand, we use the term neuromodulation to refer to endogenous macromolecules or exogenous psychoactive drugs that modulate the balance of Glu and GABA, defining general mood states of the person under study; in this sense, they could be called 'mood-actors'. Neuromodulators have been the main players in biological psychiatry in the treatment of affective disorders. On the other hand, we do not use the term neuromodulator to refer to neuropeptides, which are brain hormones that produce very specific effects. Neuropeptides are also smaller macromolecules that in some cases can cross the brain-blood barrier.

Another issue we need to clarify is why use the term 'emotional feelings', which may appear like a tautology. As explained in more detail in the next section, our use of the term 'feeling' is more restricted than our use of 'emotion'. All feelings are emotions, but not all emotions are feelings. Feelings are considered to be the conscious, subjective aspect of emotions. In affective disorders, emotional feelings are the conscious subjective experiences of the suffering person. These conscious experiences are classified in categories such as anxiety and mood disorders, depending on the type of emotional feeling that is involved.

## Concepts of Affect and Emotion

In this section, we address conceptual issues fundamental to the scientific study of emotions. The term 'emotion' has been used in neuroscience to describe a wide range of phenomena. Emotions have been considered to have both conscious and unconscious aspects (Ledoux, 1996<sup>[55]</sup>). Looking for a more detailed account, Panksepp (Panksepp, 1998<sup>[77]</sup>), Damasio (Damasio, 1999<sup>[19]</sup>) and Pereira Jr (Pereira Jr., 2013<sup>[78]</sup>), among others, have made an analysis of the concept.

Panksepp (1998<sup>[77]</sup>) used the term 'core affect' to refer to basic states common to most vertebrate species, being triggered by the release of specific hormones or neuropeptides. In this view, basic sensations as hunger and satiation would be called 'core affects'.

Damásio (1999<sup>[19]</sup>) distinguishes feelings from emotions. Emotions are psycho-physiological processes related to the state of the whole body by means of somatic markers. Feelings are mental states experienced from the first-person perspective, that is, experienced by a subject with a sense of self. Brain correlates of feeling partially overlap with, but are not identical to, brain correlates of emotion (Houde *et al.*, 2001<sup>[42]</sup>). For instance, in the case of emotional processes as facial expressions, the motor system is involved in their generation, but probably not in the generation of the corresponding feeling (e.g., feeling sad, or happy, or surprised, or terrified). One reason for this distinction is that the same pyramidal neurons of the motor system are involved in several facial expressions, irrespective of the associated feeling.

Damásio (1999<sup>[19]</sup>) further states, based on his own research that both feelings and emotions can occur unconsciously. This claim is well-supported for emotions since this concept includes somatic and behavioural processes that escape conscious mentation or control, e.g., the increase of skin conductance and cortisol release. However, we cannot find in his publications evidence to support the claim for the existence of unconscious feelings. How could feelings be unconscious? It seems that if a feeling is not conscious, then it is not experienced at all.

Pereira Jr. (2013<sup>[78]</sup>) alternatively proposed that a major difference between emotions and feelings is 'while the existence of feelings always implies some (even the slightest) degree of consciousness being instantiated, emotions - in the sense of somatic or motor activities - are not necessarily accompanied by conscious experiences' (Pereira Jr., 2013<sup>[78]</sup>). There are many lines of evidence for the existence of unconscious emotions, as reviewed by LeDoux (1996<sup>[55]</sup>); for instance, subliminal perception triggering activity of the autonomous nervous system.

Emotion can be triggered by conscious feelings but can also exist without such feelings. In this regard, chills on the spine, facial expressions and actions

on an external material are components of emotional processes (e.g., the most pungent paintings of Edvard Munch, as 'The Scream', which is frequently used in psychiatry to illustrate the panic disorder; see [http://www.en.wikipedia.org/wiki/The\\_Scream](http://www.en.wikipedia.org/wiki/The_Scream)).

Pereira Jr. (2013<sup>[78]</sup>) distinguishes two kinds of feeling: 'a "sensitive feeling" refers to the experience of states of the body, e.g., feeling hunger and thirst, heat or cold, and pain or pleasure ...an "affective feeling" refers to experiences elicited by the content of information, e.g., feeling happy or sad about something, interested in or bored of something, loving or hating something' (Pereira Jr., 2013<sup>[78]</sup>). In this conceptualisation, sensitive feelings would correspond to Panksepp's 'core affects', while affective feelings would be mostly those related to the interaction with the physical and social environment, which are often altered in affective disorders.

In this paper, we use the term 'emotional feeling' to refer to the conscious (sensitive and affective) feelings elicited by somatic emotional processes. We further assume that emotional feelings have whole-body correlates. In other words, their biological correlates are not restricted to the brain. We assume that the state of somatic systems, as the gut, heart and nervous system, participate in the determination of emotional feelings. Although the brain is surely the place of the body where signals from different parts are integrated composing conscious episodes, we observe that the brain does not work alone, but in collaboration with all other parts of the body. For instance, ingestion of a toxic substance activates serotonergic receptors in the gut system, causing pain. The feeling of pain is a product of the conjoint operation of the brain and gut systems. For this reason, in the below reasoning, we take into account also neuromodulators that act on somatic systems outside the brain.

In the above theoretical perspective, affective disorders can be conceived as disorders of the dynamics of emotional feelings, e.g., the abnormal dominance of melancholy in general depression, or of anxiety in obsessive-compulsive disorders. To improve our understanding of these disorders, it is necessary to conceptualise human emotional feelings, their normal and abnormal dynamic patterns.

## The One-Gradient Space of Emotional Feelings

How to map the main kinds of emotional feeling typical to the human species, making possible the identification of each person's affective dynamics, and then improving the diagnosis and therapy of affective disorders?

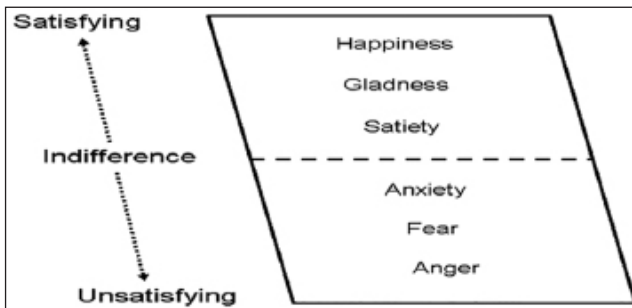
Panksepp (1998<sup>[77]</sup>) departs from the assumption that emotional feelings arise from neurobiological events that mediate instinctual action patterns; they

'sustain some unconditioned behavioural tendencies, and play a key role in the unconscious constitution of new behaviours through providing mechanisms that allow organisms to categorize world events efficiently so as to control future behaviour . . . (they) are triggered by the arousal of various subcortical circuits, located in evolutionarily ancient areas of the mammalian brain' (Almada, Pereira Jr. and Carrara-Augustenberg, 2013<sup>[1]</sup>).

Panksepp's model for affective neuroscience is based on four 'basic emotional systems' (Panksepp, 1998<sup>[77]</sup>). The seeking-system is the neural network that provides us efficient ways to elaborate energetic and goal-directed searching actions. 'The rage-system is easily aroused by thwarting and frustrations, helping us to defend ourselves and prompting behaviour when we are irritated or restrained. The fear-system tries to minimize the probability of bodily destruction. This specific circuit arose during animal evolution and serves to reduce pain. Finally, separation distress panic is a neural system that is very important in the constitution and elaboration of social-emotional processes related to attachment' (Almada, Pereira Jr and Carrara-Augustenberg, 2013<sup>[1]</sup>).

Based on the above categories, we sketched the one-gradient conceptual space of emotional feelings [Figure 1], where Panksepp's basic emotions can be located in a single line (from Unsatisfying to Satisfying) according to their valence. This illustration does not allow, or intend to provide for, a precise location of emotional feelings in the conceptual space; for instance, it does not analyse the features of different satisfactory feelings, such as satiety, gladness and happiness.

In Panksepp's work, the above emotional states are putatively generated mostly by means of the action of neuropeptides. These molecules carry very



**Figure 1: One-Gradient Conceptual Space of Emotional Feelings.**

The affective dynamics of a human individual (and possibly other animal species) ranges from satisfying to unsatisfying states, for which there are several terms in natural language, such as "happiness", "satiety", "anxiety" and "anger" (Figure created by Alfredo Pereira Jr. from a textbook sketch made by Rocha, 1999)<sup>[86]</sup>

specific actions [Table 1] while the combined actions of neuromodulators elicit general mood states.

In order to account for the dynamics of emotional feelings in the generation of affective disorders, we look for a framework featuring the actions of neuromodulators. The questions may be asked: Why is this needed? What is problematic about Panksepp's approach?<sup>[77]</sup> How does our framework correct that? How are 'neuromodulators' different from 'neuropeptides'?

The need of considering neuromodulation is evident in the psychiatric area, where drugs that modulate brain activity are largely used to treat affective disorders. In Panksepp's approach, his conception about the generation of emotional feelings is restricted to instinctive processes. Their response is not co-determined by interaction with the physical and social environment. Each neuropeptide at the left side of the table always produces the corresponding emotional feeling listed on the right side. When taking neuromodulation

**Table 1: Neuropeptide modulation and affective/emotional contents: Discoveries from 1935 to 1985 (A historical note, without updates, aimed to show some of the factors that combine to produce emotional feelings. Table created by Alfredo Pereira Jr. using data from Panksepp, 1998)**

Neuropeptide	Emotional feelings
Substance P	Pain and anger
Angiotensin	Thirst
Oxytocin	Orgasm, maternal feelings
ACTH	Stress
Insulin	Energy
Vasopressin	Male sexual arousal, dominance
Bradykinin	Pain
CCK	Satiety, panic
Prolactin	Maternal and social feelings
TRH	Playfulness
LH-RH	Female sexual arousal
Bombesin	Satiety
Neurotensin	Seeking
Enkephalin	Pain, pleasure
Endorphin	Pain, pleasure
DSIP	Sleepiness
Dynorphin	Hunger
CRF	Panic, anxiety
NPY	Hunger

ACTH: Adrenocorticotrophic hormone, CCK: Cholecystokinin, TRH: Thyrotropin-releasing hormone, LH-RH: Luteinizing hormone-releasing hormone, DSIP: Delta-sleep inducing peptide, CRF: Corticotropin-releasing factor, NPY: Neuropeptide Y

into consideration, we can account for plastic responses of the system to dynamic changes in the environment. Neuromodulators are not as specific as neuropeptides, and – more important – they seem to operate in synergy, as we propose in this paper. In the psychiatric clinic, the medical professional needs to think of different possible combinations of neuromodulation drugs, in search of the best option of treatment for the suffering person in her environment. For instance, it is well-known that inappropriate combination of drugs may induce a person recovering from major depression to commit suicide.

There is a complex temporal dynamics of psychological processes that correlates well with the underlying neuromodulation processes and cannot be addressed by consideration of instinctive responses alone. The functional difference between instinctive and plastic responses corresponds to structural differences between neuropeptides and neuromodulators. The former are smaller molecules that bind to sites of smaller receptors that have fixed functions, while the latter are more complex macromolecules that bind with more complex receptors, capable of acquiring a larger number of different configurations and carrying more flexible functions.

Both approaches, based on neuropeptides and neuromodulators, are possibly complementary and should be combined. However, a broader synthesis cannot be accomplished here; we look forward to completing it in another theoretical work. Using the Gardenfors (2000<sup>[32]</sup>) conceptual space tool, we can envisage a complex state space of emotional feelings, containing a first level composed of two dimensions that correspond to the one-gradient structure depicted in Figure 1. Parallel to this plane, a second level of organisation can be plotted, containing the domain of neuromodulation that we discuss and model below. After both levels are constructed, their connections can be traced; for instance, happiness would be closer to satisfying and sadness to unsatisfying, although they are not identical. There are many plastic ways to find satisfaction. Happiness is one of the most efficacious, but not the only one; in some contexts – as, e.g., mourning – people may feel satisfied to be sad.

## Neuromodulators and Emotional Feelings

Studies of the neural basis of emotional feelings have a long history within neuroscience and remain an active field of experimental and theoretical research. The identification of the limbic system as central to emotional processing helped to find important structures involved in primary emotions. With the development of drugs for affective disorders, monoamines were identified as factors influencing emotional processing (Cohen and Sclar, 2012<sup>[16]</sup>; Fakra *et al.*, 2010<sup>[29]</sup>; Schildkraut and Kety, 1967<sup>[95]</sup>; Timotijevic *et al.*, 2012<sup>[101]</sup>), but there is no general agreement on their proposed effects. For example, antidepressant drugs affect almost all these neuromodulators and are

used for almost all affective disorders such as anxiety, phobia and depression among others.

In this section, we briefly review differences between monoamines (Dopamine [DA], Serotonin: 5-hydroxytryptamine [5-HT] and norepinephrine [NE]), as well as acetylcholine (ACH), and propose that they underlie four basic emotional feelings: DA: Pleasure, 5-HT: Displeasure, NE: Fear/anger, and ACH: Relaxation/calmness.

### **Dopamine: Pleasure**

Dopamine has been related to brain rewarding processes since 1980, when the hedonic hypothesis was formulated (Bozarth *et al.*, 1980<sup>[9]</sup>; Bozarth and Wise, 1980<sup>[10]</sup>). DA is a rewarding signal for salient stimuli such as food, sex and other needs. The reward depends on the needs of subjects, which were independently classified by Maslow (Maslow, 1943<sup>[63]</sup>).

Many pharmacological and behavioural studies on intracranial self-stimulation established the important role of medial prefrontal rewarding DA systems in positively motivated behaviour (Mora and Ferrer, 1986<sup>[70]</sup>). Drug addiction reshapes the reward system by affecting DA release and reuptake; decreased striatum DA responses were reported in detoxified cocaine abusers (Volkow *et al.*, 1997<sup>[103]</sup>). Individuals with a history of abuse of alcohol, cocaine, heroin, or methamphetamine display lower levels of DA receptor binding compared to non-abusers (Volkow *et al.*, 1997<sup>[104]</sup>; Diana, 2011<sup>[24]</sup>; Ron and Jurd, 2005<sup>[87]</sup>).

Over the past decades, theories concerning the role of midbrain DA on behaviour have changed. Although there is no doubt that DA is involved in hedonic experiences, its effects can be divided into more detailed aspects of behaviour (Redgrave *et al.*, 1999<sup>[85]</sup>; Willuhn *et al.*, 2010<sup>[106]</sup>). For example, global DA depletion does not impair the hedonic response to a primary reward such as preference for sucrose over water. These observations have led to considering the contribution of DA to motivated behaviour towards desired goals.

Mesolimbic DA is also involved in aversively motivated behaviours. Medial hypothalamic stimulation, which has been considered to cause a primary aversive state, causes a significant decrease in extracellular DA (Rada, Mark, and Hoebel, 1998<sup>[83]</sup>). However, when rats press a lever to escape the stimulation, DA levels in the nucleus accumbens (NAc) increased instead. This is similar to a finding by (Cabib and Puglisi-Allegra, 1994<sup>[111]</sup>) that when animals were allowed to control a painful shock experience, NAc DA metabolites increased.

Schultz *et al.* (1997<sup>[96]</sup>) studied the role of DA for reward and prediction in conditioning experiments, proposing that DA is a signal of salience of the



stimulus; for example, DA neurons are activated when animals touch a small morsel of apple or receive a small quantity of fruit juice as reward. These phased activations do not discriminate between different types of rewarding stimuli, but aversive stimuli like air puffs to the hand or drops of saline to the mouth do not cause the same transient activations.

The unconditioned reaction can be connected to other stimuli.<sup>[13]</sup> For example, if the presentation of light is consistently followed by food, a rat will learn that 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 expected (Schultz *et al.*, 1997<sup>[96]</sup>). It appears therefore that learning is driven by deviations or 'errors' between the predicted time and amount of rewards. Hence, the authors proposed that DA encodes expectations about external stimuli or reward, especially when it is uncertain or deviation or error (predication error).

From the above experimental evidence, we hypothesize that DA is a signal for salient stimuli such as food, sex and other needs, participating in the generation of the feeling of pleasure.

### **Serotonin (5-hydroxytryptamine): Displeasure**

5-hydroxytryptamine has been related to depression for decades, mostly because of being targeted by antidepressant drugs; however, most prescribed drugs for depression do alter 5-HT levels. 5-HT is mostly released in the gut (about 90% of body release), where enterochromaffin cells release it in response to noxious substances in the food, making the gut move faster, thus causing vomiting or diarrhoea. Plant seeds with 5-HT exploit this reaction to speed the passage of seeds through the digestive tract. Animals such as wasps and scorpion can induce pain by means of 5-HT and other substances present in their venom.

Even in phylogenetically distant animals like the mollusc, 5-HT release is involved in the regulation of avoidance behaviour (Inoue *et al.*, 2004<sup>[44]</sup>). Drugs that block 5-HT receptors make the body unable to shut off appetite and are associated with increased weight gain (Wheeler *et al.*, 1996<sup>[105]</sup>). People with low 5-HT are at risk of showing aggressive behaviour, not caring about punishments (LeMarquand *et al.*, 1998<sup>[57]</sup>).

It was found that depressed subjects with low cerebrospinal fluid (CSF) concentrations of a 5-HT metabolite were found to display a history of suicide attempts (Roy *et al.*, 1990<sup>[88]</sup>); Engstrom *et al.*, 1999<sup>[28]</sup>; Jokinen *et al.*, 2007<sup>[53]</sup>; Lidberg *et al.*, 1985<sup>[59]</sup>; Moberg *et al.*, 2011<sup>[68]</sup>). The correlation between low CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations and increased risk for suicide has become one of the most reproducible findings in biological psychiatry

(Engstrom *et al.*, 1999<sup>[28]</sup>; Jokinen *et al.*, 2007<sup>[53]</sup>; Lidberg *et al.*, 1985<sup>[59]</sup>; Moberg *et al.*, 2011<sup>[68]</sup>).

Some other studies have suggested that the deficits in 5-HT functioning within the frontal cortex may underlie other behaviour disturbances, such as impaired impulse control and increased incidence of violent episodes (Higley *et al.*, 1996<sup>[39]</sup>; Miller, 1992<sup>[67]</sup>, Holmes *et al.*, 2002<sup>[41]</sup>; Siegel *et al.*, 2007<sup>[98]</sup>).

Some studies even suggested that low 5-HIAA in the CSF is a marker for the predisposition to a wide array of psychopathological problems such as impulse control, suicide, impulsive fire setting, violent criminal behaviour, alcohol intake and dependence (Plutchik, 1962<sup>[82]</sup>, Virkkunen *et al.*, 1987<sup>[102]</sup>; Carlberg *et al.*, 2009<sup>[14]</sup>).

In the central nervous system (CNS), 5-HT is mostly produced by neurons in the raphe nuclei and released into the extracellular space between neurons in medial prefrontal cortex, amygdala and hippocampus. It is involved in appetite, sleep and mood (Pakalnis *et al.*, 2009<sup>[75]</sup>). Opinion on these functions has been revised in the past few years. One of the main arguments related to insomnia was based on the destruction of the midbrain raphe nuclei in the cat (Saponjic, 2011<sup>[91]</sup>); but it is currently accepted that 5-HT predominantly promotes wakefulness and inhibits rapid eye movement (REM) sleep (Monti, 2011<sup>[69]</sup>), because the activity of serotonergic neurons of the dorsal raphe nuclei decreases from waking through slow wave sleep to REM sleep. Only under some circumstances does it contribute to increase in sleep propensity (Monti, 2011<sup>[69]</sup>).

5-hydroxytryptamine may indirectly act as a tranquilliser. Tryptophan, which is easily converted to 5-HT in the body, is used as a tranquilliser; and it has been proved that 5-HT is involved in the biology of torpor and hibernation, and inhibits mitochondrial respiration. Abundant evidence points to a decrease of 5-HTergic activity in anxiety, phobias, panic attacks, post-traumatic stress, and depression disorders based on effects of treatments that enhance 5-HT. The most popular kind of antidepressant increases the action of 5-HT in the brain; however, it has been difficult to establish a primary role for 5-HT deficiency in the above diseases (Fernandez and Gaspar, 2012<sup>[30]</sup>).

Selective 5-HT reuptake inhibitors may also have depression-like side effects, such as apathy, nausea/vomiting, drowsiness, weight loss and diminished libido. Actually, these drugs also affect other modulators (DA, NE); for example, in the first generation of antidepressants, the monoamine oxidase inhibitors had a similar effect on all catecholamines. Pharmaceutical companies have been looking for 5-HT-specific reuptake inhibitors. However, while it is true that these drugs increase the actions of 5-HT, it is hard to find their effects on depression. 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 (Dempsey *et al.*, 2009<sup>[22]</sup>). Injecting 5-HT or increasing its activity can cause sedation and helplessness.<sup>[48]</sup> Learned helplessness, a behavioural depression caused by exposure to inescapable stress, is considered to be an animal model of human depressive disorder. Cortical 5-HT excess is causally related to the development of learned helplessness (Petty *et al.*, 1994<sup>[80]</sup>), and learned helplessness patients have high levels of 5-HT (Kobayashi *et al.*, 2008<sup>[54]</sup>; Petty, Kramer and Moeller, 1994<sup>[79]</sup>; Petty *et al.*, 1994<sup>[80]</sup>).

Chemicals that antagonize 5-HT do seem to function as antidepressants (Martin, Gozlan and Puech, 1992<sup>[62]</sup>). 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 (Dai *et al.*, 2008<sup>[18]</sup>). The major benefit of 5-HT drugs seems to be alleviating anxiety.

Genetic studies also support this viewpoint. Pet1 is specifically expressed in the 5-HT neurons and directly activates the transcription of genes implicated in the serotonergic machinery.<sup>[73]</sup> Compared to WT and Pet +/- littermates, Pet -/- mice have an 80% reduction in 5-HT tissue levels, with no significant changes in the levels of DA (Hendricks *et al.*, 2003<sup>[38]</sup>). These mice showed normal ambulatory activity in a novel arena; however, they explored more the aversive areas, which suggests lacking of a dislike marker due to low 5-HT. In addition, these mice showed increased levels of aggression as measured by the resident-intruder assay (Hendricks *et al.*, 2003<sup>[38]</sup>).

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 catalysing this reaction. Tph2 is exclusively expressed in the 5-HT neurons of the raphe nuclei. Genetic deletion of Thp2 was obtained in several groups. The depressive-like behaviour of the Thp2 -/- mice was evaluated (Savelieva *et al.*, 2008<sup>[94]</sup>), which finds that these mice spent less time immobile in the test, a result that is suggestive of an antidepressant effect.

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 died within a few days after birth (Zhang *et al.*, 2005<sup>[107]</sup>). In contrast, heterozygote Vmat2 +/- mice, having a 34% decrease in brain 5-HT, were viable and showed normal growth rate and behaviour. These animals also showed a significant reduction in the level of DA 42% and NE, 23%. Interestingly, they showed pronounced depressive-like phenotype characterised by increased immobility (Fukui *et al.*, 2007<sup>[31]</sup>). 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 (Narboux-Neme *et al.*, 2011<sup>[72]</sup>). No depression-like phenotype was observed; instead they showed less latency to reach out for the food pellet in a novelty suppressed feeding test, suggesting an anxiolytic-like phenotype.

Overall, both pharmacological and genetic studies reviewed above suggest that 5-HT action is related to generation of the feeling of displeasure.

### **Norepinephrine: Fear/anger**

An event is anticipated (expected) or not anticipated (surprising). If what happens was anticipated, people feel calm; if it happens surprisingly, the first reaction is to be scared and angry. For example, the door was knocked very loudly while you were focusing on your reading; the first reaction is that you become scared, and then angry. After opening the door, you may feel happy (if the person knocking the door is someone you like) or sad (if the person is not liked). The neuromodulator underlying both fear and anger is NE.

In the peripheral autonomous nervous system, NE acts as a sympathetic neurotransmitter. Together with hypothalamic-pituitary-adrenal hormones, NE induces the stress that underlies '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 stress. It might also be involved in anxiety disorders, especially in panic/fear disorders (Itoi and Sugimoto, 2010<sup>[46]</sup>).

Norepinephrine release induces fight/anger or flight/fear, which are early evolutionary adaptations to allow better coping with dangerous and unexpected situations. 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. These are twin emotions supported by NE release.

Norepinephrine is released from the locus coeruleus (LC) in the case of stressful events to keep the brain alert to the unexpected stimuli and inhibit irrelevant stimuli, a function that has been described as increasing 'signal to noise' rate in the afferents<sup>[23]</sup> (Morilak *et al.*, 2005<sup>[71]</sup>; Avery *et al.*, 2012<sup>[5]</sup>; George *et al.*, 2013<sup>[33]</sup>).

The LC is the largest NE nucleus in the brain, projecting axons to almost all brain regions. Many studies have been conducted to show its implication in sleep, attention and alertness, anxiety and stress response (Bremner *et al.*, 1996a<sup>[11]</sup>, 1996b<sup>[12]</sup>; Itoi, 2008<sup>[45]</sup>). Robust activation of the LC has been reported

after stressful stimuli in cats: an increase in firing was observed following exposure to noxious air puff stimuli or visual threat (Rasmussen, Morilak, and Jacobs, 1986<sup>[84]</sup>). Electrical stimulation of LC resulted in behaviours observed in fearful or threatening situations in the wild (Levine, Litto, and Jacobs, 1990<sup>[58]</sup>; Sara and Bouret, 2012<sup>[92]</sup>).

It has been recognised that the amygdala plays a prominent role in stress-elicited fear and anxiety (LeDoux, 1998<sup>[56]</sup>). Electrical stimulation of the amygdala promotes stress-like behavioural and autonomous reactions, whereas ablation shows a marked increase of tameness, loss of motivation, decrease of fear response to aversive stimuli and a more rapid extinction of conditioned avoidance responses acquired preoperatively (Shumake *et al.*, 2010<sup>[97]</sup>). NE and DA may be released together to induce anger and aggressive behaviours. The interaction between NE and 5-HT is less documented. Serotonergic neurons in the raphe nuclei project to fear-related amygdala areas (Graeff *et al.*, 1993<sup>[35]</sup>; Asan, Steinke, and Lesch, 2013<sup>[3]</sup>).

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. We can conjecture that at low levels of 5-HT people are likely to feel more anger when surprised, inducing impulsive behaviours, violent or aggressive. Loud noise increases midbrain tryptophan hydroxylase activity (Boadle-Biber *et al.*, 1989<sup>[7]</sup>; Azmitia, Liao, and Chen, 1993<sup>[6]</sup>), but is blocked by a lesion of the central amygdala (Singh *et al.*, 1990<sup>[99]</sup>; Armbruster *et al.*, 2010<sup>[2]</sup>).

Within the circuits of fear, it has been proposed that central serotonergic activity plays a crucial role by enhancing fear through the raphe nuclei-amygdala pathway (Graeff *et al.*, 1993<sup>[35]</sup>; Ling *et al.*, 2009<sup>[60]</sup>; Goel *et al.*, 2014<sup>[34]</sup>). Serotonergic cells in raphe nuclei firing activity rises with restraint and confrontation (Jacobs, 1991<sup>[49]</sup>; Jacobs and Fornal, 1991<sup>[50]</sup>; Ling *et al.*, 2009<sup>[60]</sup>; Goel *et al.*, 2014), and 5-HT levels rise during inescapable shock treatment but not during escapable shocks (Maswood *et al.*, 1998<sup>[64]</sup>), when DA is released. Considering these dynamical aspects of emotion, there is uncertainty regarding whether a stimulus will predict threat or reward.

In summary, NE release has been experimentally related to 'fight or flight' behaviours, inducing the emotional feelings of fear and anger.

### **Acetylcholine: Calmness/willingness**

Although there are few reports about cholinergic involvement in emotional feelings, ACH is a major player in the affective space since it sets the pace for cognitive operations that stabilize affective drives. In the peripheral nervous system, ACH acts as a parasympathetic neurotransmitter, being 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. In the CNS, ACH can boost cognitive functions; its uptake inhibitors have been used for Alzheimer's disease. It might, therefore, be conceived as the cognitive part of emotion, regulating the expectation of rewards (Delgado, Gillis, and Phelps, 2008<sup>[21]</sup>).

The opposite emotional feelings for fear/anger are calmness/willingness, or 'cholinergic emotions'. Darwin used related words in his book about emotions (Ekman, 2003<sup>[27]</sup>). He found that even bees get angry and described angry dogs as retracting upper lips, exposing teeth for biting. In a similar fashion, dogs stand erect, hairs on its back upright to appear large, thus appearing threatening. On the contrary, the dog gets down close to the ground to show affection or submission. Hence, the opposite emotional feeling for anger would be 'affectionate', and the opposite emotion for fear might be 'courage'. ACH underlies these emotions by inhibiting the excitability of the cortex (Eggermann and Feldmeyer, 2009<sup>[26]</sup>; Gullidge *et al.*, 2007<sup>[37]</sup>). The significance of ACH-related emotional feelings lies in that they can help people relax from stressful events. For example, ACH-related emotions help psychological therapy with phobic, manic and anxious patients. In addition, nostalgic 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.

This is not to say that ACH-related emotions are all positive: Apprehension and worrying should also belong to this group. Actually, cholinergic involvement in depression has long been suggested, since 1972 (Janowsky *et al.*, 1972<sup>[50]</sup>). At the time when the hypothesis was first published, the primary evidence was that a number of cholinesterase inhibitors had been shown to induce depression (Janowsky, 2011<sup>[52]</sup>), presumably by increasing central ACH levels (Janowsky, el-Yousef, and Davis, 1974<sup>[51]</sup>). For example, physostigmine, a centrally acting cholinesterase inhibitor, was shown to decrease manic symptoms and increase depressed reaction. Later on, many studies provided information that largely supported the hypothesis (Houlihan *et al.*, 2002<sup>[43]</sup>; Janowsky, 2011<sup>[52]</sup>; Mearns, Dunn, and Lees-Haley, 1994<sup>[66]</sup>). The theory was further supported by animal studies showing that mice bred specifically for sensitivity to cholinergic agents demonstrated depression-like behaviours (Overstreet, 1993).

Other studies found that learned stress, a widely used preclinical model of depression, could be induced (Dilsaver and Alessi, 1987<sup>[25]</sup>). In addition, the mood depressing effects of monoamine reserpine, which has 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. In addition, reserpine has been reported to have central cholinergic properties. The reserpine-induced effect might be due

to a combination of monoamine depletion and cholinergic activation, shifting NE-ACH balance to a cholinergic dominance (Curro Dossi, Pare, and Steriade, 1991<sup>[17]</sup>).

There are many reports about the interaction between ACH and catecholamines. For example, the antagonistic effects of NE and ACH in affective disorders were reflected in their synaptic wiring in the amygdala (McGaugh and Cahill, 1997<sup>[65]</sup>): ACH carries the influence of the amygdala to other brain structures; NE inhibits the activity of ACH (Packard, Cahill, and McGaugh, 1994<sup>[74]</sup>). Through these synaptic wires, the amygdala filters its incoming sensory streams of information, looking for 'dangerous' stimulus features, which would require the organism to engage in certain species-specific instincts, such as freezing or starting (Samson, Frank, and Fellous, 2010<sup>[90]</sup>). Similar synaptic wiring can be found in the substantia nigra, where the interaction between DA and ACH is well-documented for cases of Parkinson's disease. The inhibition of ACH on DA is also involved in the predication error experiments. As we know, ACH is involved in conditioned learning: after learning, a stimulus (e.g., light) will not induce DA release because ACH dominates and inhibits DA release. Similarly, DA released during feeding signals food reward, and the increase of ACH in NAc has a role in the onset of satiation (Avena *et al.*, 2006<sup>[4]</sup>). This increase in ACH is attenuated with sham feeding, where food is drained from a gastric fistula after ingestion. Thus, food-induced DA release goes unopposed by ACH. Hoebel and colleagues (Hoebel, Avena, and Rada, 2007<sup>[40]</sup>) suggested that the DA and ACH balance in NAc may affect motivation: While DA enables a person to start moving, ACH acts as a control to prevent over-responding and facilitates stopping.

An interaction between ACH and 5-HT has also been reported. The selective 5-HT reuptake inhibitor fluoxetine has demonstrated the ability to alleviate behavioural depression in the forced swim test, one of the potential mechanisms being to suppress cholinergic activities in the NAc (Chau *et al.*, 2011<sup>[15]</sup>). Tobacco smoking also supports the relationship between ACH and depression. Depression rates are much higher in smokers with a history of major depression; they have a harder time quitting smoking and are at risk of developing a major depression episode. Smokers also have lower levels of monoamine oxidase A (Dani and Harris, 2005<sup>[20]</sup>). Many patients with depression fail to derive sufficient benefit from available treatment options and up to a third never reach remission, despite multiple trials of appropriate treatment. ACH uptake inhibitors might be an alternative drug for aggression, phobia or mania. Novel antidepressant drugs targeting ACH receptors appear to hold promise (Philip *et al.*, 2010<sup>[81]</sup>).

The brain circuits of neuromodulation are displayed in Figure 2. NA is released in the brain stem and spreads first to anterior regions and cerebellum, and second to posterior cortical areas. ACH is released from the basal and medial nuclei and spreads in all directions. DA is released from the substantia nigra,

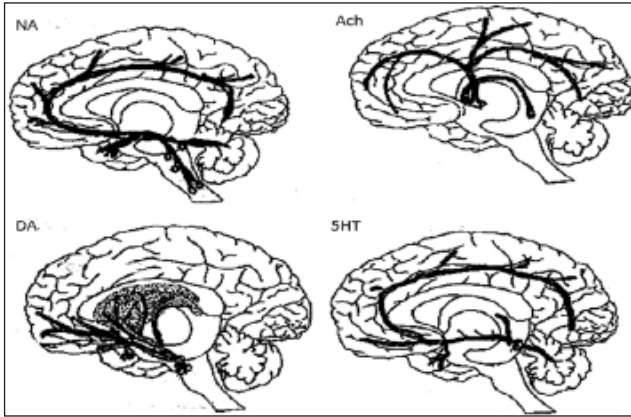


Figure 2: Brain circuits of neuromodulation (Figure adapted by Alfredo Pereira Jr: from a public Internet site: <http://www.karlabermeo.blogspot.com.br/2011/04/neurotransmisores.html>)

reaching the amygdala, nucleus acumbens and striatum. 5-HT is released from the raphe and takes a pathway similar to NA, spreading to anterior areas and cerebellum, and then to posterior cortex

## Functional Neuromodulation in Emotional Dynamics

The earliest dimensional study of emotion was done by Wundt in 1897, identifying three dimensions of emotion: pleasant-unpleasant, tension-relaxation and excitation-calm. Russell (2003<sup>[89]</sup>) proposed two dimensions for emotions: hedonic (pleasure-displeasure) and arousal (rest-activated). Ekman (2003<sup>[27]</sup>) devised a list of six basic emotions: anger, disgust, fear, happiness, sadness and surprise (Sauter *et al.*, 2010<sup>[93]</sup>). Plutchik (1962<sup>[82]</sup>), followed by Palumbo and Jellema (2013<sup>[76]</sup>) proposed eight primary emotions: anger, fear, sadness, disgust, surprise, anticipation, trust and joy, and arranged them in a colour wheel.

We argue that these six or eight emotions can be better understood in an integrated model that accounts for their oppositions and complementarities. Even though there are many standards, the most important is that primary emotional feelings should exclude each other. A second rule is that they should be able to compose all complex emotions, as in the case of the colour space, where three primary colours combine to generate all the others.

In a recent study on human facial expressions (Jack, Caldara and Schyns, 2012<sup>[47]</sup>), the authors make a claim for the existence of four basic emotional feelings: happy, sad, fear/surprise (i.e., fast-approaching danger) and disgust/



anger. This result is convergent with our previous reasoning on specific effects of neuromodulation on basic emotional feelings.

To illustrate the dynamics of four basic emotional feelings, we elaborate on an analogy with colours. There are only three primary different colours corresponding to the kinds of cone cells in the eye. The emotional feeling conceptual space is possibly more complex than the well-known colour space, containing at least four generating factors that modulate emotional feelings towards a complexity of affective states. Neuromodulation moves somatic systems towards four attractors in the landscape: pleasure, displeasure, fear/anger and calmness/willingness.

This landscape contains two gradients: Pleasure-displeasure and surprise-anticipation; therefore, we represent the conceptual space of neuromodulation of emotional feelings by means of a quadrant [Figure 3].

We suggest that the dynamics of emotional feelings is partially driven by neuromodulation: DA is a pleasure promoter, 5-HT is a displeasure promoter, NE is a fear/anger promoter and ACH is a calmness/willingness promoter. The quadrant offers a two-gradient view of the conceptual space of basic emotional feelings.

The dynamics of emotional feelings in everyday life can be seen represented in the diagram. If life is normally calm, everything is as expected; if something happens, people first feel scared and then blame things after fear is gone; quickly people will feel happy or sad depending on whether what happened fits their needs. Finally, things pass away, and people feel calm, happy, or missing and wanting for what was lost. We claim that the opponent and complementary

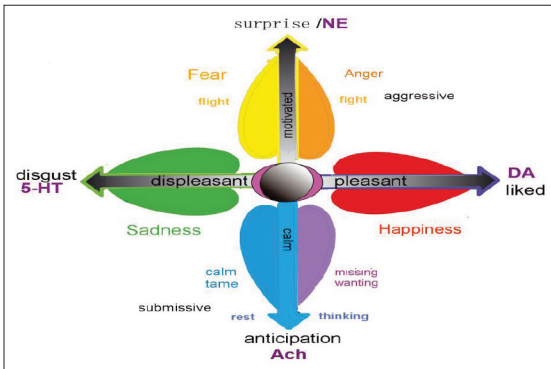


Figure 3: The quadrant of neuromodulation of emotional feelings. (Figure created by Fushun Wang)

relations depicted in the diagram can express the basic emotional dynamics involved in affective disorders. These can be understood as imbalances in the quadrant dynamics caused by hyper or hypo-action of one or more neuromodulators, combined with other psychosocial factors not addressed - for methodological reasons - in the current stage of our modelling.

## Concluding Remarks [Figure 4: Flowchart of Paper]

Human affective dynamics is a very complex process involving the action of several brain electrochemical agents and psychosocial factors. In this paper, we make an approach towards a simplified model related to the action of four neuromodulators and respective psychoactive drugs used in psychiatry to treat affective disorders. We begin by making some conceptual definitions and assumptions: affective disorders are disorders in the dynamics of emotional feelings, which are conscious phenomena driven by the action of neuromodulation.

Neuromodulation is conceived as a regulatory processes acting on the balance of excitation and inhibition in the whole brain. This balance is primarily generated by the combination of Glu and GABA release and action. Furthermore, neuropeptides contribute to generate feeling sensations such as hunger, thirst and satiation, but these sensations are specific, while the action of neuromodulators is more general, producing global mood states in the brain and soma.

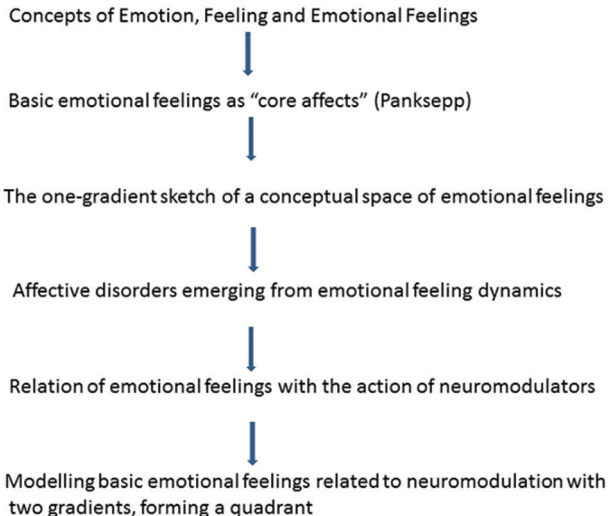


Figure 4: Flowchart of paper

In a second step, we briefly review the contribution of each of four neuromodulators for the determination of affective states, and how their imbalance is related to most common affective disorders. In the third step, we represent them in a functional quadrant, where all possible combinations can be plotted.

A better understanding of human affective dynamics requires more effort, building on both the one-gradient and the two-gradient sketches presented here, as well as in psychosocial approaches. In spite of the limitations of our study, we hope it could be useful for the mental health professional looking for an integrated view of the action of neuromodulators and respective psychoactive drugs used in biological psychiatry.

## Take Home Message

Although affective dynamics of human individuals is very complex and difficult, both conceptually and empirically (in experimental and therapeutic domains), today it is possible to find in the specialised literature sufficient information to build simplified models that can help understand the universe of emotional feelings and how brain endogenous chemicals and exogenous psychoactive drugs affect them.

### Conflict of Interest

None declared.

### Declaration

This is our original unpublished work, not submitted for publication elsewhere.

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## Questions that this Paper Raises

1. What is the relation between emotion, feeling and affective disorders?
2. How many basic emotional feelings do human beings have?
3. What is the relation between different kinds of neuromodulation and different kinds of emotional feelings?
4. How does the combination of different kinds of neuromodulation and/or corresponding psychoactive drugs used in psychiatry determine human mood states?
5. How do neuromodulators interact with neurotransmitters and brain hormones (neuropeptides)?



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