CAPTURING THE DYNAMICS OF PANIC DISORDER
A System Dynamics Translation of the Contemporary Biological and Psychological Conceptualization of Panic Disorder

by

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To God: *the One and Only; the Eternal, the Uncaused Cause of all that exists, the Incomparable. The Knower of the Invisible and the Visible, the Most Gracious, the Most Merciful, the Sovereign, the Holy One, the Source of Peace, the Granter of Security, the Guardian over all, the Majestic, the Irresistible, the Supreme. The Creator, the Originator, the Shaper out of naught. To Him belong the Most Beautiful Names: whatever is in the heavens and on earth, doth declare His Praises and Glory: and He is the Exalted in Might, the Wise.* (*Qur'an* 112 & 59: 22-24).

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"The highest activities of consciousness have their origins in physical occurrences of the brain, just as the loveliest melodies are not too sublime to be expressed by notes." **(W. Somerset Maugham)**

The present study undertakes a full system dynamics (SD) translation of the contemporary biological and psychological conceptualizations of panic disorder (PD). It makes explicit the dynamic processes implicit in the narrative presentations in the literature. It shows that the proposed structure in the PD theories is capable of generating the expected panic behaviour. However, it highlights some interesting "grey areas" in these theories that need further research. Finally, it serves as a facilitator for the discussion about PD for it provides an easy-to-understand illustrative language for the researchers of different fields to critically examine the biological, psychological, social and cognitive aspects of PD.

Keywords: system dynamics, biological, psychological, panic disorder (PD), dynamic processes, behaviour, grey areas, facilitator, social, cognitive

1. Introduction

This section defines panic disorder (PD), discusses its prevalence and significance, the types of panic attacks associated with PD, agoraphobia, and some technical terms which are to be used in the detailed discussion to come. Then it outlines the context of the present study and, finally, highlights the *dynamic* problem and the research goal.

1.1 What is *Panic Disorder*?

Panic disorder is classified as a form of anxiety disorder: a broad category of psychological disorder in which anxiety is a prominent feature (Rachman and De Silva 2004, 7; Berman 2005, 6). According to Rachman and De Silva (2004, 5-6), in the widely used and comprehensive classification of psychological disorders set out by the American Psychiatric Association (APA), the defining features of PD are:

1. A person has repeatedly experienced unexpected panic attacks: the discrete episode of intense sensation of fear or discomfort.

2. At least, one of the panic attacks was followed by persistent worry, lasting a month or more, of having another panic attack or by a significant change in the lifestyle or behaviour related to the panic attacks.

3. During the attacks, at least four of the following sensations develop abruptly and reach a peak within 10 minutes: shortness of breath or smothering, dizziness or

faintness, pounding heart (palpitations), trembling or shaking, feeling of choking, sweating, stomach distress or nausea, feeling that one's surroundings or oneself are not quite real (derealization), feeling of being detached from oneself (depersonalization), feeling of numbness or tingling sensations (paresthesias), hot flushes or chills, chest pain or discomfort, fear of dying and fear of losing control or going crazy.

4. These attacks are not directly caused by a drug or a general medical condition.

Most panic attacks last for less than 30 minutes (American Psychological Association 2005). In PD, panic attacks may occur as often as daily or several times per week (Rachman and De Silva 2004, 6) depending upon the severity of the disorder. PD patients often have these attacks with an increasing frequency (Wehrenberg and Prinz 2007, 55).

1.2 Prevalence and Significance:

According to Roy-Byrne et al., PD is a common mental ailment affecting up to 5% of the population at some point in life. *"It is often disabling and associated with substantial functional morbidity and reduced quality of life."* It is costly for individuals as well as society as evident from the increased use of health-care, absenteeism and reduced productivity. (Roy-Byrne, Craske and Stein 2006, 1023) According to Rachman and De Silva, approximately 15 out of 1000 people in the general population develop PD at some point in their lives. The size of the problem is nearly the same throughout the world and no ethnic differences have been found. (Rachman and De Silva 2004, 23)

According to the National Institute of Mental Health (2008), PD affects about 6 million American adults and is twice as common in women than men. According to Beamish, Belcastro and Granello (2002), there are between 3 and 6 million Americans suffering from PD. PD is rarely diagnosed or uncommon in children (Wehrenberg and Prinz 2007, 53; Rachman and De Silva 2004, 26) but begins to strike more frequently in late adolescence or early adulthood (National Institute of Mental Health, 2008). According to Bouton, Mineka and Barlow (2001), PD is more likely to strike the individuals between their mid-teens and 40 years of age.

PD can be largely disabling for it has an adverse effect on many aspects of a person's life like marital relationship, mobility, social contacts and activities, employment and economic status (Rachman and De Silva 2004, 23-4).

The comorbidity of PD with other anxiety and depressive disorders is so high that as many as 55% of PD patients also have one or more of such disorders (Barlow and Durand 2005).

1.3 Types of Panic Attacks associated with PD:

Whalen and McKinney write:

"The presence of panic attacks alone is not necessarily indicative of panic disorder... However, when panic attacks randomly occur on a regular basis they can be symptomatic of a larger problem, panic disorder...

To be diagnosed with panic disorder, patients must worry persistently about having another attack, worry that the attack is symptomatic of a larger problem, or make some noteworthy changes in their behavior, such as avoiding certain people or places. This worry must be present for at least one month. The attacks cannot be connected with any drug use, licit or illicit, nor can they be due to any other medical condition. Patients should not be diagnosed with panic disorder if their panic attacks can be correlated with the specific stressors." (Whalen and McKinney 2007, 12-3)

In PD, the panicky sensations are unprovoked, unexplained and often occur from an unforeseen source, whereas in a panic attack (without the presence of PD), one is keenly aware of the source of one's fearful sensations, for example, heights, snakes or spiders (Roy-Byrne, Craske and Stein 2006, 1023).

Barlow and Durand, as per DSMV-IV[1], describe three basic types of panic attacks: situationally bound, unexpected and situationally predisposed[2]. The unexpected and situationally predisposed attacks commonly relate to PD whereas situationally bound attacks are common in specific or social phobia (Barlow and Durand 2002, 113-15).

1.4 PD with Agoraphobia:

The occurrence of repeated panic attacks may result in restricting patients' daily life activities. They may start avoiding the places or situations in which they fear that an attack may take place. Similarly, they may develop a tendency to avoid the situations from which escape might be difficult, for example, tunnels, bridges, underground trains, cinemas, traveling unaccompanied etc. In many cases, patients also become afraid of

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1 *"The DSMV-IV (IV depicts edition) is a reference book containing the classification of mental disorders used by most psychiatrists, psychologists, social workers and other mental health professionals."* (Berman 2005, 2)

2 *"If you know you are afraid of high places or of driving over long bridges, you might have a panic attack in these situations but not anywhere else; this is a situationally bound (cued) panic attack. By contrast, you might experience unexpected (uncued) panic attacks. The third type of panic attack, the situationally predisposed, is in between. You are more likely, but not inevitably, to have an attack where you have had one before, for example, in a large mall. If you don't know whether it will happen today, and it does, the attack is situationally predisposed."* (Barlow and Durand 2002, 114)

being on their own at home without the presence of a trustworthy person who can provide safety and help in case of panic. If these fears and consequently the avoidance of "unsafe" places or situations becomes obsessive, it is an indication of PD with agoraphobia. (Rachman and De Silva 2004, 6-7) The avoidance in agoraphobia can be seen as a "coping mechanism" to deal with the overwhelming anxiety. The sufferers of PD without agoraphobia tend to use methods like drug or alcohol abuse as a coping mechanism. (Whalen and McKinney 2007, 13)

1.5 The *Fear Emotion*, *Feeling of Fear* and *Anxiety*:

In the present study, the difference between *emotion of fear* and the conscious *feeling/sensation of fear* is taken into consideration. Where the "fear emotion" is referred to, it means the unconscious hard-wired biological (stress response) functioning of the nervous system whereas the "feeling of fear" means the conscious perception of this functioning. In other words, the latter is a product of the conscious mind – the label given to the unconscious stress response function or emotion (LeDoux 1996).

Fear, as a combination of both emotion and feeling, may be defined as an immediate alarm reaction to danger which protects us by activating a massive response from the autonomic nervous system (the unconscious emotion of fear) that, along with our subjective sense of terror (the conscious feeling of fear) motivates us to escape or possibly to attack (Barlow and Durand 2002, 114).

Anxiety may be defined as the bodily symptoms of physical tension, and apprehension about the future – the feelings that one cannot control or predict the upcoming events (Barlow and Durand 2002, 113-15).

LeDoux highlights the difference between anxiety and fear emotion as follows:

> *"Anxiety and fear are closely related. Both are reactions to harmful or potentially harmful situations. Anxiety is usually distinguished from fear by the lack of an external stimulus that elicits the reaction - anxiety comes from within us, fear from the outside world. The sight of a snake elicits fear, but remembrance of some unpleasant experience with a snake or the anticipation that you may encounter a snake are conditions of anxiety."* (LeDoux 1998, 228)

It is noteworthy that fear and anxiety are normal bodily responses to the real or imagined dangers but when they are recurrent and persistent enough to impede daily life, then a fear or anxiety disorder (such as, PD) exists (LeDoux 1998, 228). An emotional state gives rise to anxiety and fear which result into a panic attack or, if put simply, to *the fear occurring at an inappropriate time* (Barlow and Durand 2002, 113-15).

1.6 Context of the Present Study:

The present study does not merely focus on panic attacks but a larger problem – *panic disorder (PD)* – in which, as discussed above, frequent panic attacks occur without any specific stressor. The issue of agoraphobia, which sometimes results from PD, is not addressed in this study.

There are a number of theories which explain why PD occurs, including psychological and biological ones (Salkovskis 1998). The psychological theories relate PD to the environment and personality traits (Psyber Square 1999), for instance, a history of childhood separation anxiety (LeDoux 1998, 258). Whereas, the biological theories relate it to the human anatomy and brain chemistry. Most practising psychotherapists, however, view PD as an outcome of both, the human anatomy and psychology (Psyber Square 1999).

The present study considers the biological as well as psychological and cognitive aspects of PD. It is centred around the malfunctioning s*tress response system* (discussed in Sec. 3.3) of the brain and the "conditioning[3] theory". The former is modelled as the main structure responsible for PD and then the biological, psychological and cognitive causes of this malfunctioning are addressed as proposed by most of the modern researchers (See Sec. 5).

1.7 Dynamic Problem:

The dynamic problem under consideration is the presence of abrupt (usually peaking within a minute), unreasonable and unnecessary discrete episodes of intense feeling of fear or anxiety, in an individual, which take a while until they drop back to their initial level (Rachman and De Silva 2004, 1, 5; Wehrenberg and Prinz 2007, 59-61; Berman 2005, 6). Fig. 1.1 illustrates the pattern of these fear episodes (or panic attacks) over time. On the Y-axis, 0 to 5 is supposed to be the normal fear level (no significant fear, anxiety or discomfort present); 5 to 10 high and above that, so extreme that it may be labelled as "panic". In PD, the panic attacks may occur as often as daily or several times per week (Rachman and De Silva 2004, 6). These attacks usually occur with an increasing frequency (Wehrenberg and Prinz 2007, 55). If PD is left untreated, the panic attacks may become chronic (Rachman and De Silva 2004, 27) and last for years (Federal Citizen Information Center, Pueblo, Colorado).

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3   It is a process in which the conditioned stimulus (e.g., the smell of coffee) is paired with and precedes the unconditioned stimulus (the panic attack) until the conditioned stimulus alone is sufficient to elicit the response (the panic disorder) (Dictionary Reference 2008).
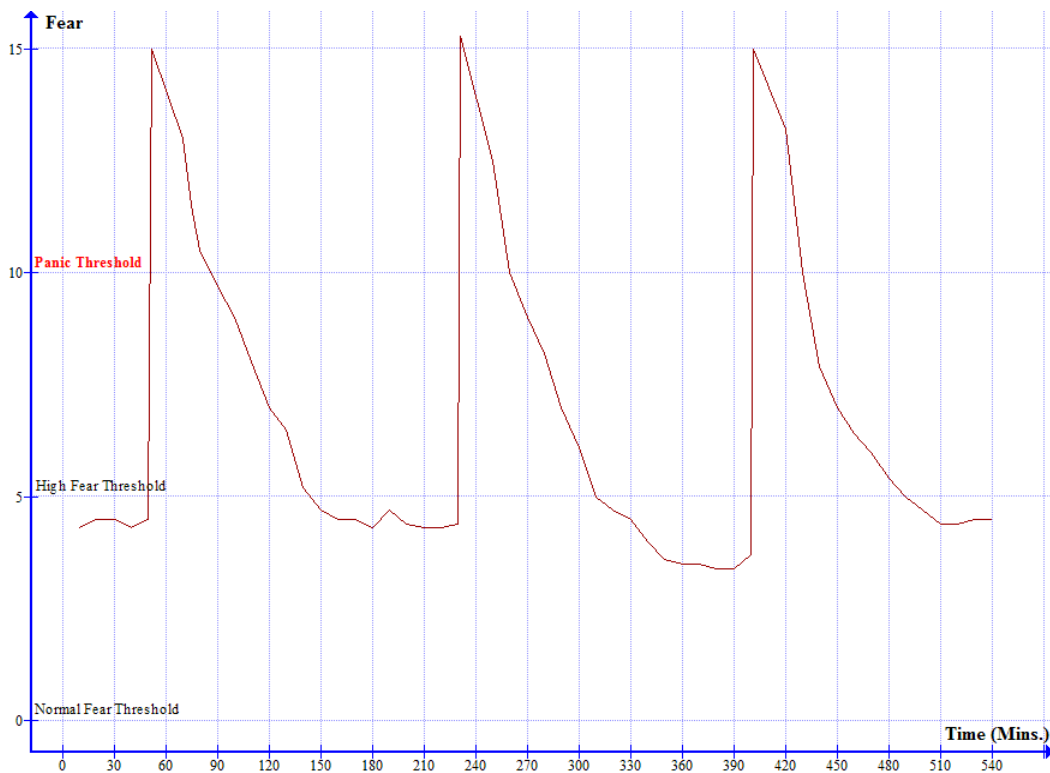
Fig. 1.1: A Self-Drawn Reference Mode[4] Showing Panic Attacks Over Time Using the *Feelings of Fear* Symptom

Feeling of fear and other cognitive symptoms of panic develop in response to physical symptoms of racing heart, choking, stomach distress and/or trembling etc. (Wehrenberg and Prinz 2007, 55), therefore, the sensations of intense fear are directly proportional to the physical symptoms of a panic attack. What it implies is that first the heart rate, for example, will exhibit the same behaviour pattern as shown in Fig. 1.1 and then the feelings of fear will follow it. In Fig. 1.2, the *fear* on the y-axis is interchanged with the *average heart rate* to appreciate this fact.

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4   A set of graphs and other descriptive data showing the development of the problem over time (Sterman 2000, 90).
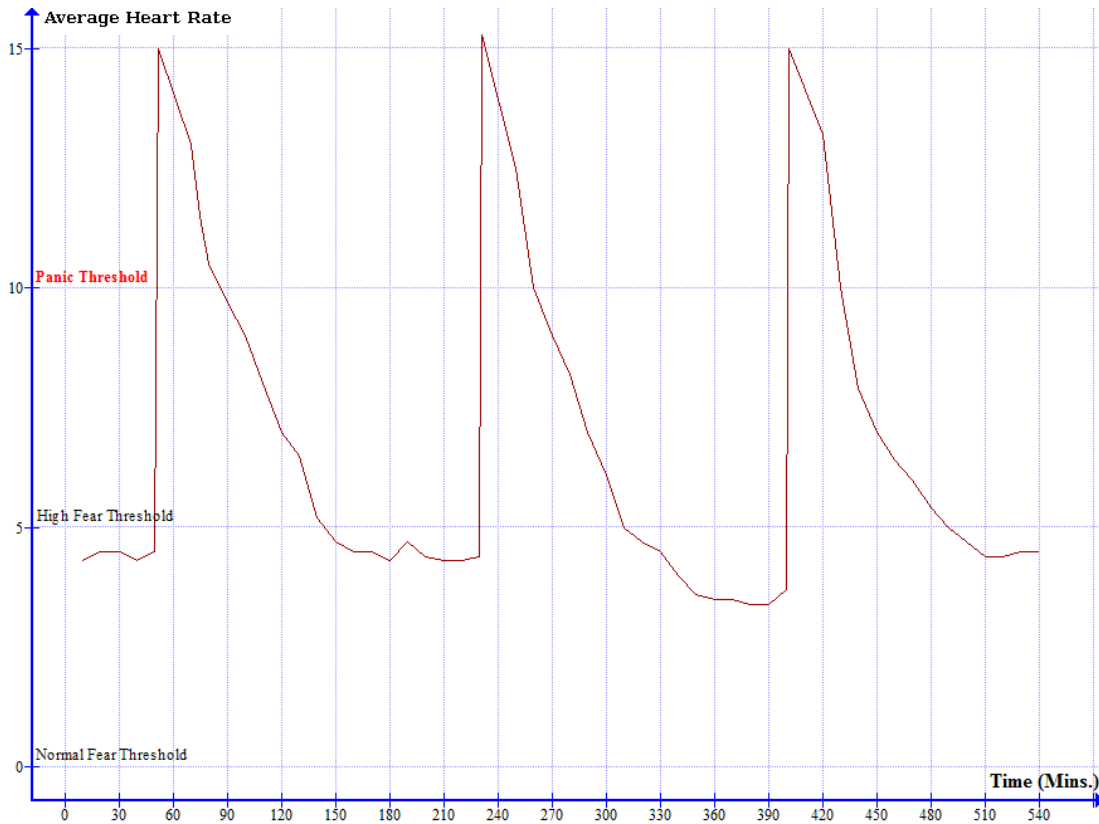
Fig. 1.2: A Self-Drawn Reference Mode Showing Panic Attacks over Time Using the
Average Heart Rate Symptom

1.8 Research Goal:

The literature in biology and psychology contains theories for the occurrence of the problematic panic behaviour pattern shown in Fig. 1.2. The research goal of the present effort is to synthesize the predominant biological and psychological theories of PD[5] and further translate them into a system dynamics (SD) simulation model. The whole effort is expected to:

• Make explicit the dynamic processes implicit in the narrative presentations of the contemporary PD theories which would make it easy to visualize and understand them.

• Briefly analyse the pros and cons of PD theories and test whether the proposed structures within these theories generate the expected behaviour shown in the reference mode (See Sec. 1.7).

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5 These theories explain how a panic attack is triggered, how the panic symptoms manifest and how panic attacks change into PD.

- Help form a bridge between abnormal psychology, psychiatry, biological psychology etc. and SD. This may encourage other researchers to apply SD methods to a wide range of interesting brain-based behaviours some of which are highlighted in this study.

- Provide a common, easy-to-understand and illustrative language (the SD translations) to further understand and critically examine the biological, psychological and cognitive conceptualizations of PD.

2. Research Method: System Dynamics Translation

This section describes the method of system dynamics (SD) translations – the research method being used in this study.

A full *system dynamics (SD) translation* of a narrative theory includes the identification of a theory in text or diagrams, converting it into causal links and loops, formulating and simulating it, and eventually testing its predictive claims (Wheat 2007). The present work is an example of an SD translation which starts from identifying the PD theories from various text books and academic papers. This is what has been done in the literature review section. In the next section, an effort will be made to convert the narrative descriptions of these theories into causal links and then use those links to identify the implicit feedback loops within these theories. After that, a separate section will deal with converting the identified loops into a stock and flow model, simulation experiments of which are expected to help test these theories and, like each step of this translation effort, better understand the physiology and psychology of PD.

SD translations have been successfully applied to many theories from different fields, for example, Luna and Davidsen (2007) have translated Velásquez's (1997) work regarding innovation performance in the capital good sector in Colombia (Luna and Davidson 2007), Campbell (2007) has translated Okin's (1989) theory regarding justice, gender and family and Wheat (2007) has translated Sach's (2005) poverty trap theory from the field of economics. Richardson's (1991) book *Feedback Thought in Social Science and System Theory* also contains many "partial" SD translations i.e., feedback loop diagramming without stock-and-flow simulation modeling. His work focuses on providing a careful and an incisive analysis of the feedback mechanism in social science and systems framework (Bailey 1992).

From Psychology, Richmond et al (1997, 35-47) have taken Freud's theory of personality (presented in Wortman and Loftus 1985) and provided a full SD translation of one of the theory's main constructs, "the id". Their translation work is divided into four sections. In the first section, words from the textbook are used to develop a simple snapshot (or a *map* in the authors' terminology) of the structural relationships which lie beneath Freud's conception of the id. The second section transforms that map into a simulation model. The third section reveals the dynamics, implied by the theory, through simulation and highlights a weakness in Freud's conception of pleasure – providing an impetus to extend the model and, hence, the theory itself. The fourth section summarizes the illustration and provides suggestion of how to further improve the model. (Richmond et al. 1997, 36) To highlight the need of SD translations, they write in the introduction of their translation work:

"Textbooks rely on verbal descriptions as the primary vehicle for exposition of concepts. Such descriptions are far more ambiguous, and open to multiple interpretation... In

addition, verbal descriptions do not lend themselves to rigorous testing... Stock/flow framework provides a disciplined language that can help students (and faculty!) to 'pin down', and make sense of, important qualitative ideas in the textbooks. As the words on a page are translated into a map of the concept or theory, the associated abstractions become more concrete and operational. Ambiguities are squeezed out, and any internal inconsistencies are brought into sharp focus. The questions that arise during model construction, testing and extension will provide ample fodder for informed classroom discussion, and can provide the impetus for further directed research into the subject matter." (Richmond et al. 1997, 35)

The goals of all the translation works[6] mentioned above may be summarized as follows:

- To make explicit the dynamic processes implicit in the narrative presentations.

- To test whether the proposed structures generate the expected behaviour.

- To analyze the pros and cons of each theory.

- To provide a common, simple and clear language (SD model) to further discuss each theory and open up new research horizons.

The goal of the present effort is to make explicit the biological and psychological aspects of PD through an easy-to-understand illustrative language and briefly analyze the strengths and weaknesses of the PD conceptualizations which includes testing whether the structures proposed in these conceptualizations generate the expected behaviour (shown in the reference mode – Fig. 1.2). It also attempts to provide a common ground for carrying out further discussion on the PD theories. The whole effort is expected to improve the understanding of PD, provide a critical feedback to the theorists and serve as an impetus for further guided research.

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6   Except for Richardson's (1991) partial translations aiming at analyzing the feedback mechanism.

3. Literature Review

This section provides a detailed viewpoint of the contemporary biological, psychological and cognitive researchers about the origin, development and persistence of PD over time. The direct quotes presented in this section will be interpreted and translated in Sec. 4.

3.1 Panic Disorder (PD) Theories:

There are many theories about the origin of PD which may be categorized under two main headings: biological and psychological.

Biological Theories: The biological theories consider PD as an illness caused by a lesion, a biochemical deficiency, or some other structural or functional abnormality. This approach includes Klein's original biological and suffocation-alarm hypotheses (Klein 1980, 1981; Klein and Klein 1988, 1989a, 1989b), Charney's neuropharmacological hypotheses (Charney and Heninger 1986), Leibowitz et al.'s neuroanatomical hypothesis (Gorman, Liebowitz, Fyer and Stein 1989) and the hyperventilation syndrome theories of Lum (1976) and Ley (1985a, 1985b).

Psychological Theories: The psychological theories proposes that panic is the outcome of normal processes which may be quantitatively but not qualitatively different from everyday experience. This approach includes van den Hout's interoceptive conditioning hypothesis (Hout van den 1988) and the cognitive hypotheses advocated by Beck (1988), Clark (1986a, 1986b, 1988), Ehlers (1988), and Salkovskis (1988a).

Barlow's "false-alarm" hypothesis (1988, 1991) include many of the processes which are psychological in nature. However, it also shares a key characteristic with the biomedical hypothesis in that it starts from the supposition of dysfunction in a biological "alarm" mechanism. (Salkovskis 1998)

The present study translates both the biological as well as psychological theories of panic. As per these theories, the brain's stress response reaction[7] is modelled (See Sec. 5) as the main structure responsible for PD and it is illustrated how the conditioning, chemical imbalances and faulty cognitions contribute to its unnecessary triggering. This approach in which PD is conceptualized as the outcome of both the biological and psychological interplay is used by most of the practising psychotherapists (Psyber Square 1999).

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7 The stimulation of different brain chemicals (emotion of fear) which lead to the fight or flight sympathetic arousal.

3.2 The Origin of PD:

According to Wehrenberg and Prinz (2007, 57-8), PD may originate from:

- A state of trauma which leaves an individual excessively sensitive to the cues and reminds of the traumatic event, e.g., war, rape, injury, accident, death or loss of a loved one etc.

- Early disturbances in relationship with parents and/or caretakers which leaves an individual with a sense of insecurity.

- An unsettling state of "psychological conflict" e.g., extreme love coexisting with an extreme fear of losing it which creates a dilemma for an individual who can neither afford to let go love merely because of fear nor live comfortably with it as the extreme fear becomes a necessary "by-product" of love.

- Biological causes e.g., neurotransmitter[8] imbalances and structural dysfunctions in the brain which may be inborn or developed as a result of different physical and mental issues.

Whatsoever the reason why panic originates, it always results in an over-reactive brain that repeatedly provokes fight or flight reaction without any sound reason (Wehrenberg and Prinz 2007, 57-8).

3.3 The *Fight or Flight* or *Stress Response Reaction*:

"Two frogs fell into a bowl of cream. One didn't panic, he relaxed and drowned. The other kicked and struggled so much that the cream turned to butter and he walked." (Unknown)

The fight or flight reaction, also known as the *"acute stress response reaction"* (Psychologist World 2008) is very important to understand as the unnecessary triggering of this mechanism is hypothesized to be the cause of PD (See Sec. 3.4). It is a *"hard-wired"* automatic biological response of the nervous system to a stressor; also referred to as the *"fear emotion"* (LeDoux 1996). If intense enough, it triggers the sympathetic nervous system activation (the sympathetic arousal) which brings about certain physiological changes in the body to function appropriately in the emergency situations (Wehrenberg and Prinz 2007, 28, 59).

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8 *"A stimulatory or inhibitory chemical released from nerve cells that acts as a messenger between nerve cells (neurons) or between neurons and other tissues such as muscles or glands".* (Adolor Corporation 2008)

During an emergency or dangerous situation, the brain prepares the body for action by marshalling resources to enable it to attack the source of the danger or to flee from it. Clarke and Gillet (1997, 44) explain: *"To increase energy, sugar is released into the bloodstream. To hasten the distribution of blood to the muscles, the heart beats faster. To reduce bleeding, the blood flows to the skin is restricted. These physiological changes all facilitate survival in the face of danger. They are commonly referred to as the 'fight or flight' response. This concept has its origins in a time when most dangers were physical, such as attacks from the wild animals. For such dangers, it was appropriate to decide, if you were stronger than the attacker, that you would fight; or, if the attacker was stronger than you, that it was safer to flee."*

Stress may be triggered by both internal bodily or mental conditions and external stimuli. The internal conditions may be hunger, thirst, illness or distressing thoughts, whereas, the external stimuli fire alarm, an angry face, the smell of smoke or pain etc. The sensations caused by the stress response, for example, panting respiration, sweating and a pounding heart, are the physical changes needed to fight or flee from the source of stress or danger. (Wehrenberg and Prinz 2007, 59)

"The beauty of the stress response system is that it works continuously without intentional monitoring to provide the kind of energy we need to meet the ordinary ups and downs of everyday living", Wehrenberg and Prinz (2007, 59) explain. It is immediately provoked when one sits in the examination hall, hears a loud scream or encounters an angry face. Without consuming any time in thinking over it, the brain responds to the situation and immediately prepares the body for action. The stress response turns itself off when it becomes clear that the stress is manageable or unrelated – when one knows the answers to all the questions in the exam, the loud scream is of a child playing with her father or the angry face of boss is due to someone else's mistake.

Consuming time may, in many dangerous situations, prove to be fatal that is why God has provided man with this instant stress response mechanism to ensure survival in the face of danger. For instance, while walking besides a busy road, if one hears a loud scream of a horn with screeching of the braking wheels, one would be immediately in a position to react to it courtesy the instant arousal provided by the stress response reaction. Without the stress response, considerable amount of time would have consumed in analysing the situation and, by the time it were fully analysed and consciously realised, the vehicle may already have hit the pedestrian.

According to Wehrenberg and Prinz (2007, 28 and 59-60) the internal functioning of the stress response reaction starts with the perception of stress. When stress is perceived in the amygdala, it signals to the hypothalamus to initiate an outburst of hormones and neurochemicals that activate all the internal organs to prepare the body to either fight off or flee from the cause of the stress:

(1) The amygdala signals the hypothalamus to release corticotrophin release factor (CRF)[9].

(2) CRF stimulates the release of adrenocorticotropin hormone (ACTH) from the pituitary, which causes the adrenal gland to release adrenalin[10] from the medulla and cortisol from the adrenal cortex. Cortisol and adrenalin release energizes the body.

(3) The hypothalamus stimulates the release of norepinephrine (NE)[11] in the pons. NE initiates the fight or flight sympathetic arousal which prepares the whole body for an efficient and effective response to the perceived stress. When this response is made, the stress response system is turned off by cortisol:

As the end point in a feedback loop, cortisol signals to the hypothalamus that the CRF has done its work and does not need to be released any longer. The CRF has produced the necessary heightened arousal, and the cortisol is received in the hypothalamus as a "turn off" so the body and brain can go back to the normal after the brief arousal caused by the adrenalin-norepinephrine spike." (Wehrenberg and Prinz 2007, 59-60) This is how a normal brain functions in response to a stressor. Fig. 3.1 illustrates the stress response system.

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9   CRF is also known as the stress response hormone **(**Wehrenberg and Prinz 2007, 60), corticotrophin releasing hormone (CRH) and corticoliberin (On-line Medical Dictionary).

10 Adrenalin is also known as epinephrine (Rosenzweig, Breedlove and Watson 2005, 92).

11 Norepinephrine is also known as noradrenalin (Barlow and Durand 2002, 44).
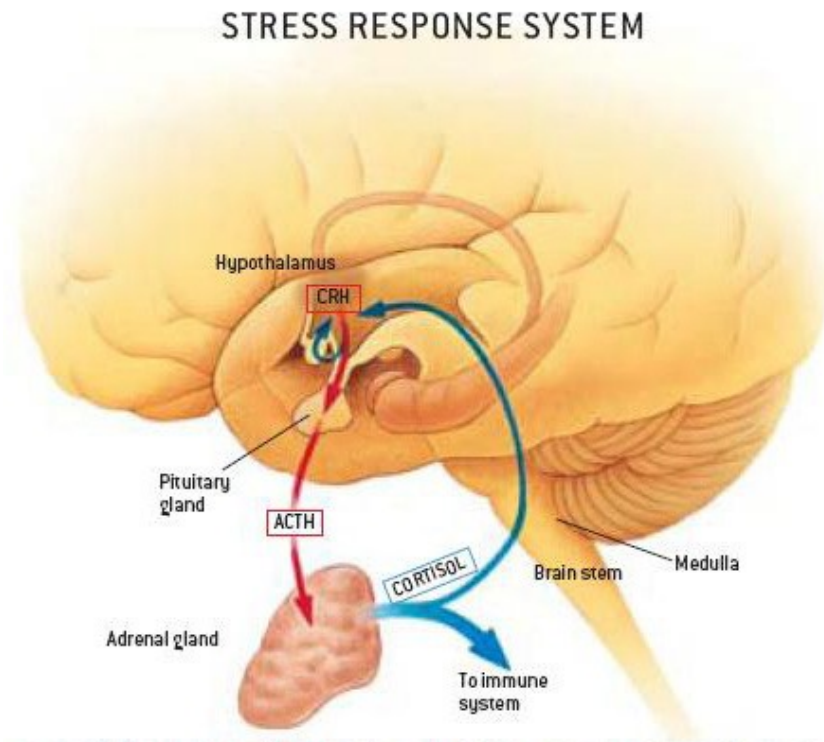
STRESS RESPONSE SYSTEM

Fig. 3.1: The Stress Response System (Source: *Roberto Osti; The Scientific American*)

3.4 PD – the Outcome of an Unnecessary Stress Response:

> ***"The trouble is that I'd let my gestures freeze. The trouble was not in the kitchen or the tulips but only in my head, my head." (Anne Sexton)***

Wehrenberg and Prinz write:

> *"The intense arousal of a panic attack is the physical state of terror, without a reason for the terror. As humans who think about our condition, we want reasons for what our bodies feel. It feels psychologically disorganizing not to have an explanation for what we feel physically (Gazzaniga, 2005)."* (Wehrenberg and Prinz 2007, 59)

Terror without any apparent reason is an undesirable state which the brain somehow has to handle. Experiencing panic for the first time, the brain does not reason in a sound, objective manner, perhaps, because it does not have any clue of what is going on. In order to make sense of the situation, it draws connections between the panic and what the sufferer was doing, thinking or feeling at the time the attack took place. If the sufferer was

flying, the brain might reason that the panic was caused by flying rather than understanding that the person was undergoing a biological event. Even though flying had nothing to do with the panic, the thought and behaviour would follow the brain's reasoning and the sufferer would be inclined to avoid flying in the future. **(**Wehrenberg and Prinz 2007, 59) See Sec. 3.5.2 for details.

The panic attacks of a PD patient are *"*a *condition of experiencing the stress response without a stressor"*, Wehrenberg and Prinz (2007, 59) explain. They are an outcome of a false activation of stress response reaction without any real danger in the sufferer's environment. It is an extremely aversive state which confuses the body and mind. All of a sudden one starts feeling danger and find one's body preparing to fight or flee from it while one is comfortably sitting in a cosy restaurant having a cup of coffee with friends... The only way for PD patients to ward off their panic attacks is to understand although their terror episodes are real but they are totally 'unnecessary'. (Wehrenberg and Prinz 2007, 60-1)

Another problem associated with the PD patients is that once the stress response (emotion of fear) initiates in their brains, it is difficult to turn it off because of either neurochemical imbalances, inborn over-reactive stress response system, traumatic life events or a combination of such factors. This problem is discussed in detail in the forthcoming sections.

3.5 The Role of Amygdala in Panic:

"Panic is a sudden desertion of us, and a going over to the enemy of our imagination." (Christian Nevell Bovee)

The amygdala functions as the brain's early warning system. It constantly remains alert to the potential threats, dangers, unfamiliar and unusual things in the external environment. It assigns an emotional significance to the incoming stimulus, such as, "harmful!", "unpleasant", "threatening!" etc. and directly stimulates the stress response reaction before the prefrontal cortex (PFC) can exert any modulating influence on it. It directly connects to the parabrachial nucleus for panting respiration, the hypothalamus for initiating the stress response reaction, the locus coeruleus (pons) for stimulating the release of norepinephrine (NE) and the periacquaductal gray, which may initiate freezing and modulate pain responses. (Wehrenberg and Prinz 2007, 28) Panting respiration is the hallmark of a panic attack (Wehrenberg and Prinz 2007, 34). NE spike triggering the fight or flight activity results in increased heart rate and other panic symptoms such as sweating, flushing, tremor and feelings of fear (Wehrenberg and Prinz 2007, 16).

3.5.1 Amygdala, Cortex and the Stress Response:

The amygdala has a dual sensory input system. The input carrying information about the external stimulus first runs from the eyes, ears and other sense organs to the thalamus from where it diverges to two independent pathways. One pathway directly leads to the amygdala, whereas, the other first passes through the left prefrontal cortex (PFC) and then reaches the amygdala via anterior cingulate gyrus (ACG)[12]. The former pathway is shorter and, hence, faster as compared to the latter. (See Fig. 3.2) Each of these pathways has a distinct role in the brain.
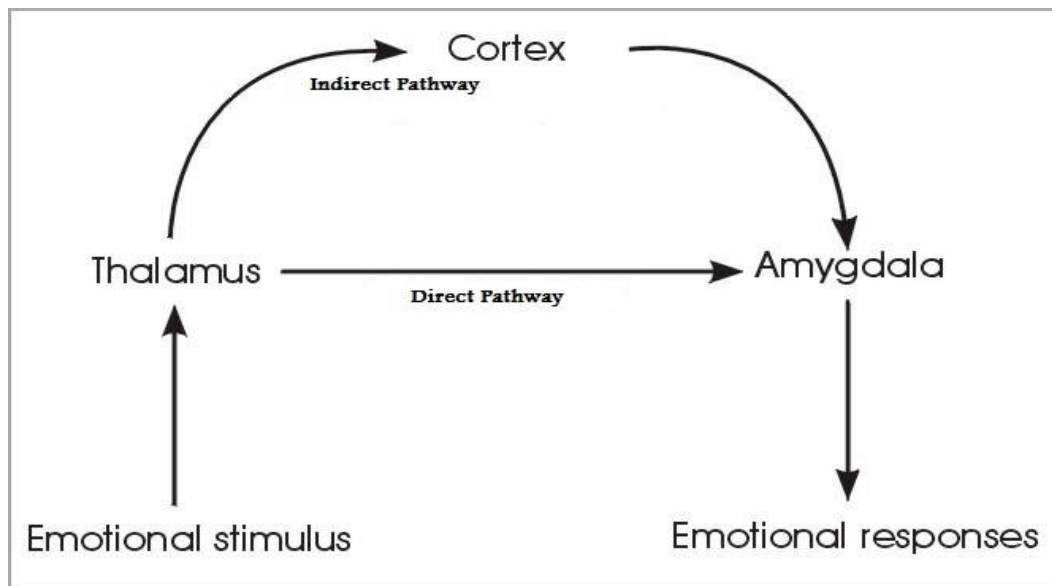

Fig. 3.2: The Direct and Indirect Pathways to the Amygdala (Source: LeDoux 1998, 164)

Though the direct thalamo-amygdala pathway is quick but it is "crude" for it lacks the ability to examine the stimulus. It can only provide the amygdala with a notion that there is a prima facie threat in the environment which allows the amygdala to begin to respond to the potentially threatening stimulus before any waste of time in comprehending what the stimulus is. This can be very useful for time is crucial in dangerous situations. By having the amygdala ready for action, the thalamo-cortical-amygdala pathway takes a moment to examine the stimulus and determine if the threat is real or perceived. It is the PFC where the stimulus is processed in its entirety. The PFC integrates the sensory information about the stimulus with the information from the hippocampus about the details or context of the current stimulus, compares all of this with the long-term memory of the former situations, and then decides whether fight or flight activity is required. This refined signal (with the PFC's decision) is sent down to the amygdala through the anterior cingulate gyrus (ACG) to help it make the appropriate response. If the signal indicates that the threat is real, the amygdala carries on activating the stress response reaction which prepares the body to fight off or flee from the threat. If it suggests otherwise, i.e.,

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12 ACG is a subdivision of PFC (Wehrenberg and Prinz 2007, 12).

the threat is only perceived, the amygdala stops stimulating the stress response reaction which allows the body and brain to go back to their normal state. For example, the amygdala may detect smoke in the environment, a potentially dangerous stimulus, but fear may not be the appropriate response. It is through the thalamo-cortical-amygdala pathway that the amygdala would learn that the smoke from a burning piece of toast is cause for action but not fear, so it does not need to trigger the stress response reaction. (LeDoux 1998, 164; Holt 1998, 2; Wehrenberg and Prinz 2007, 194-95)

The utility of this whole mechanism requires that the *thalamo-cortical-amygdala* pathway be able to override the direct *thalamo-amygdala* pathway which is not the case in the individuals with certain emotional disorders e.g., PD. The direct pathway is hypothesized to be a predominant mode of functioning in such individuals. (LeDoux 1998, 164)

Rosenzweig et al. suggest that the fear-inducing stimulus reaches the amygdala via three distinct inputs. First directly from the thalamus to the amygdala, second from the thalamus to the cortex to the amygdala and third from the thalamus to the cortex to the hippocampus to the amygdala (Rosenzweig, Breedlove and Watson 2005, 472). However, Holt holds that the last mentioned input does not take part in the fear circuitry (Holt 1998, 2). Although there lies a disagreement whether the hippocampal input takes part in eliciting the fear emotion, at least, the presence of two fear-eliciting inputs to the amygdala is agreed upon, i.e., the *thalamo-amygdala* and *thalamo-cortical-amygdala.*

3.5.2 The Role of Amygdala in Learning Negative Experiences:

Wehrenberg and Prinz discuss how the negative experiences are learned by the amygdala as follows:

> *"The amygdala learns what is dangerous. It learns from experience if sensory inputs are threatening or not. It very quickly forms associations between specific situations and pain, danger or negative outcome. Therefore, after a frightening experience, and especially after a trauma, the amygdala maintains alertness to all future signals that a similar experience is about to occur. For example, if a person is in a car accident that is significantly frightening or painful, all of the aspects of that experience are learned by amygdala as signals of danger: tires squealing, smells of fuel, or smoke, sirens, and even the specific place on the road, the weather conditions, or other features of the accident. Any aspect of the genuinely frightening experience could be learned by the amygdala as a signal to watch for in the future. Whenever one of those signals is perceived by the amygdala, the person will feel frightened. Even when the sound, smell, or place is not presently dangerous, the amygdala may react as if it is, because the association formed in the amygdala between danger and the stimulus will cause the amygdala to start the fear or panic response."* (Wehrenberg and Prinz 2007, 28-9)

LeDoux explains two types of memory systems working in the brain; one forming the explicit (conscious) and the other implicit (unconscious) memories. The former he relates to the combined functioning of the hippocampus and cortex while the latter to the amygdala. He writes:

"Suppose you are driving down the road and have a terrible accident. The horn gets stuck on. You are in pain and generally traumatized by the experience. Later, when you hear the sound of a horn, both the implicit (unconscious) *and the explicit* (conscious) *memory systems are activated. The sound of the horn (or a neural representation of it), having become a conditioned fear stimulus, goes straight from the auditory system to the amygdala and implicitly elicits bodily responses that typically occur in situations of danger: muscle tension (a vestige of freezing), changes in blood pressure and heart rate, increased perspiration, and so on. The sound also travels through the cortex to the temporal lobe memory system, where explicit declarative memories are activated. You are reminded of the accident. You consciously remember where you were going and who you were with. You also remember how awful it was. But in the declarative memory system there is nothing different about the fact that you were with Bob and the fact that the accident was awful. Both are just facts, propositions that can be declared, about the experience. The particular fact that the accident was awful is not an emotional memory. It is a declarative memory about an emotional experience. It is mediated by the temporal lobe memory system and it has no emotional consequences itself. In order to have an aversive emotional memory, complete with the bodily experiences that come with an emotion, you have to activate an emotional memory system, for example, the implicit fear memory system involving the amygdala."* (LeDoux 1998, 200-01)

He further writes:

"Hippocampal circuits, with their massive neocortical interconnections, are well suited for establishing complex memories in which lots of events are bound together in space and time. The purpose of these circuits, according to Eichenbaum, is to provide representational flexibility. No particular response is associated with these kind of memories – they can be used in many different ways in many different kinds of situations. In contrast, the amygdala is more suited as a triggering device for the execution of survival reactions. Stimulus situations are rigidly coupled to specific kinds of responses through the learning and memory functions of this brain region. It is wired so as to preempt the need for thinking about what to do." (LeDoux 1998, 224)

LeDoux illustrates the purpose and importance of the stress response, which includes the memory functions of the amygdala, with the help of a predator-prey example: Imagine you are a prairie dog, he argues, and all of a sudden you spot a bobcat which you know to be a serious enemy. The sight or sound of the bobcat goes straight to your amygdala and

out comes the instant freezing response. If you had to make a deliberate decision about what to do, you could get so bogged down in decision making that you might be eaten before you made the choice. And if you started to move nervously while trying to decide, you would surely attract the predator's attention and certainly decrease your likelihood of surviving. Freezing is not the only autonomic response but it is a fairly universal initial response to detection of danger throughout the animal kingdom. Automatic responses like freezing are a gift of evolution. They have the advantage of having been "test-piloted" through the ages, whereas, the reasoned responses do not come with this kind of fine-tuning. (LeDoux 1998, 175-76)

It is clear from the above discussion that the amygdala quickly forms associations between the pain, danger and specific situations. This information is stored in an implicit (unconscious) memory system which may, later on, activate specific emotional responses in an individual leading to the panic symptoms of trembling, choking, derealization, freezing, fear or sweating etc. Thus the implicit memory system may largely contribute to the development of PD.

3.5.3 The Cognitive Error and Kindling:

Wehrenberg and Prinz explain the cognitive error and kindling along with their correlation to PD as follows:

"The cognitive symptoms of panic disorder develop in response to the physical symptoms... The cognitions come from the most startling aspect of a panic attack – the intense, sudden, and shocking realization that this might be what it feels like to die. Driven to the emergency room with a terrorizing, "What if I am dying?" fear, people develop the cognitive error that their symptoms are evidence of a serious problem, which expands their panic attacks into panic disorder... The erroneous thoughts that the person is dying, losing control, or going crazy maintain the mindless fear of another panic attack. In other words, people react to the sensations without using logical thought to examine their frightened, reactive cognitions.

The more often the brain goes into a panic attack, the more easily a panic attack can be set off the next time, regardless of why the panic started. This process is called kindling. The faulty cognitions that develop during a panic attack do not disappear when the rapid heart rate goes down. Fear causes hypervigilant attention to physiological arousal and magnifies every small tingle or twitch. The fear that those sensations will develop into panic will actually create panic (Casey, Newcombe, & Oei, 2005)... The inner dialogue may go something like this:

'I have felt panic before. I have a physical sensation. I wonder if it is panic. I'd better pay attention. I will hypervigilantly monitor my physical sensations. Uh, oh!

I feel every sensation getting faster – heart rate, breathing. Yes, I am sure this is panic! Oh, no! I hate this. Now my heart is really fast and my breathing is shallow.'

Sure enough, the panic attack comes on full swing, as self-talk made all the sensations worse. This circular interaction between physiology and thinking is easily begun." (Wehrenberg and Prinz 2007, 55-6)

The role of norepinephrine (NE) neurotransmitter in creating the hypervigilance[13] is discussed in Sec. 3.8.2.

LeDoux illustrates the concept of kindling as follows:

"...Because conscious memories are formed during anxiety attacks (i.e., panic attacks)*, the bodily sensations associated with those attacks, when recognized consciously, become potent elicitors or at least facilitators of anxiety. "* (LeDoux 1998, 258)

He further explains, in detail, how these bodily sensations – rapid heart rate, panting respiration, sweating etc. may drive anxiety into PD:

"The most complete conditioning theory of panic has been developed by Wolpe. He has argued that the first panic attack is the result of experiencing the consequences of hyperventilation, which increases the carbon dioxide in the lungs and blood and results in a variety of unpleasant bodily sensations (dizziness, racing heart, the feeling of suffocation). The hyperventilation can arise for a variety of reasons. Certain drugs like cocaine, amphetamine, or LSD, or exposure to toxic chemicals in the workplace, can be the cause...

According to Wolpe, the cause of the first panic attack is not important. It can be organic or psychological. Regardless once panic occurs, the stimuli that happen to be present at the time will become conditioned fear stimuli. But unlike typical fear conditioning situations, the critical stimuli are internal rather than external. For example, an elevation of blood pressure that occurs in response to hyperventilation might become a conditioned fear stimulus. If blood pressure happens to increase for some other reason, such as talking to a superior or being in some other socially tense situation, the noxious sensations previously elicited by hyperventilation, having been conditioned to increases in blood pressure levels, are now brought on. These sensations are then noticed and interpreted as indicative of the onset of a panic attack. In contrast, the conditioned stimulus (elevation of blood pressure) is not easily noticed, and the panic appears to be spontaneous." (LeDoux 1999, 259-60)

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13 *"Abnormally increased arousal, responsiveness to stimuli, and scanning of the environment for threats."* (Dorland's Medical Dictionary for Health Consumers 2007)

This explanation is consistent with Wehrenberg and Prinz's explanation of kindling and cognitive error, however, LeDoux has gone into more detail. He has illustrated how the individual panic symptoms get conditioned with the panicky sensations and, along with the faulty cognitions, elicit more of such attacks – expanding the problem into PD. Another point he has added is that the first panic attack may be the result of hyperventilation which itself may arise due to several biological reasons. Next, he explains how the amygdala participates in the process of kindling and cognitive error or, in other words, the conditioned panic:

> *"There are neurons[14] in the lower brain stem that are very sensitive to changes in blood level of carbon dioxide. The amygdala, it turns out, receives inputs from the neurons in this region. The amygdala also receives information about the status of the internal organs – the rate at which the heart is beating, the level of blood pressure and other vital statistics from the inner core of the body. By integrating these internal signals about the sate of bodily organs (the conditioned stimuli) with information about the level of carbon dioxide in the blood (the unconditioned stimulus), the amygdala could form synaptic linkages between the co-occurring events, allowing the internal signals to substitute for the carbon dioxide effects in producing the profound activation of the sympathetic nervous system through the outputs of the amygdala. Once the sympathetic nervous system is activated in this way, the person becomes aware of the bodily arousal and is reminded, through* explicit (conscious) *memory, that the symptoms being experienced tend to occur in panic attacks, suggesting that one might be starting. These conscious memories and thoughts about the possibility of panic might, then, by way of projections to the amygdala from the hippocampus and neocortex, lead to further and continued activation of the sympathetic nervous system, and to the built-up of a full-blown panic attack. Alternatively, in case of false feedback about the status of heart rate or other bodily functions, the chain of events probable starts with cortical cognitions (for example, the belief that the heart is beating faster), which then serve as retrieval cues for explicit memories of past experiences in which fast heart*

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14 A neuron is an individual nerve cell (the basic cell unit of the brain and spinal cord), responsible for transmitting information (Berman 2005, 127; Barlow and Durand 2002, Glossary-11) to, from or inside the brain and spinal cord (Clarke, Valerie and Susan Gillet 1997, 38).
"Neurons speak to one another, and at times to muscles and glands, in an electrical as well as chemical language. A wave of electrical voltage travels down a nerve cell's axon (the transmitting component of a neuron which carries neural impulses away from the neuron and passes this information on to a neighbouring neuron, muscle or gland) *(Stevens, 1979) and when it reaches the axon's terminals* (tiny knobs at the end of an axon's terminal branch which store the cell's chemical neurotransmitter substance) *the terminal buttons release a few thousand molecules of a chemical substance called neurotransmitter. The amount of neurotransmitter released is dependent upon how many times the axon is fired. Individual neurons cannot fire more or less strongly, but fire in an all-or-none fashion. Intense stimulation will produce more frequent signals and will increase the amount of neurotransmitter released. The neurotransmitter then travels across the gap and either allows or prevents the electrical message continuing on to the next neuron."* (Clarke, Valerie and Susan Gillet 1997, 40-1)

beating occurred (past panic attacks). These conscious thoughts and explicit memories, again by way of connections from neocortical areas and the hippocampus to the amygdala, then trigger the amygdala and its sympathetic flows as before." (LeDoux 1999, 260-1)

Any panic symptom, no matter why it occurs, would activate the amygdala and, through its outputs, the sympathetic fight or flight arousal. This would happen because the amygdala is already conditioned to associate the panicky symptoms with danger – remember that the amygdala learns what is dangerous and very easily forms associations between specific situations and pain, danger or negative outcome. (Wehrenberg and Prinz 2007, 28) For example, it may easily associate the panicky symptom of pounding heart with the suffering and fear one undergoes during a panic attack and, thus, start seeing the pounding heart as an enemy against which fight or flight activity must be initiated (See Sec. 3.5.2 for details).

In the last mentioned quote the panic-like symptoms, which activate the amygdala, occur due to the rising carbon dioxide levels in the blood. Once the activation of the amygdala arouses the body for a fight or flight activity, the subject would get aware of this condition and believe that he/she is on the verge of another panic attack. This belief would then further activate the amygdala and, through it, the fight or flight activity leading to a full blown panic attack.

3.6 The Inborn Over-reactive Stress Response System:

There may be children who are born with an expeditious or extremely intense stress response system. *"They may have too many CRF-producing neurons that generate too much stress response in relation to the intensity of the trigger."* People with myriad CRF-producing neurons have a tendency to make a mountain out of a molehill (Wehrenberg and Prinz 2007, 62-3).

3.7 The Basal Ganglia (BG) and Panic:

The sudden and unexpected panic attacks, often called "out of the blue panic attacks", are hypothesised to be the result of random firings of neurons in the basal ganglia (BG). This firing may trigger panic attacks in the same way as a short circuit suddenly establishes an unexpected electric connection. Such an activity in the BG may start at any age, but as in all panic states, once it starts it may quickly and easily develop into the psychological state of Panic Disorder (PD). (Wehrenberg and Prinz 2007, 69) The role of Gamma Aminobutyric Acid (GABA) neurotransmitter in suppressing the sporadic neuronal firing in the BG is discussed in Sec. 3.8.3.2.

3.8 The Effect of Neurotransmitters on Panic:

"I may be a lunatic, but then, wasn't my lunacy caused by a monster that lurks at the bottom of every human mind? Those who call me a madman and spurn me may become lunatics tomorrow. They harbor the same monster." (Akutagawa Ryunosuke)

Though it is an enormous oversimplification but certain psychological disorders are caused by biochemical imbalances; access or deficiencies in certain neurotransmitter systems. For example, abnormal activity of the neurotransmitter serotonin (SE) is often described as causing depression. Changes in neurotransmitter activity may make people more or less likely to exhibit certain kinds of behaviour in certain situations. The broad based disturbances in the human functioning are almost always associated with the interactions of the various neurotransmitter systems rather than alterations in the activity of any single neurotransmitter (Barlow and Durand 2002, 42-3).

3.8.1 Serotonin (SE):

Serotonin (SE) is a neurotransmitter which has a significant impact on the functioning of many brain structures and systems including those that affect anxiety. Its role in PD is most clear in its function to help maintain balance in the neurochemical feedback between those neurochemicals which affect mood, anxiety, attention and reward. Most important of all these is its impact on norepinephrine (NE) levels, which is postulated as a cause of panic. *"SE and NE function in a feedback loop with each other. In a healthy brain, when SE is sufficiently available, NE levels remain balanced."* (Wehrenberg and Prinz 2007, 100)

3.8.1.1 SE and NE Feedback Mechanism:

Wehrenberg and Prinz further explain SE and NE feedback mechanism as follows:

"When SE is insufficient in the nervous system it can contribute to the sensation of panic. Because of the feedback mechanism between SE and NE transmitters, when SE is low, NE increases as a means to try to boost production of SE. When SE levels rise, NE production can drop off. In a brain in which SE production is impaired for some reason and when NE production cannot stimulate it sufficiently, the levels of SE rapidly become too low. That combination is postulated to cause symptoms of depression. An interesting adjunct to the hypothesis for NE causes of panic disorder is that if the increased NE cannot raise SE levels sufficiently, symptoms of anxiety and depression may both occur because the balance between these neurotransmitters is impaired, causing several systems in brain function to

become disturbed." (Wehrenberg and Prinz 2007, 100)

3.8.1.2 The Effect of SE on the Panic Related Brain Structures:

Wehrenberg and Prinz discuss the effect of SE on the vital brain structures involved in PD as follows:

"When SE is dysregulated, the limbic system[15] is more active and less able to modulate its activity...

In the prefrontal cortex (PFC), activity to solve problems occurs. It takes some energy to look for good solutions and evaluate their chance of working. When SE levels are low, the PFC has lower energy and interrupted concentration, making it harder to ward off anxiety. Low SE levels in the PFC also make it harder to see positive outcomes, as there is less energy to modulate the negativity of the limbic system." (Wehrenberg and Prinz 2007, 175-6)

Citing the work of Maron et al. (2004), they write:

"It is possible that there is not enough serotonin to allow the interior cingulate gyrus (ACG) to dampen limbic signals of distress." (Wehrenberg and Prinz 2007, 69)

As it is discussed above (Sec. 3.5.1), the PFC sends modulating information to the amygdala through the ACG (Wehrenberg and Prinz 2007, 194) which needs an appropriate level of serotonin to function efficiently and effectively (Wehrenberg and Prinz 2007, 45).

3.8.2 Norepinephrine (NE):

Some PD patients are known to have an excess release of NE[16] which causes an outburst of anxiety-producing symptoms. The chronic excess activation of NE may sensitize the brain to easily trigger a panic attack. NE may be excessively activated in stressful and traumatic situations. (Wehrenberg and Prinz 2007, 96-7) Some other ways paving way to excessive NE release in the brain are summarized by Wehrenberg and Prinz as follows:

One way that NE neurons release too much NE is related to a hypersensitivity to an alpha-2 auto-receptor antagonist. When a neurotransmitter is released into a

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15 *"A loosely defined, widespread group of brain nuclei that innervate each other to form a network; involved in mechanisms of emotion and learning."* (Rosenzweig, Breedlove and Watson 2005) The limbic system includes the thalamus, amygdala, hippocampus, cingulate cortex and some other brain structures (Rosenzweig, Breedlove and Watson 2005).

16 From NE neurons in the locus coeruleus - the brain center that houses most of the NE nerve cells (Wehrenberg and Prinz 2007, 96-9).

synapse[17], it can be received at any site – postsynaptic or presynaptic – that is prepared to receive it (See Fig. 3.3). *An auto-receptor is on the presynaptic neuron and receives the neurotransmitter it releases. An alpha-2 auto-receptor is a presynaptic NE receptor located on the NE neuron that is releasing the NE. If activated (i.e., if it receives an NE molecule), the alpha-2 auto-receptor will slow down the release of NE. It has a breaking effect on NE release. When the braking action stops, more NE is released. This is how a healthy brain functions to regulate the release of NE.*

In some cases, however, the alpha-2 presynaptic NE auto-receptor is antagonized (blocked). Therefore, the NE is not braked as it should be. This results in an increased release of NE neurotransmitters, because the braking action of the alpha-2 auto-receptor is inhibited. So, one cause of PD may be hypersensitivity to any chemical that blocks the alpha-2 auto-receptor. This hypersensitivity results in too much release of NE, which causes the heightened physical sensation of panic. This explanation for panic is supported by the reaction to certain medications that exacerbate panic symptoms in people with PD. For example, the medication yohimbine is an alpha-2 antagonist. When administrated to PD patients, it triggers an exaggerated anxiety response. Caffeine, also an alpha-2 auto-receptor antagonist, similarly causes heightened anxiety and panic in PD patients...

Another possibility related to NE is that the patient has a hyposensitive alpha-2 NE auto-receptor. If a PD patient is not sufficiently sensitive at the alpha-2 auto-receptor site, the receptor will not shut down release of NE. The normal braking action does not occur. The end result is an increased release of the NE neurotransmitter." (Wehrenberg and Prinz 2007, 96-9)

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17 *"The small junction across which a nerve impulse passes from one nerve cell to another nerve cell, a muscle cell, or a gland cell. The synapse consists of the synaptic terminal, or presynaptic ending, of a sending neuron, a postsynaptic ending of the receiving cell that contains receptor sites, and the space between them (the synaptic cleft). The synaptic terminal contains neurotransmitters and cell organelles including mitochondria. An electrical impulse in the sending neuron triggers the migration of vesicles containing neurotransmitters toward the membrane of the synaptic terminal. The vesicle membrane fuses with the presynaptic membrane, and the neurotransmitters are released into the synaptic cleft and bind to receptors of the connecting cell where they excite or inhibit electrical impulses."* (The Free Dictionary 2008) See Fig. 3.3.
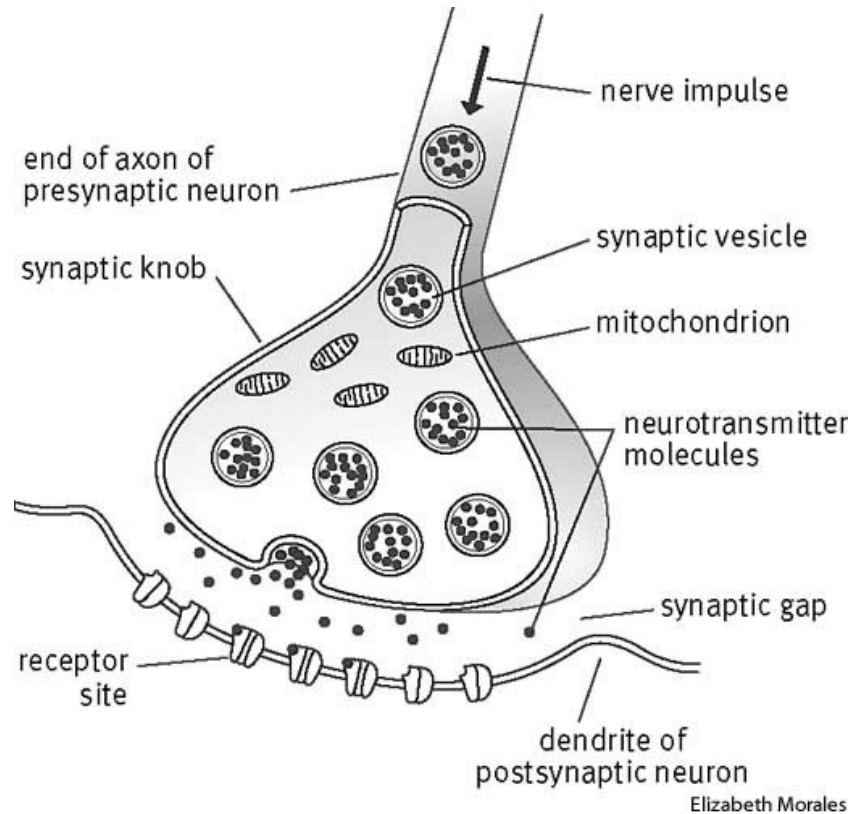
Fig. 3.3: Chemical Activity between Presynaptic and Postsynaptic Neurons (Source: The Free Dictionary 2008)

3.8.2.1 NE – the Initiator of Fight or Flight Activity:

During the stress response, NE sets off the "fight or flight" sympathetic arousal after being stimulated by adrenalin (AD) (Wehrenberg and Prinz 2007, 47, 60). In a panicky state, NE triggers blood pressure to rise as part of the fight or flight response to the fear emotion (Wehrenberg and Prinz 2007, 47). In addition, it activates the peripheral nervous system (PNS)[18] which, in turn, activates heart, muscles and extremities. As NE boosts, so does heart rate and blood pressure, and anxious symptoms such as sweating, flushing, and tremor (involuntary shaking of the body or limbs) appear. (Wehrenberg and Prinz 2007, 16)

3.8.2.2 NE and Hypervigilance:

High levels of NE are known to create sensations of hyperarousal[19]. Chronic high levels

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18 A subdivision of the nervous system. The sympathetic nervous system (SNS), which is responsible for the arousal of the brain and body is a subdivision of the PNS (Clarke, Valerie and Susan Gillet 1997, 44).

19 *"A state or condition of muscular and emotional tension produced by hormones released during the fight-or-flight reaction"*. (Gale Encyclopedia of Medicine 2008)

of NE lead to hypervigilance, which is a hallmark of generalized anxiety disorder[20], trauma and PD. It keeps people high alert and makes them response vigorously to stimulation in their environment. Such people cannot relax and become exhausted from their perpetual alertness to the external world. (Wehrenberg and Prinz 2007, 47-8, 55-6)

3.8.3 Gamma Aminobutyric Acid (GABA) and Benzodiazepines:

Wehrenberg and Prinz describe the role of GABA and Benzidiazepines in panic as follows:

"Another neurochemical involved with the etiology of PD is gamma aminobutyric acid (GABA). GABA is associated with relaxing the nervous system. Enhancing the effectiveness of GABA increases the sense of overall calmness and relaxation. If GABA is not working well, a person may manifest significant anxiety and paniclike symptoms.

Benzodiazepines are endogenous (internal) brain chemicals that affect GABA neurotransmitters. In a PD patient, the ability of the benzodiazepines to modulate GABA may be out of balance. Consequently, GABA may not calm the nervous system effectively. The imbalance may have several possible causes:

- *The benzodiazepine receptor site[21] on a GABA neurotransmitter may be insufficiently sensitive to the effects of the benzodiazepine neurochemical.*

- *The receptor site may have difficulty receiving the benzodiazepine.*

- *The brain may not be making enough endogenous benzodiazepine.*

- *The GABA receptor area may be dysregulated."* (Wehrenberg and Prinz 2007, 100)

They further write while discussing the causes of generalized anxiety disorder (GAD):

"GABA is a ubiquitous neurochemical, active in all regions of the brain. Its function is to slow chains of neuronal firing. GABA may specifically cause problems in several brain regions related to GAD:

- *The anterior cingulate gyrus. When GABA is not working well there may be*

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20 *"A constant, excessive worry with restlessness, fatigue, irritability, and sleep disturbances; GAD patients can also experience their minds going blank, muscle tension, and feeling on edge."* (Berman 2005, 125)

21 *"A protein molecule on the surface of a cell that receives and binds neurotransmitters, hormones, etc."* (Berman 2005, 127)

a tendency to increase rumination[22]. This is because of the failure to slow activity in the ACG, where the brain does considerable work shifting from one idea to another. Thus, rumination may be the result of inefficient GABA-A functioning."

- *The limbic system. Slow, inefficient GABA may also contribute to overactivity in the limbic system, where negativity is stirred.*

- *The prefrontal cortex needs GABA to help slow and stop deliberate cognitions of worry. When it is low on GABA, it will be unable to suppress worry in any part of the brain effectively."* (Wehrenberg and Prinz 2007, 177)

Though the above discussion is in context of GAD but it is related to the present study as well for the GABA dependent ACG, limbic system and PFC functioning is vital to the etiology of PD (See Sec. 3.5.1 and 3.8.1.2).

3.8.3.1 Chloride Conductance in GABA Neurons:

Wehrenberg and Prinz describe the role of chloride ion conductance in panic as follows:

"An additional aspect of the benzodiazepine-GABA connection relevant to the etiology of panic is that the brain may be producing too much anxiogenic inverse agonist (a substance that binds to a benzodiazepine receptor and causes a slowing down of chloride ion transmission). When chloride ions travel through the nerve cell they help relax the nervous tissue, slowing its activity. When the benzodiazepine receptor site is activated by a benzodiazepine, chloride (a negatively charged ion) is more available to flow through the nerve cell. In other words, chloride conductance is increased by a benzodiazepine at the receptor site.

If people with PD have too much inverse agonist[23] binding to the benzodiazepine receptors site on the GABA-A receptor complex, this inverse agonist then acts opposite to the benzodiazepine. It causes a decrease in the chloride ion conductance in the nervous tissue. This results in heightened anxiety.

In PD patients a dysregulation of this chloride channel receptor complex may be caused by a problem at the benzodiazepine receptor." (Wehrenberg and Prinz 2007, 100-01)

They further explain:

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22 Preoccupying thoughts, about almost any type of worry, in face of which concentration and attention fail (Wehrenberg and Prinz 2007, 121).

23 *"Chemical substance that produces effects opposite those of a particular neurotransmitter."* (Barlow and Durand 2002, Glossary-9)

"A GABA neuron has two GABA receptor sites: GABA-A and GABA-B. If activated, the GABA-A receptor site modulates the amount of chloride that is transmitted through the neuron. An increased chloride flow has an overall relaxing effect on the cell and subsequently on the nervous system. So, if GABA-A is not working efficiently, anxiety and tension are heightened." (Wehrenberg and Prinz 2007, 177-78)

3.8.3.2 Basal Ganglia (BG), GABA and Panic:

Wehrenberg and Prinz write:

"Erratic firing of neurons in the BG, a mild seizurelike activity resulting from problems with GABA function, triggers panic attacks." (Wehrenberg and Prinz 2007, 26)

Discussing the effect of insufficient or ineffective GABA in the BG of a GAD patient, they write:

"GABA is an important neurochemical in the BG which set the overall level of mental energy or tone. GABA slows down the rate of firing of neurons. In the BG of a client with GAD, it is likely that GABA is insufficient or not allowing the relaxation of the neurons, leading to excessive firing of the neurons in the BG." (Wehrenberg and Prinz 2007, 128)

Though GAD is under discussion here but, as mentioned above, the excessive firing of neurons in the BG can also trigger panic attacks (See Sec. 3.7).

***Summary*:** There are many theories about the origin of panic disorder (PD) which may be categorized under the two main headings: biological and psychological. However, most of the practising psychotherapists view PD as an outcome of both the human anatomy and psychology. The present study tends to provide a full system dynamics (SD) translation of the contemporary biological and psychological conceptualizations of PD.

Stress response is a hard-wired automatic biological response of the nervous system to a stressor or danger. The panic attacks of a PD patient are the outcome of "unnecessary" stress response reaction, i.e., without any real danger. The amygdala plays a vital role in initiating such a stress response before the cortex could analyze the situation in detail and inform the amygdala that stressing is not the appropriate response. The amygdala quickly forms association between pain, danger and specific situations. This information is stored in an unconscious memory system which may, later on, serve to repeatedly activate the stress response reaction.

The more often a brain goes into a panic attack, the more easily a panic attack can be set off the next time. In respond to the physical symptoms of panic attacks, the cognitive symptoms develop which expand panic attacks into PD. These cognitive symptoms include erroneous thoughts that a person is dying, losing control or going crazy etc.

There may be problems with certain brain structures and functions of some individuals which contribute to the development of PD. Some individuals have naturally over-reactive stress response system which generates a lot of stress in relation to the intensity of the trigger. Similarly, some individuals have sporadic firings of neurons in the basal ganglia which causes out of the blue panic attacks.

Various neurotransmitters are important to the etiology of PD. Low levels of serotonin (SE) in the nervous system may largely contribute to the sensation of panic. Some people have an excess release of norepinephrine (NE) which results in a cascade of symptoms that are anxiety producing and lead to panic symptoms. Gamma Aminobutyric Acid (GABA) is another neurotransmitter which when not working well in the brain may manifest significant anxiety and panic-like symptoms in an individual.

4. Translating the PD Theories into Links and Loops

This section translates the key aspects of the Panic Disorder (PD) conceptualizations into the system dynamics (SD) causal links. These links are then taken a step further and used as the building blocks of the *causal loop diagrams* (CLDs). A full stock and flow model translation will be presented in the next section. The general procedure adopted in the present section is that the relevant quote(s), to each segment (for example, cognitive error and kindling), will be presented from the literature which will be interpreted and then represented in the form of causal link(s). Finally, at the end of each segment, its individual causal links will be grouped together to make a unified whole in the form of a CLD. This exercise is expected to help highlight the implicit *dynamic hypothesis[24]* in the literature for the problematic behaviour shown in the reference mode (Fig. 1.2). Appendix 1 contains an overview of the method and interpretation of causal links and CLDs.

The various aspects of PD, discussed in the literature review in detail, are summarized with the help of a sub-system diagram (presented in Fig. 4.9 below) to provide an overview of the forthcoming translations. The figure shows that the *fear inducing information* or the very *first stimulus* enters into the brain and starts a self-reinforcing vicious panic cycle. It first arouses the amygdala which initiates the *fear emotion* that brings on the panic symptoms (the first panic attack). These *panic symptoms* give rise to a state of *cognitive error and kindling* and also contribute in forming *new stimuli* for future panic attacks. The *panicky sensations* shown within the c*ognitive error and kindling* circle also take part in the creation of new stimuli. *Cognitive error and kindling* intensifies the *fear emotion* and through it the *panic symptoms* which reinforce back *cognitive error and kindling*. The *newly created stimuli* frequently arouse the amygdala and with it the whole panic cycle – leading to various panic attacks over time or, in technical terminology, PD. *GABA* is a calming neurotransmitter and it helps calming down the amygdala whenever it is aroused.

---

24 A working theory of how the dynamic problem arose from the structure of the system (Sterman 2000, 95).

Fig. 4.9: A Sub-system Diagram Summarizing Various Aspects of PD

4.1 Translation of the Amygdala and Prefrontal Cortex (PFC) Circuitry:
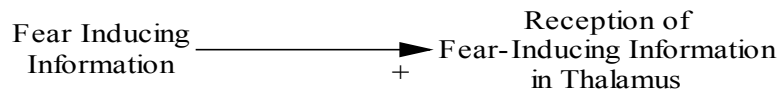
Link 1, 2 and 3:

Quotes:

> *"Information about external stimuli reaches the amygdala by way of direct pathways from the thalamus as well as by way of pathways from the thalamus to the cortex to the amygdala."* (LeDoux 1998, 164)

> *What is known about the amygdala is that it has a dual sensory input system. Both inputs run from the eyes, ears, and other sense organs to the thalamus. At that point the inputs diverge. One pathway leads directly to the amygdala while the other first passes through the cortex.* (Holt 1998, 2)

Interpretation:

As suggested by LeDoux, Holt and Rosenzweig et al. (2005, 472), the thalamus receives the fear-inducing information first and then relays it to the amygdala directly as well as through the prefrontal cortex (PFC). It means that the fear inducing information is first perceived in the thalamus (See Link 1) and when it exists in the thalamus, it exists in the amygdala (See Link 2) and PFC as well (See Link 3).

Links:

Fear Inducing Information ⟶ Reception of Fear-Inducing Information in Thalamus
+

Link 1

Reception of Fear-Inducing Information in Thalamus ⟶ + Reception of Fear-Inducing Information in Amygdala

Link 2

Reception of Fear-Inducing Information in Thalamus ⟶ + Reception of Fear-Inducing Information in PFC
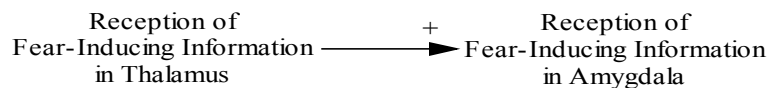
Link 3

Link 4:

Quotes:

"The direct thalamo-amygdala path is a shorter and thus a faster transmission route than the pathway from the thalamus to the cortex to the amygdala. However, because the direct pathway bypasses the cortex, it is unable to benefit from cortical processing. As a result it can only provide the amygdala with a crude representation of the stimulus. It is thus a quick and dirty processing pathway." (LeDoux 1998, 164)

"The amygdala is prepared to handle the things that are frightening by stimulating fear circuitry. It connects to the hypothalamus to set the stress response system in action. It also connects to the locus coeruleus to get NE pumping to start fear responses... This flurry activity all occurs without mediation from the PFC. It is an instantaneous response, and all of it begins before the PFC can receive the sensory information the amygdala is responding to." (Wehrenberg and Prinz 2007, 194-95)

Interpretation:

The direct amygdo-thalamus pathway is shorter and faster as compared to the pathway from the thalamus to the cortex to the amygdala so the amygdala gets thalamic input first (LeDoux 1998, 164; Holt 1998, 2; Wehrenberg and Prinz 2007, 26) See Sec. 3.5.1 for details.

Unlike the amygdala, the cortex has an ability to do a clean and thorough analysis of the fear-inducing information. It is after this analysis that it lets the amygdala know if the fear-inducing information is real and a fight or flight activity is required or it is fake and needs no such activity. As the thalamic (fear-inducing) input, first, directly reaches the amygdala bypassing the cortex, it is void of any cortical analysis at this stage. This makes the amygdala perceive the fear-inducing information as a "threat" does not matter even if it is not dangerous at all in reality and its "crude" stress perception immediately boosts up to prepare the body for a fight or flight from the threat.
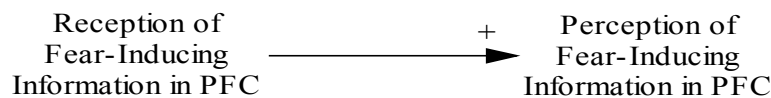
Link:

Link 4

Link 5:

Quote:

"The left PFC integrates the sensory information with information from the hippocampus about the details or context of the current sensory data, compares all of this with long-term memory of former situations, and then decides whether action is called for." (Wehrenberg and Prinz 2007, 194)

Interpretation:

The PFC takes some time, using information from various brain regions, to analyse whether the fear-inducing information is *actually* dangerous. Note that, in a PD patient, this information is typically fake and, hence, after its thorough analyses, the cortex has to send a "calm down" message to the amygdala.

Link:

Reception of   +   Perception of
Fear-Inducing ⟶ Fear-Inducing
Information in PFC   Information in PFC

Link 5

Link 6 and 7:

Quote:

"Is it necessary to be afraid or not? The PFC answers that question and then sends information through the anterior cingulate gyrus (ACG) to the amygdala to help it learn whether a stimulus is currently a cause for alarm or not. This is learning at a very practical level." (Wehrenberg and Prinz 2007, 194)

"In the cortex the frightening stimulus is analyzed in detail, using information from many parts of the brain, and a message is sent back down to the amygdala. While having both systems in place may appear to be redundant, its purpose is invaluable. The initial signal, activating the amygdala and its corresponding physiological behaviors, prepares the body for immediate reaction to the stimulus. This is part of the startle circuit. Its physiological effects are similar to the initial stages of fear. By having the body ready for action, the second circuit can then take a moment to analyze the signal in its entirety to determine whether or not the threat is real or perceived. If the threat is real, then the body is already on the go, if perceived, than nothing has been lost." (Holt 1998, 2)
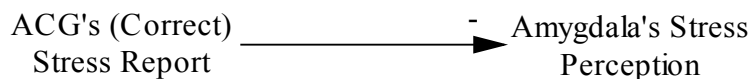
Interpretation:

The PFC sends its analytical results to the amygdala, about the fear inducing information, through the anterior cingulate gyrus (ACG) which makes the amygdala adjust its stress perception accordingly. For instance, if the fear-inducing information is a loud roar while one is walking through a jungle, the amygdala's stress level would immediately boost up in order to prepare one's body for a fight or flight activity. The PFC would take a little bit of time to analyse the reality of the sound in detail by integrating information from other brain regions. It may find out that the roar is not of an actual lion but a mere mobile phone's ring tone ringing in one's pocket. This message would be sent to the amygdala and, as a result, its perception of stress would immediately drop back to normal. Thus, the PFC exerts a "tone down" influence onto the amygdala in the absence of a real threat. However, once a stress response is initiated, it is difficult for the cortex of a panic patient to turn it off (by toning down the amygdala) (LeDoux 1998, 164) because of any of the possible disorders, for instance, certain chemical imbalances.

It is important to note here, once again, that the stimuli which cause panic attacks in a PD patient are not dangerous in reality, therefore, in PD's case, the relation of the PFC and amygdala will typically be of a *negative modulation* i.e., the PFC toning down the amygdala's activity. The correct perception of the fear-inducing information in the PFC would make the ACG convey the correct stress report to the amygdala. The amygdala's stress perception would immediately fall after receiving this report.

Links:

Correct Perception of Fear   +   ACG's (Correct)
Inducing Information in PFC   ——————▶   Stress Report

Link 6

ACG's (Correct)   -   Amygdala's Stress
Stress Report   ——————▶   Perception
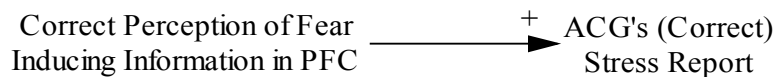
Link 7

Unfortunately, in a panic patient the PFC cannot influence or convey its message dominantly to the amygdala. In contrast, the thylamo-amygdala direct pathway, which possibly is responsible for the control of the emotional responses, dominates (LeDoux 1998, 164). This allows the amygdala's stress perception to stay high for a prolonged period of time even when the fear-inducing information is fake or not worth stressing for.

Table 4.1 summarizes the sources for the connections discussed above (See Sec. 3.5.1 for details).

Link 1	Fear Inducing Information → (+) Reception of Fear-Inducing Information in Thalamus
Description	The thalamus receives the fear-inducing information first from the sensory organs.
Source	LeDoux 1998, 164; Holt 1998, 2; Rosenzweig, Breedlove and Watson 2005, 472; Wehrenberg and Prinz 2007, 26
Link 2	Reception of Fear-Inducing Information in Thalamus → (+) Reception of Fear-Inducing Information in Amygdala
Description	The thalamus passes the fear-inducing information on to the amygdala. When this information exists in the thalamus, it also exists in the amygdala with a slight delay.
Source	LeDoux 1998, 164; Holt 1998, 2; Rosenzweig, Breedlove and Watson 2005, 472; Wehrenberg and Prinz 2007, 26
Link 3	Reception of Fear-Inducing Information in Thalamus → (+) Reception of Fear-Inducing Information in PFC
Description	The thalamus passes the fear-inducing information onto the PFC. When this information exists in the thalamus, it also exists in the PFC with a slight delay.
Source	LeDoux 1998, 164; Holt 1998, 2; Rosenzweig, Breedlove and Watson 2005, 472; Wehrenberg and Prinz 2007, 26
Link 4	Reception of Fear-Inducing Information in Amygdala → (+) Amygdala's (Crude) Stress Perception
Description	The amygdala perceives the fear-inducing information as dangerous, unpleasant or stressful. The reception of fear inducing information in the amygdala boosts its perception of stress.

Source	LeDoux 1998, 164; Holt 1998, 2; Wehrenberg and Prinz 2007, 28
Link 5	Reception of Fear-Inducing Information in PFC $\xrightarrow{+}$ Perception of Fear-Inducing Information in PFC
Description	The PFC forms a correct perception of the fear-inducing information by integrating information from various brain regions.
Source	Holt 1998, 2; Wehrenberg and Prinz 2007, 194
Link 6	Correct Perception of Fear Inducing Information in PFC $\xrightarrow{+}$ ACG's (Correct) Stress Report
Description	The PFC exerts a modulating effect onto the amygdala through the ACG. The more clear and effective the PFC's perception of the fear-inducing information, the more the ACG's correct stress report to the amygdala.
Source	Wehrenberg and Prinz 2007, 194
Link 7	ACG's (Correct) Stress Report $\xrightarrow{-}$ Amygdala's Stress Perception
Description	The more efficient the ACG's correct stress reporting to the amygdala, the less the stress perception of the amygdala.
Source	Holt 1998, 2; LeDoux 1998, 164; Wehrenberg and Prinz 2007, 194

Table 4.1: The Translation of the Fear-Inducing Information, Amygdala and PFC Connections

Synthesizing the Links:

The *fear inducing information*[25] is first *received in the thalamus* (See Fig. 4.1). From there, it is relayed on to the *amygdala* as well as *prefrontol cortex (PFC)*. The *amygdala's crude stress perception* instantly boosts up upon receiving this information. It is being referred to as "crude" because there is no thinking or analysis of the *fear-inducing information* involved in this instant boost up. However, on the other hand, the *cortex* analyses the same *fear information* in detail taking help from some other brain regions

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25 For reader's convenience, all the variable names used in the CLDs are italicized in the dynamic hypothesis sections.

(these regions are not shown in Fig. 4.1) to see whether it is worth stressing for but this does not happen without a cost which is time (See Loop 'B1'). First, the *fear inducing information* is received in the *cortex* far too late as compared to its reception in the *amygdala* (The delay mark on the arrow from *stimuli reception in thalamus* to *PFC's perception gap* highlights this delay). Secondly, involving other brain regions and analysis of the very *information* causes a further delay in this process. This allows the *amygdala's crude or blind stress perception* to stay high for some time until the *PFC* regulates it back through the *anterior cingulate gyrus (ACG)* (See Loop 'B2'). In the case of a PD patient, as the *fear inducing information* is typically fake, the *cortex* has to tone down the *amygdala's stress perception* rather than reinforcing it which would be the case if the *fear inducing information* were real, for example, an encounter with a snake or a known serial killer.

One contributing factor to the panic attacks of a PD patient may be that the circuitry between the *amygdala* and *cortex* (shown in Fig. 4.1) may not be working properly. The *PFC* may not have enough energy to perform its work or the *ACG* may not calm down the *amygdala's stress perception* properly due to some reason. This allows the *amygdala's stress perception* to stay high for a prolonged period of time which literally means that the amygdala would keep stimulating the stress response hormone, and through it, the fear emotion - eventually leading to the panic symptoms (see Sec. 4.3).
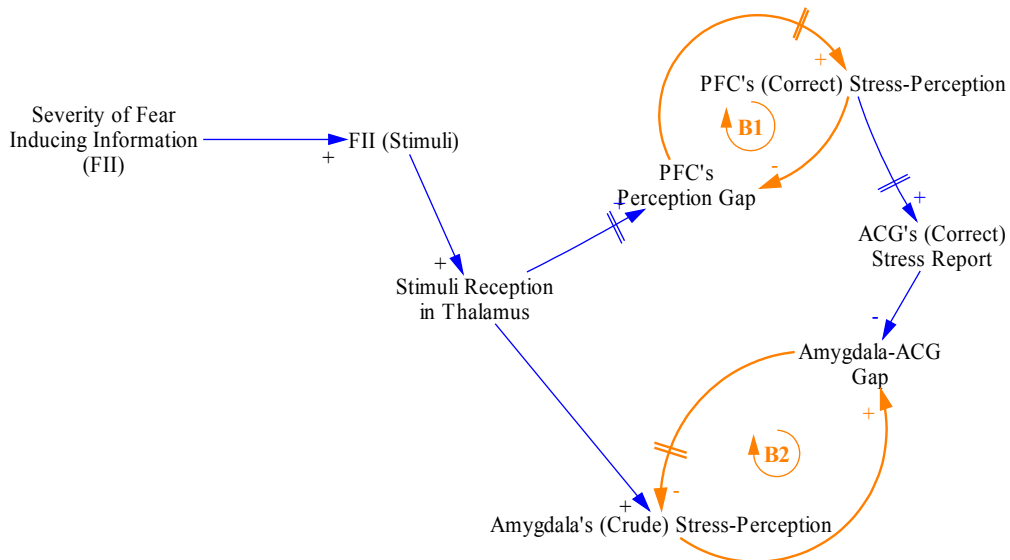
Fig.4.1: A CLD Showing the Fear Inducing Information (FII), Amygdala and PFC Connections

4.2 Translation of Norepinephrine (NE) and Serotonin (SE) Feedback System:

Link 8 and 9:

Quote:

"SE and NE function in a feedback loop with each other. In a healthy brain, when SE is sufficiently available, NE levels remain balanced.

When SE is insufficient in the nervous system it can contribute to the sensation of panic. Because of the feedback mechanism between SE and NE transmitters, when SE is low, NE increases as a means to try to boost production of SE. When SE levels rise, NE production can drop off." (Wehrenberg and Prinz 2007, 100)

Interpretation:

It means that the lower the SE levels, the higher the NE production and, hence, levels in the brain as compared to what the NE levels would have been in the presence of comparatively higher SE levels (Link 8 represents this relation). On the other hand, the higher the NE levels, the higher the SE production and, hence, levels in the brain (Link 9 represents this relation).

Links:

SE Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ NE Levels
                                            −

Link 8

NE Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ SE Levels
                                            +

Link 9
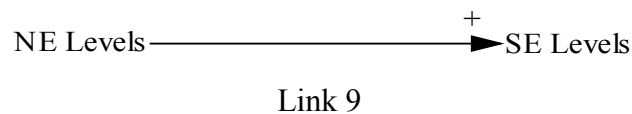
Link 10:

Quote:

In a brain in which SE production is impaired for some reason and when NE production cannot stimulate it sufficiently, the levels of SE rapidly become too low. ...If the increased NE cannot raise SE levels sufficiently, symptoms of anxiety and depression may both occur because the balance between these

neurotransmitters is impaired, causing several systems in brain function to become disturbed." (Wehrenberg and Prinz 2007, 100)

Interpretation:

When the SE production is impaired for some reason, NE cannot stimulate it. It means that when there is an SE impairment in the brain, it would result in the lower SE levels as compared to what they would otherwise have been.

Link:

$$\text{SE Impairment} \xrightarrow{\quad - \quad} \text{SE Levels}$$

Link 10
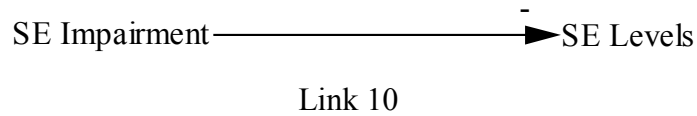
The whole process through which SE and NE contribute to PD will be translated later on (Secs. 4.3, 4.5 and 4.8); for now it is important to understand the internal SE/NE feedback mechanism.

Link 8	$\text{SE Levels} \xrightarrow{\quad - \quad} \text{NE Levels}$
Description	The more the SE levels, the less is the NE production and, hence, levels as compared to what they would otherwise have been.
Source	Wehrenberg and Prinz 2007, 100; 104
Link 9	$\text{NE Levels} \xrightarrow{\quad + \quad} \text{SE Levels}$
Description	The more the NE levels, the more is the SE production and, hence, levels.
Source	Wehrenberg and Prinz 2007, 100; 104
Link 10	$\text{SE Impairment} \xrightarrow{\quad - \quad} \text{SE Levels}$
Description	The more the SE impairment, the less the SE levels.
Source	Wehrenberg and Prinz 2007, 100

Table 4.2: The Translation of the Mutual NE and SE Connections

Synthesizing the Links:

When *serotonin (SE)* is low in the brain, it stimulates the *norepinephrine (NE)* production which, in return, stimulates the production of *SE*. When *SE* is sufficiently produced, it stops stimulating the *NE* production. This *SE* and *NE* feedback system is highlighted in Fig. 4.2. In this figure, *SE* and *NE* both adjust to the same goal, i.e., the *NE-SE desired ratio*. The low *SE* levels increase the *NE* (divided) *by SE* value and with it *NE by SE ratio gap* which results in increasing the *SE activation rate* and, hence, the *SE* levels (See Loop 'B', Fig. 4.2). Note that as the *SE* levels rise, the *NE by SE* value decreases causing the *NE by SE ratio gap* to diminish which slows down the *SE activation rate* as a result of which the *SE* levels do not keep rising infinitely but balance towards a certain level. This process seeks to "balance" the fallen *SE* levels back to normal, therefore, it is highlighted as a balancing loop. Now take *NE*. When the low *SE* levels increase the *NE by SE* value and with it the *NE-SE ratio gap*, it results in increasing the *NE activation rate* and with it the *NE* levels. When the *NE* levels rise, the *NE by SE ratio gap* increases which increases the *SE activation rate* and with it the *SE* levels. With the rising *SE* levels, the *NE-SE ratio gap* diminishes which slows down the *NE activation rate* and, hence, *NE* does not keep rising infinitely but balances towards a certain level. Without the involvement of *SE*, *NE* would only reinforce itself through the *NE-SE ratio gap* that is why this feedback process is highlighted as a reinforcing one.
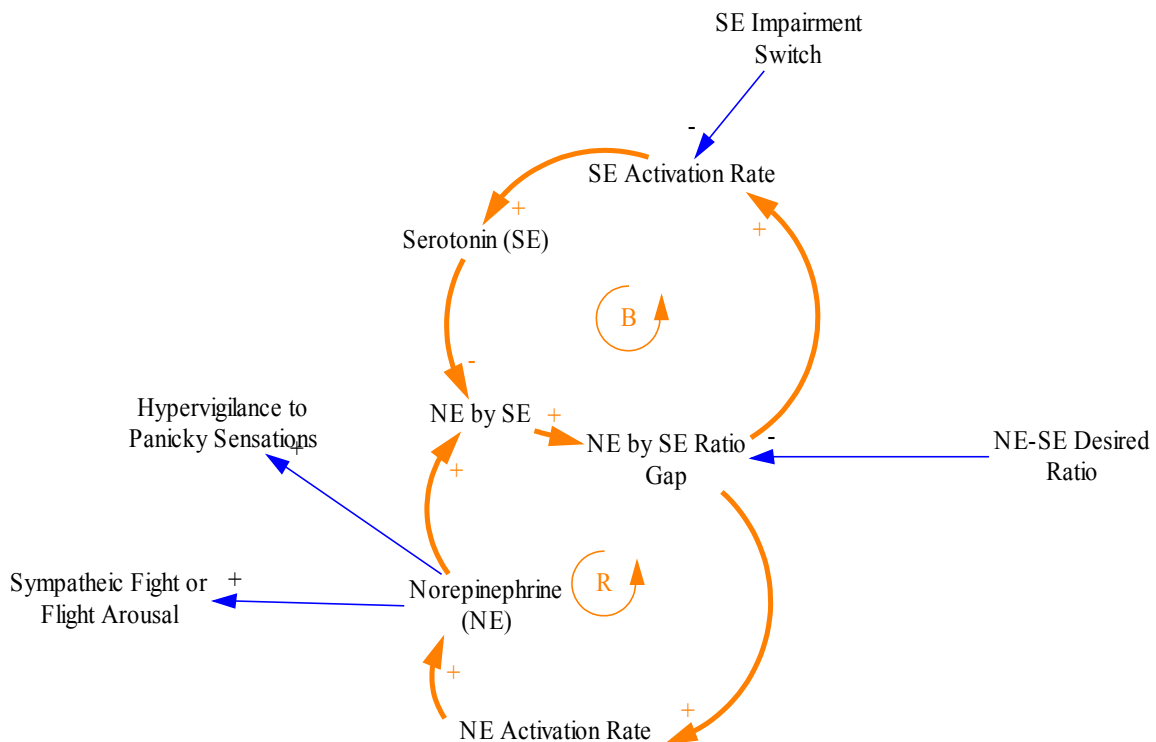
Fig. 4.2: The NE/SE Feedback System

45

In a brain in which the *SE* production is impaired for some reason, the loop which balances the *SE* levels becomes inactive. To be precise, when the *SE* levels fall, they increase the *NE-SE ratio gap* (through increasing *NE by SE*) which, contrary to its normal response, cannot increase the *SE activation rate* and, hence, the *SE* levels (See Fig. 4.2.1 - the dotted line highlights the broken link of the balancing loop). On the other hand, this *gap* increases the *NE activation rate* and through it, the *NE* levels. The rising *NE* levels further increase this *gap* which again, in this *SE impairment* scenario, only keeps reinforcing the *NE* levels and remains unable to do any good to the fallen *SE* levels. Eventually, this leads to the high levels of *NE* in the brain which not only result in the panicky symptoms by activating the *sympathetic nervous system (SNS)* but also create *hypervigilance to the panic-like sensations*. This raises a fundamental question here: How will NE levels come back to normal (or adjust towards some level) after being constantly reinforced in an SE impairment case? The answer to this question could not be found in the literature. The impact of *sympathetic arousal* on panic attacks will be discussed later in Sec. 4.5 and the role of *hypervigilance* in converting panic attacks into panic disorder (PD) will be made explicit in Sec. 4.8. The low levels of *SE* also contribute to PD independent of SE/NE feedback mechanism; this issue will be undertaken in Sec. 4.3.
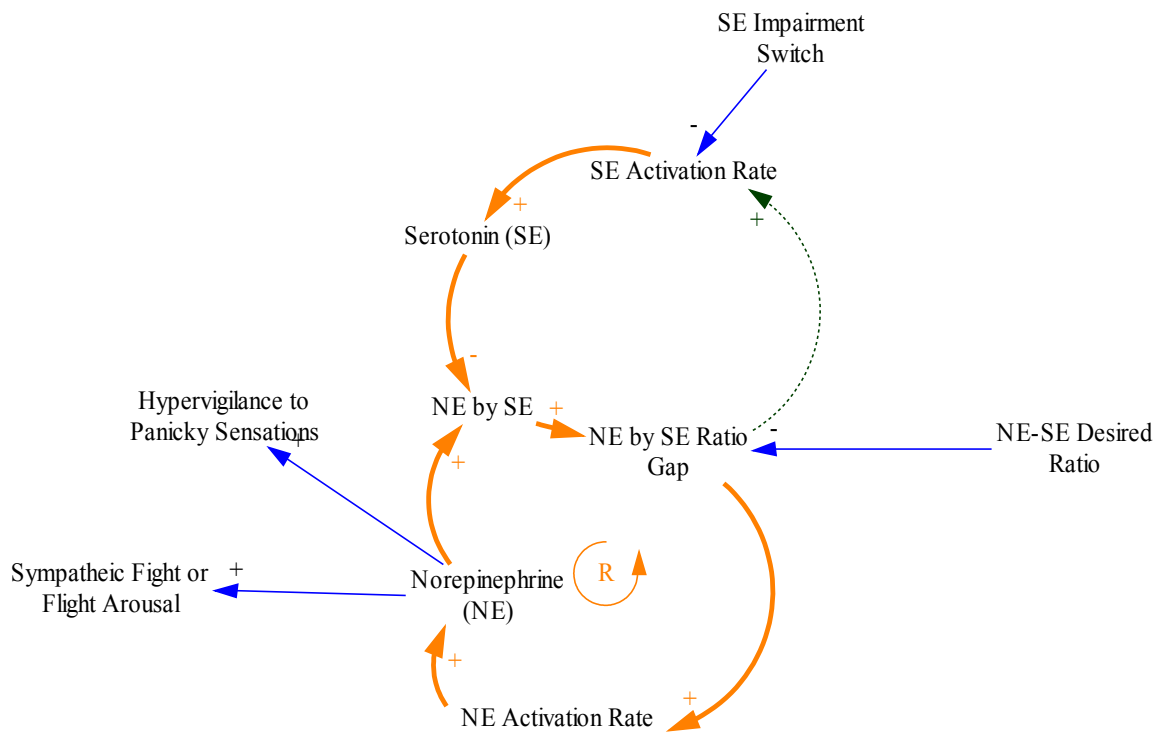
Fig. 4.2.1: The NE/SE Feedback System when SE is Impaired

Simplified Syntheses:

To simplify the above dynamic hypothesis, the most important of the variables used in

Fig. 4.2 are selected here to make a simplified CLD (Fig. 4.2a) which will later be used to develop a simple yet concise stock and flow model. In this simplified diagram, the variable *hypervigilance to panicky sensations* is dropped as, in the "bigger picture" (the whole PD conceptualization), the very variable may easily be bypassed (See Sec. 4.8).
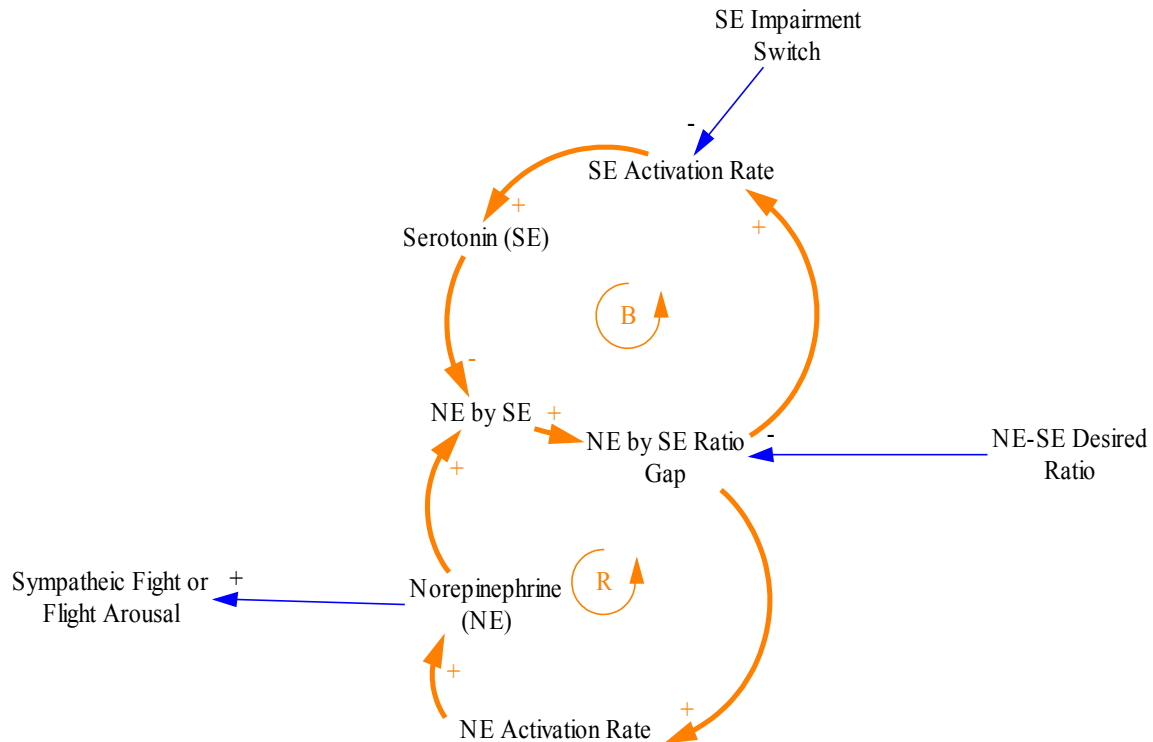

Fig. 4.2a: A Simplified NE and SE Feedback CLD

4.3 Translation of the Activation of the Stress Cycle (Fear Emotion) through the Amygdala:

When the amygdala's stress perception goes up, it immediately starts preparing the body to fight or flee from the perceived danger. It activates different hormones and chemicals in the body which provide an individual with the required energy to either fight or escape from the plausible danger (See secs. 3.4 and 3.5).

Link 11:

Quote:

"The amygdala directly connects to the parabrachial nucleus for panting respiration." (Wehrenberg and Prinz 2007, 28)

Interpretation:

The amygdala and hypothalamus initiate the stress response reaction (Wehrenberg and Prinz 2007, 31). During the stress response, the amygdala directly connects to the parabrachial nucleus to initiate panting respiration (Wehrenberg and Prinz 2007, 28; 34) typical of panic attacks (Wehrenberg and Prinz 2007 34). It means that the more the amygdala's perception of stress, the more the panting respiration as compared to the normal respiration.

Link:

Amygdala's Stress Perception $\xrightarrow{\quad +\quad}$ Panting Respiration
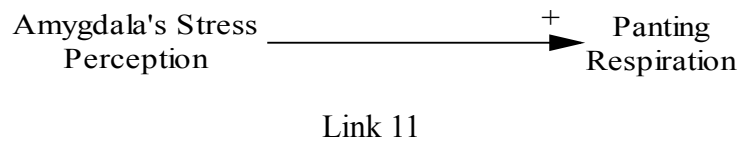
Link 11

Link 12:

Quotes:

> *"The amygdala directly connects to the hypothalamus to initiate stress response."* (Wehrenberg and Prinz 2007, 28)

> *"When a stress is perceived... the hypothalamus releases corticotrophin release factor (CRF), often called the stress response hormone[26]."* (Wehrenberg and Prinz 2007, 59-60)

Interpretation:

After the amygdala has assigned an emotional tone to a stimulus such as dangerous, unpleasant or threatening (Wehrenberg and Prinz 2007, 28), it connects to the hypothalamus to make it release the *stress response hormone* (Wehrenberg and Prinz 2007, 31). It means that the more the amygdala's arousal, the more the CRF release and, hence, levels.

---

26 CRF is also known as the corticotrophin releasing hormone (CRH) and corticoliberin (On-line Medical Dictionary).

Link:

Amygdala's Arousal or $\xrightarrow{\quad + \quad}$ CRF Levels
Stress Perception
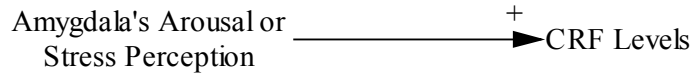
Link 12

Link 13, 14 and 15:

Quote:

> *"CRF causes the pituitary to release adrenocorticotropin hormone (ACTH), which instructs the adrenal gland to release adrenalin (from the medulla) and cortisol (from the adrenal cortex)."* (Wehrenberg and Prinz 2007, 60)
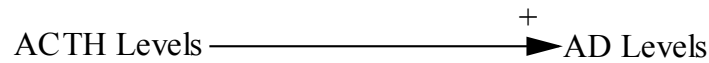
Interpretation:

The CRF activates the release of *adrenocorticotropin hormone* (ACTH). The ACTH carries out two important functions simultaneously; it makes the *adrenal glands* release the *adrenalin* as well as c*ortisol* (Wehrenberg and Prinz 2007, 31; 60). It means that the more the CRF levels, the more the ACTH levels (See Link 13). Also, the more the ACTH, the more the AD (See Link 14) and cortisol levels (See Link 15).

Links:

CRF Levels $\xrightarrow{\quad + \quad}$ ACTH Levels

Link 13

ACTH Levels $\xrightarrow{\quad + \quad}$ AD Levels

Link 14

ACTH Levels $\xrightarrow{\quad + \quad}$ Cortisol Levels
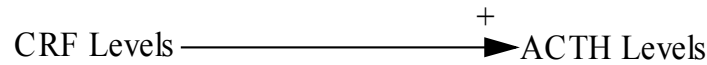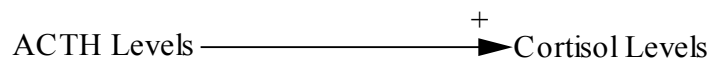
Link 15

Link 16:

Quote:

"Thus (during the stress response)*, instead of using the physical arousal to move, your body may increase adrenalin flow, making you feel shaky and weak."* (Wehrenberg and Prinz 2007, 60).

Interpretation:

Increased adrenalin (AD) secretion makes one feel shaky and weak. The more the AD levels, the more the sensation of shakiness.
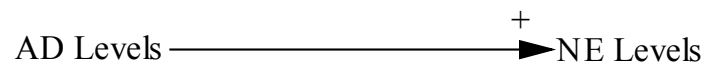
Link:

AD Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯► Shakiness
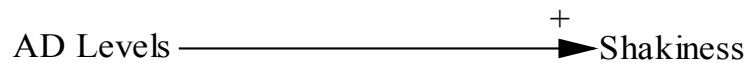
Link 16

Link 17 and 18:

Quotes:

"Norepinephrine is stimulated during the stress response by adrenalin." (Wehrenberg and Prinz 2007, 47)

"The hypothalamus signals for the release of norepinephrine (NE) in the pons, which sets off 'fight or flight' activity." (Wehrenberg and Prinz 2007, 60)

Interpretation:

AD stimulates norepinephrine (NE) which turns on the fight or flight activity. The more the AD levels, the more the NE levels. The more the NE levels, the more the sympathetic fight or flight arousal. NE also works in a negative feedback loop with SE (See Secs. 3.8.1.1 and 4.2).

Links:

$$\text{AD Levels} \xrightarrow{\quad + \quad} \text{NE Levels}$$

Link 17

$$\text{NE Levels} \xrightarrow{\quad + \quad} \begin{array}{c} \text{Fight or Flight} \\ \text{Sympathetic Arousal} \end{array}$$
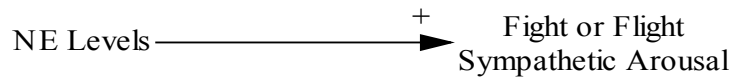
Link 18

Link 19, 20 and 21:

Quotes:

"When SE (Serotonin) is dysregulated, the limbic system is more active and less able to modulate its activity...

In the prefrontal cortex (PFC), activity to solve problems occurs. It takes some energy to look for good solutions and evaluate their chance of working. When SE levels are low, the PFC has lower energy and interrupted concentration, making it harder to ward off anxiety. Low SE levels in the PFC also make it harder to see positive outcomes, as there is less energy to modulate the negativity of the limbic system." (Wehrenberg and Prinz 2007, 175-6)

"It is possible that there is not enough serotonin to allow the interior cingulate gyrus (ACG) to dampen limbic signals of distress." (Wehrenberg and Prinz 2007, 69)

Interpretation:

When SE is low in the brain, it contributes to panic in the following ways:

- The limbic system, including the amygdala, remains unable to modulate (tone down in PD case) its activity.

- The PFC cannot properly tone down the amygdala's activity through the interior cingulate gyrus (ACG).

- The PFC itself has lower energy because of which it cannot perform its analysis work effectively. (See Sec. 3.8.1.2 for details.)

It means that the less the SE levels, the more the amygdala's perception of stress due to its heightened activity. In other words, the more the SE levels, the less the amygdala's perception of stress (See Link 19). Also, the more the SE levels, the more effective the ACG's correct stress reporting to the amygdala (See Link 20) and the more efficient the PFC's perception of the stimulus due to the availability of sufficient energy to work (See Link 21).

Links:

SE Levels ⟶ — Amygdala's Stress Perception

Link 19

SE Levels ⟶ + ACG's (Correct) Stress Report

Link 20

SE Levels ⟶ + Perception of Fear-Inducing Information in PFC
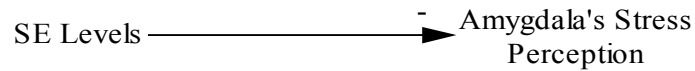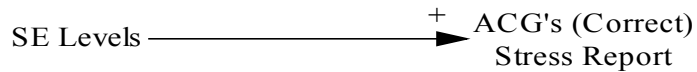
Link 21

Link 22:

Quote:

> *"The stress response system turns itself off with cortisol. As the end point in a feedback loop, cortisol signals to the hypothalamus that the CRF has done its work and does not need to be released any longer. The CRF has produced the necessary heightened arousal, and the cortisol is received in the hypothalamus as a "turn off" so the body and brain can go back to the normal after the brief arousal caused by the adrenalin-norepinephrine spike."* (Wehrenberg and Prinz 2007, 60)

Interpretation:

The cortisol where provides fuel for the stress response (Wehrenberg and Prinz 2007, 31-2) also serves to turn it off by signalling the hypothalamus to stop releasing CRF after it has produced the necessary heightened arousal. With this turning off, the brain and body come back to the normal state. It means that, in this case, the more the cortisol

levels, the less the CRF.

Link:

Cortisol Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ CRF Levels
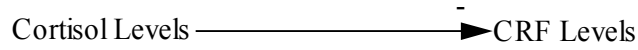
Link 22

Link 11	Amygdala's Stress Perception ⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ Panting Respiration
Description	When the amygdala perceives something as dangerous, it incites panting respiration. The more the perception, the more the panting respiration as compared to the normal respiration.
Source	Wehrenberg and Prinz 2007, 28; 34
Link 12	Amygdala's Arousal or Stress Perception ⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ CRF Levels
Description	When the amygdala assigns a negative emotional tone to a trigger, it makes the hypothalamus release CRF. The more the amygdala's arousal, the more the CRF levels.
Source	Wehrenberg and Prinz 2007, 31-2
Link 13	CRF Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ ACTH Levels
Description	CRF activates the release of ACTH. The more the CRF levels, the more the ACTH levels.
Source	Wehrenberg and Prinz 2007, 31-2
Link 14	ACTH Levels ⎯⎯⎯⎯⎯⎯⎯⎯⎯▶ AD Levels
Description	ACTH makes adrenal glands release AD. The more the ACTH, the more

	the AD.
Source	Wehrenberg and Prinz 2007, 31-2
Link 15	ACTH Levels $\xrightarrow{\ +\ }$ Cortisol Levels
Description	ACTH makes adrenal glands release cortisol. The more the ACTH, the more the cortisol.
Source	Wehrenberg and Prinz 2007, 31-2
Link 16	AD Levels $\xrightarrow{\ +\ }$ Shakiness
Description	The increase flow of AD generates feelings of shakiness. The more the AD levels, the more the sensation of shakiness.
Source	Wehrenberg and Prinz 2007, 60
Link 17	AD Levels $\xrightarrow{\ +\ }$ NE Levels
Description	AD stimulates NE. The more the AD, the more the NE levels.
Source	Wehrenberg and Prinz 2007, 47
Link 18	NE Levels $\xrightarrow{\ +\ }$ Fight or Flight Sympathetic Arousal
Description	NE turns on the fight or flight activity by activating the sympathetic nervous system. The more the NE levels, the more the sympathetic arousal.
Source	Wehrenberg and Prinz 2007, 47; 60
Link 19	SE Levels $\xrightarrow{\ -\ }$ Amygdala's Stress Perception
Description	SE helps tone down the amygdala's activity. The more the SE levels, the less the amygdala's perception of stress.
Source	Wehrenberg and Prinz 2007, 175-6

Link 20	SE Levels ⟶ $+$ ACG's (Correct) Stress Report
Description	The ACG's correct stress reporting activity depends on the SE levels in the brain. The more the SE levels, the more effective the ACG's correct stress reporting.
Source	Wehrenberg and Prinz 2007, 69
Link 21	SE Levels ⟶ $+$ Perception of Fear-Inducing Information in PFC
Description	SE provides energy for the PFC to work. The more the SE levels, the more the PFC's correct perception rate.
Source	Wehrenberg and Prinz 2007, 176
Link 22	Cortisol Levels ⟶ $-$ CRF Levels
Description	Cortisol makes the hypothalamus stop releasing CRF. The more the cortisol, the less the CRF.
Source	Wehrenberg and Prinz 2007, 60

Table 4.3: The Translation of the Fear Emotion Circuitry i.e., the Stress Response at Chemical Level

Synthesizing the Links:

When stress is perceived in the *amygdala*, it initiates the stress response reaction by stimulating the *stress response hormone. CRH* activates the whole chain of chemicals by simulating *adrenocorticotropin hormone (ACTH)* which stimulates *adrenalin (AD)* which further stimulates *norepinephrine (NE). NE* when stimulated in this way activates *serotonin (SE)* as discussed in Sec. 4.2. *SE* provides energy for the *prefrontal cortex (PFC)* to work; the more the *SE*, the greater the *PFC's* energy to carry out its *correct perception of stress*. The *PFC*, upon realising that the *fear-inducing stimulus* is fake (which is a typical case in PD), tones the *amygdala* down through the *anterior cingulate gyrus (ACG)*. This whole circuitry is highlighted in Fig. 4.3 with the help of the balancing loop 'B1'. It is a balancing loop as it weakens the *amygdala's stress perception* which initiates the stress response reaction. Note that the *amygdala's stress perception* is connected to the *panting respiration*, *AD* to the *shakiness* and *NE* to the *sympathetic*

arousal.

SE levels effect the *ACG's correct stress reporting activity* in the way that the more the *SE* levels, the more effective the *ACG's correct stress reporting to the amygdala.* This cause-and-effect relation is highlighted in Loop 'B2' of Fig. 4.3. Rest of this loop consists of the same variables as that of Loop 'B1'. 'B2' is a balancing loop as, like 'B1', it helps lower the *amygdala's stress perception* which, when rises, initiates the stress response reaction (emotion of fear).

SE levels, in addition to indirectly effecting the *amygdala's stress perception* through the functioning of *PFC* and *ACG*, directly effect it as well. Sufficient *SE* levels in the brain help the *amygdala* tone down its *stress perception*. This relationship is highlighted in Loop 'B3' (Fig. 4.3). It is a balancing loop as its overall function helps calming down the *amygdala's stress perception*.

SE works in a feedback loop with *NE* which is already discussed in Sec. 4.2. In Fig. 4.3, it is highlighted with the help of the balancing Loop 'B4'. Loops 'B1', 'B2', 'B3' and 'B4 all include *SE* as an important variable. When *SE* is low, the *PFC* and *ACG* cannot work efficiently to help tone down the unnecessary activation of the *amygdala* (*amygdala's stress perception*) in a PD patient (See Loops 'B1' and 'B2', Fig. 4.3). More so, the *amygdala* itself cannot tone down its *stress perception* in the absence of sufficient *SE* levels (See Loop 'B3', Fig. 4.3). Consequently, the *amygdala's stress perception* stays high in a PD patient activating the stress response reaction for no apparent reason. Low *SE* levels stimulate the production of *NE* so that *NE* may help rising the depleting *SE* levels. *NE*, however, cannot serve this purpose as the *SE* is impaired due to some reason in such a way that, no matter how high *NE* levels may get, the *SE* levels cannot rise. Hence, the *SE* levels rapidly diminish and, courtesy the SE/NE feedback mechanism, the *NE* levels keep rising. (See Loop 'B4', Fig. 4.3) The excessive production of *NE* triggers the *fight or flight sympathetic arousal* for no good reason. This unnecessary or false activation of the *fight or flight activity* is actually referred to as a panic attack that a PD patient frequently suffers from.

The stress response reaction turns itself off with *cortisol*. *ACTH* where stimulates the production of *AD*, stimulates *cortisol* as well. *Cortisol* helps stop the production of *CRH* which is the chemical with which the stress response reaction initiates. This feedback process is highlighted through Loop 'B5' in Fig. 4.3. It is a balancing loop as it has a braking effect on the production of *CRH*.
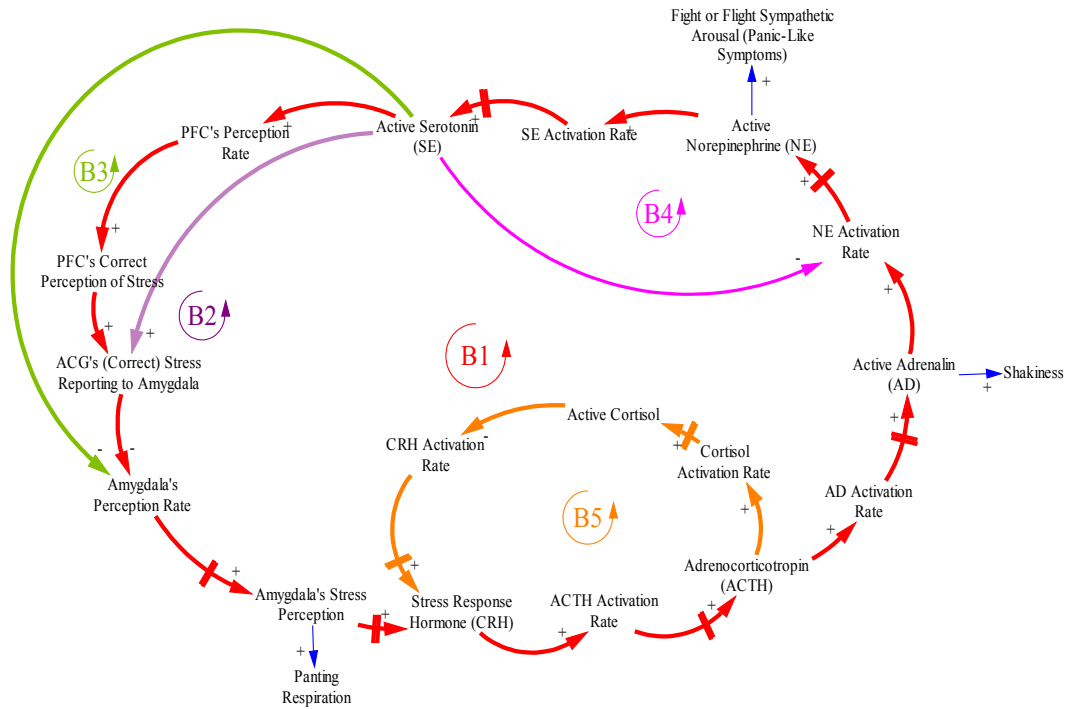
Fig. 4.3: A CLD Highlighting the Activation of the Stress Cycle through the Amygdala

Simplified Syntheses:

In this section, an effort is made to simply the CLD presented in Fig. 4.3. Activation of the neurotransmitters *ACTH* and *AD* is bypassed in the fear emotion shown in the simplified Fig. 4.3a as this much of detail, more than helping anything, may prove unnecessary for the forthcoming stock and flow model. The symptoms of *panting respiration* and *shakiness* are also excluded from Fig. 4.3a. All of these symptoms would form, more or less, similar stock and flow structure and exhibit similar behaviours, therefore, instead of modelling all of them, perhaps, it would be enough to model only the *heart rate* which would represent the presence or absence of a panic attack. Note that the variable *fight or flight sympathetic arousal (panic-like symptoms)* is replaced by the variable *heart rate* which means that the *heart rate* is now representing all the panic-like symptoms.
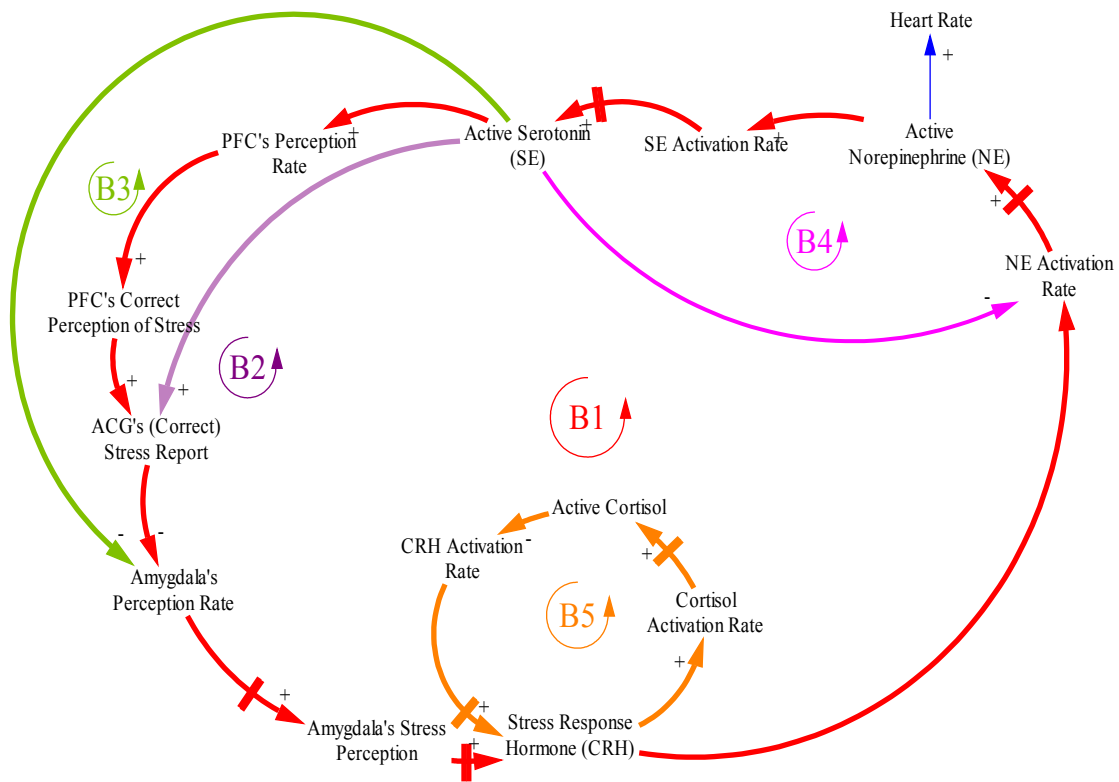
Fig. 4.3a: A Simplified CLD of the Stress Response Reaction

4.4 Translation of the Inborn Over-reactive Stress Response System:

Link 23:

Quote:

> *"Children may be born with a stress response system that reacts too quickly or too intensely. They may have too many CRF-producing neurons that generate too much stress response in relation to the intensity of the trigger. People with too many CRF neurons make mountains out of every molehill."* (Wehrenberg and Prinz 2007, 44-5)

Interpretation:

The corticotrophin release factor (CRF) is crucial in generating fight or flight activity. It is the release of this hormone by the hypothalamus which initiates the stress response reaction (Wehrenberg and Prinz 2007, 59-60). When an individual has more CRF-producing neurons than normal, even an ordinary stimulus which would not trigger the stress response in other individuals, would trigger it in such an individual. It means that

the more the CRF levels, the more intense is the stress response (See Sec. 4.3 for a detailed picture of the stress response system).

$$\text{CRF Levels} \xrightarrow{\ +\ } \begin{array}{c}\text{Stress Response}\\ \text{Reaction}\end{array}$$
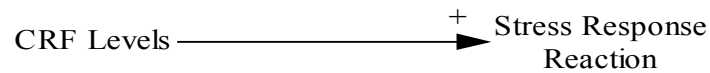
Link 23

Synthesizing the Links:

Some people are born with an over-reactive stress response system. Their brains have too many CRF-producing-neurons which result in generating too strong a stress response in relation to the intensity of the stimulus. See Fig. 4.3 (Loop 'B1') which shows that the more the *CRH*, the more the *adrenocorticotropin hormone (ACTH)* production leading to a stronger stress response reaction which ultimately results in a panic attack.

4.5 Translation of the Excess Release of Norepinephrine (NE), Fight or Flight Activity and Hypervigilance:

Link 24, 25 and 26:

Quote:

> *"...One cause of PD may be hypersensitivity to any chemical that blocks the alpha-2 auto-receptor. This hypersensitivity results in too much release of NE, which causes the heightened physical sensation of panic. This explanation for panic is supported by the reaction to certain medications that exacerbate panic symptoms in people with PD. For example, the medication yohimbine is an alpha-2 antagonist. When administered to PD patients, it triggers an exaggerated anxiety response. Caffeine, also an alpha-2 auto-receptor antagonist, similarly causes heightened anxiety and panic in PD patients."*(Wehrenberg and Prinz 2007, 98)

Interpretation:

The more the presence of alpha-2 antagonist agents, the more the blockage of alpha-2 receptor sites (See Link 24). The more the blockage of alpha-2 receptors, the less the efficiency of alpha-2 receptors (See Link 25). The less the efficiency of alpha-2 receptors, the more the levels of NE in the brain (See Link 26). See Sec. 3.8.2 for details.
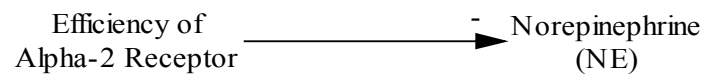
Links:

Alpha-2　　　　————————＋————→　　　Blockage of
Antagonists　　　　　　　　　　　　　　　Alpha-2 Receptor

Link 24

Blockage of　　　　————————－————→　　　Efficiency of
Alpha-2 Receptor　　　　　　　　　　　　Alpha-2 Receptor

Link 25

Efficiency of　　　　————————－————→　　　Norepinephrine
Alpha-2 Receptor　　　　　　　　　　　　(NE)
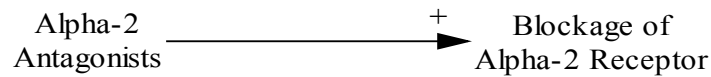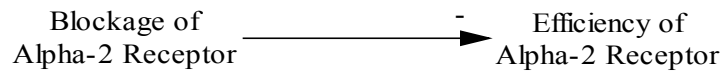
Link 26

Link 27:

Quote:

"Another possibility related to NE is that the patient has a hyposensitive alpha-2 NE auto-receptor. If a PD patient is not sufficiently sensitive at the alpha-2 auto-receptor site, the receptor will not shut down release of NE. The normal braking action does not occur. The end result is an increased release of the NE neurotransmitter." (Wehrenberg and Prinz 2007, 99)

Interpretation:

The more the hyposensitivity (low or diminished sensitivity to the stimulation) at the alpha-2 receptor sites, the less the efficiency of the alpha-2 receptor sites. Note that the low efficiency of the alpha-2 receptors means the excess release of NE (See link 26).

Link:

Hyposensitivity of　　　————————－————→　　　Efficiency of
Alpha-2 Receptor　　　　　　　　　　　　Alpha-2 Receptor
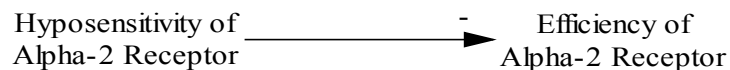
Link 27

Link 28:

Quote:

"Levels of NE that are too high create sensations of hyperarousal. Levels that are constantly too high lead to hypervigilance, a hallmark of generalized anxiety disorder and trauma." (Wehrenberg and Prinz 2007, 47)

Interpretation:

The more the NE levels, the intenser is the hypervigilance to the panic-like sensations, for example, racing heart, choking or shaking. See Sec. 3.5.3 for a detailed discussion of how hypervigilance increases the frequency of panic attacks.

$$NE \xrightarrow{\;\;+\;\;} \text{Hypervigilance to (Panicky) Sensations}$$
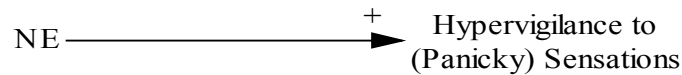
Link 28

Link 29 to 35:

Quote:

"Norepinephrine (NE) activates the PNS (Peripheral Nervous System)*, in turn activating heart, muscles, and extremities. As NE rises, so does heart rate and blood pressure, and anxious symptoms such as sweating, flushing, and tremor occur."* (Wehrenberg and Prinz 2007, 16)
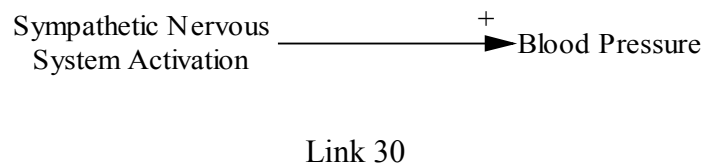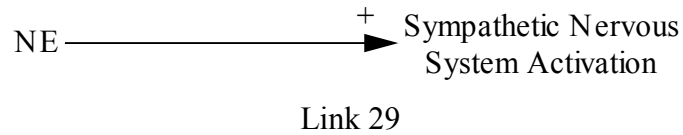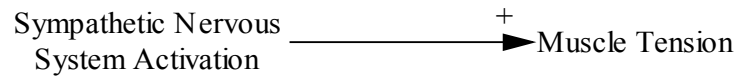
Interpretation:

During a stress response reaction, the malfunctioning of which is hypothesised to be the cause of panic disorder (PD), NE activates the sympathetic nervous system (SNS) (Wehrenberg and Prinz 2007, 59, 60). Note that the SNS is a subdivision of PNS (peripheral nervous system) which is being referred to in the above quotation (Clarke, Valerie and Susan Gillet 1997, 44). It is the activation of SNS which results in the behavioural symptoms of a panic attack (LeDoux 1999, 260-1). These symptoms, as mentioned in the above quote, are increased blood pressure and heart rate, sweating, flushing, shaking and muscular tension.

From this discussion, it is clear that the more the levels of NE during a stress response

reaction, the intenser is the arousal of SNS as compared to its arousal otherwise (See Link 29). The intenser the arousal or activation of the SNS: the higher the blood pressure (See Link 30), the faster the heart rate (See Link 31) and the more the sweating (See Link 32), flushing (See Link 33), tremor (See Link 34) and muscular tension (See Link 35).

Links:

NE $\xrightarrow{+}$ Sympathetic Nervous System Activation

Link 29

Sympathetic Nervous System Activation $\xrightarrow{+}$ Blood Pressure

Link 30

Sympathetic Nervous System Activation $\xrightarrow{+}$ Heart Rate

Link 31

Sympathetic Nervous System Activation $\xrightarrow{+}$ Sweating

Link 32

Sympathetic Nervous System Activation $\xrightarrow{+}$ Flushing

Link 33

Sympathetic Nervous System Activation $\xrightarrow{+}$ Tremor (Shaking)

Link 34

Sympathetic Nervous   +   Muscle Tension
System Activation

Link 35

Link 24	Alpha-2 Antagonists + Blockage of Alpha-2 Receptor
Description	The more the alpha-2 antagonists, the more the blockage of alpha-2 receptors.
Source	Wehrenberg and Prinz 2007, 98
Link 25	Blockage of Alpha-2 Receptor - Efficiency of Alpha-2 Receptor
Description	The more the blockage of alpha-2 receptors, the less the efficiency of alpha-2 receptors.
Source	Wehrenberg and Prinz 2007, 98
Link 26	Efficiency of Alpha-2 Receptor - Norepinephrine (NE)
Description	The less the efficiency of alpha-2 receptors, the more the levels of NE.
Source	Wehrenberg and Prinz 2007, 98
Link 27	Hyposensitivity of Alpha-2 Receptor - Efficiency of Alpha-2 Receptor
Description	The more the hyposensitivity at the alpha-2 receptor sites, the less the efficiency of alpha-2 receptor sites.
Source	Wehrenberg and Prinz 2007, 99

Link 28	NE ————————→ Hypervigilance to + (Panicky) Sensations
Description	The more the NE, the intenser is the hypervigilance to the panic-like sensations.
Source	Wehrenberg and Prinz 2007, 47
Link 29	NE ————————→ Sympathetic Nervous + System Activation
Description	The more the levels of NE during a stress response reaction, the intenser the arousal of the SNS.
Source	Wehrenberg and Prinz 2007, 16, 59, 60
Link 30	Sympathetic Nervous ——————→ Blood Pressure System Activation +
Description	The more the arousal of the SNS, the higher the blood pressure.
Source	Wehrenberg and Prinz 2007, 16
Link 31	Sympathetic Nervous ——————→ Heart Rate System Activation +
Description	The more the arousal of the SNS, the faster the heart rate.
Source	Wehrenberg and Prinz 2007, 16
Link 32	Sympathetic Nervous ——————→ Sweating System Activation +
Description	The more the arousal of the SNS, the more the sweating.
Source	Wehrenberg and Prinz 2007, 16

Link 33	Sympathetic Nervous System Activation $\xrightarrow{+}$ Flushing
Description	The more the arousal of the SNS, the intenser the flushing.
Source	Wehrenberg and Prinz 2007, 16
Link 34	Sympathetic Nervous System Activation $\xrightarrow{+}$ Tremor (Shaking)
Description	The more the arousal of the SNS, the more the shaking.
Source	Wehrenberg and Prinz 2007, 16
Link 35	Sympathetic Nervous System Activation $\xrightarrow{+}$ Muscle Tension
Description	The more the arousal of the SNS, the more the muscular tension.
Source	Wehrenberg and Prinz 2007, 16

Table 4.3: The Translation of the NE's Role in Fight or Flight and Hypervigilance

Synthesizing the Links:

Excess release of *NE* is hypothesised to be a cause of panic disorder (PD). This excess release, in addition to low SE levels (discussed in Sec. 4.2), has another important contributing factor which is the *efficiency of alpha-2 receptor site*[27]. The more efficient it is, the less the *NE* production. The *efficiency of alpha-2 receptor site* may be low due to the presence of *alpha-2 antagonist agents*, which serve to block the receptor site, and/or the *hyposensitivity* of a PD patient at the very receptor site (See Fig. 4.4).

Excess *NE* leads to a state in which one *hypervigilantly* monitor one's panic-like sensations. This *hypervigilance* contributes to trigger more panic attacks. This issue will be taken up in the forthcoming discussion of the cognitive error and kindling in Sec. 4.8. In addition, excess *NE* production activates the sympathetic nervous system which leads to the panic symptoms of *tremor, racing heart, flushing, muscular tension, sweating* and

---

27 *"An alpha-2 auto-receptor is a presynaptic NE receptor located on the NE neuron that is releasing the NE. If activated (i.e., if it receives an NE molecule), the alpha-2 auto-receptor will slow down the release of NE. It has a breaking effect on NE release. When the braking action stops, more NE is released. This is how a healthy brain functions to regulate the release of NE."* (Wehrenberg and Prinz 2007, 97)

high blood pressure (See Fig. 4.4). For clarity and simplicity, certain feedback loops, that *NE* takes part into, are removed from Fig. 4.4. For a high-level view of how *NE* contributes to the whole panic system, see Figs. 4.2, 4.3 and 4.8.
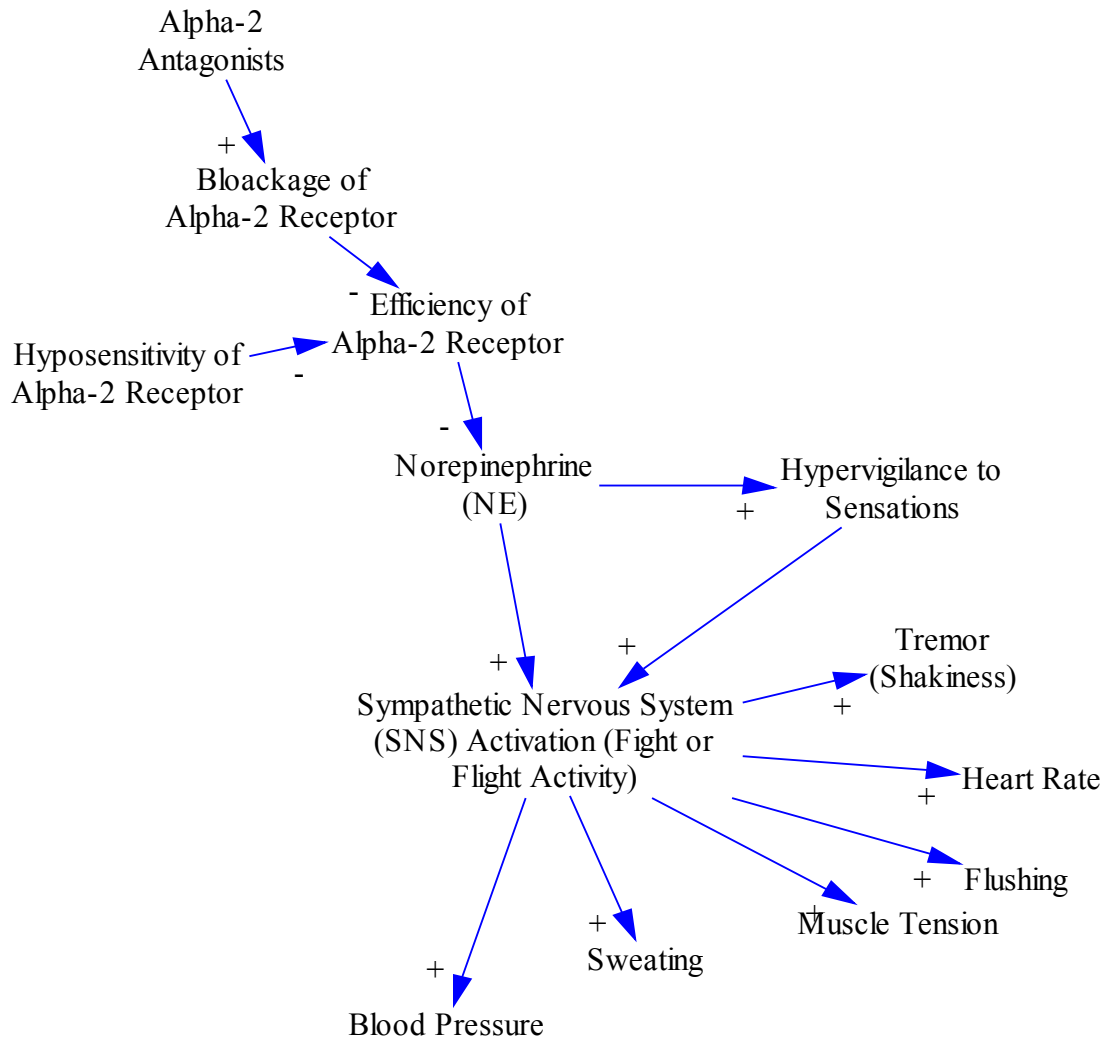

Fig. 4.4: NE, Fight or Flight Activity and Hypervigilance

Simplified Syntheses:

To simplify Fig. 4.4, some of its less necessary details are omitted in Fig. 4.4a. The omitted variables include the factors on which the *efficiency of alpha-2 receptor* depends, *hypervigilance to sensations* and panic symptoms except for the *heart rate*. The variables on which the *efficiency of alpha-2* depends are exogenous anyway, the *hypervigilance* may easily be bypassed in the "bigger picture" as the *conscious fear of another panic attack* may directly be connected to the *panicky sensations* (See Fig. 4.8a) and the various panic symptoms may be represented, in the forthcoming stock and flow model, with the help of only one symptom as the stock and flow structure for all these symptoms is going

to be the same.
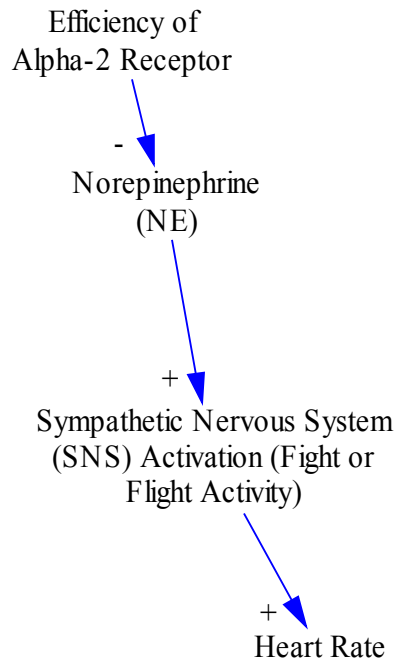
Fig. 4.4a: A Simplified CLD of NE and Fight/Flight Activity

4.6 Translation of the Role of GABA in Panic:

GABA neurotransmitter is present everywhere in the brain. Its function is to relax the nervous system by slowing or braking chains of neuronal firing (Wehrenberg and Prinz 2007, 44-5).

Link 36 and 37:

Quotes:

> *"When GABA is not working well there may be a tendency to increase rumination. This is because of the failure to slow activity in the ACG, where the brain does considerable work shifting from one idea to another."* (Wehrenberg and Prinz 2007, 177)

> *"Slow, inefficient GABA may also contribute to overactivity in the limbic system, where negativity is stirred."* (Wehrenberg and Prinz 2007, 177)

> *"The prefrontal cortex needs GABA to help slow and stop deliberate cognitions of worry. When it is low on GABA, it will be unable to suppress worry in any part of the brain effectively."* (Wehrenberg and Prinz 2007, 177)

Interpretation:

When GABA is not working properly in the brain, it cannot slow down the over-reactive anterior cingulate gyrus (ACG) and the amygdala which are actively involved in the malfunctioning stress response system responsible for PD. Also, it cannot help the prefrontal cortex (PFC) modulate the amygdala's activity through the ACG when the amygdala initiates the stress response without any real stressor.

In other words, the more the efficiency of GABA, the more efficiently the PFC would influence the ACG to tone down the amygdala's stress perception (by its correct stress reporting to the amygdala) (See Link 37) and the less over-reactive the amygdala would be in its perception of stress as compared to what it would otherwise have been (See Link 37). (See Sec. 3.8.3 for details.)

Links:

Efficiency of GABA $\xrightarrow{\text{\Large +}}$ ACG's (Correct) Stress Report

Link 36

Efficiency of GABA $\xrightarrow{\text{\Large --}}$ Amygdala's Stress Perception
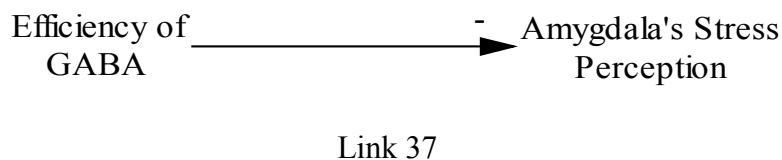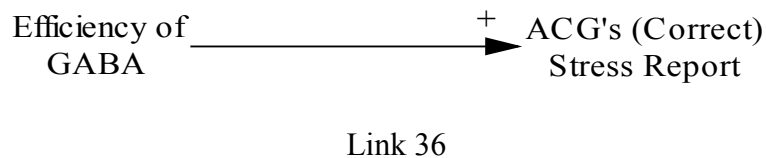
Link 37

Link 38 - 45:

Quote:

> *"Benzodiazepines are endogenous (internal) brain chemicals that affect GABA neurotransmitters. In a PD patient, the ability of the benzodiazepines to modulate GABA may be out of balance. Consequently, GABA may not calm the nervous system effectively. The imbalance may have several possible causes:*
>
> • *The benzodiazepine receptor site[28] on a GABA neurotransmitter may be insufficiently sensitive to the effects of the benzodiazepine neurochemical.*

---

28 *"A protein molecule on the surface of a cell that receives and binds neurotransmitters, hormones, etc."* (Berman 2005, 127)

- *The receptor site may have difficulty receiving the benzodiazepine.*

- *The brain may not be making enough endogenous benzodiazepine.*

- *The GABA receptor area may be dysregulated.*

An additional aspect of the benzodiazepine-GABA connection relevant to the etiology of panic is that the brain may be producing too much anxiogenic inverse agonist (a substance that binds to a benzodiazepine receptor and causes a slowing down of chloride ion transmission)." (Wehrenberg and Prinz 2007, 100-01)

Interpretation and Links:

Benzodiazepines are naturally occurring brain chemicals which affect GABA's functional efficiency. Benzodiazepines' effectiveness to modulate GABA may be low due to any of the several possible reasons including problems at the GABA receptor site, insufficient levels of benzodiazepines in the brain and the presence of too much anxiogenic inverse agonist. The problems at the GABA receptor site include the dysregulation of the receptor area, difficulty in receiving benzodiazepines on the receptor area and insensitivity of the receptor area to the benzodiazepines (See secs. 3.8.3 and 3.8.3.1 for details).

From the above discussion, it may be concluded that the efficiency of GABA depends on the effectiveness of benzodiazepines to affect GABA. Therefore, the more the effectiveness of benzodiazepines to affect GABA, the more the inhibiting efficiency of GABA over various brain activities.

<div align="center">

Effectiveness of
Benzodiazepines to Affect   —————→ $\overset{+}{\text{Efficiency of}}$
GABA   GABA
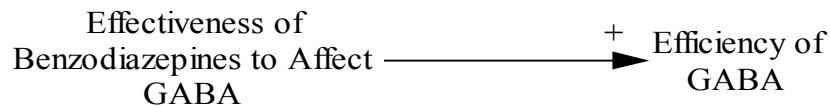
Link 38

</div>

It may also be inferred here that the efficiency of GABA must be dependent on the GABA levels in the brain in a way that the more the GABA levels, the more the efficiency of GABA.

<div align="center">

GABA   —————————→ $\overset{+}{\text{Efficiency of}}$
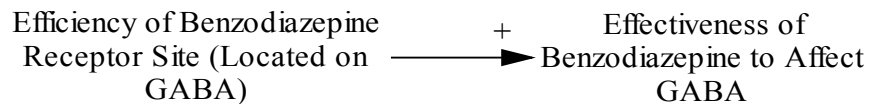   GABA
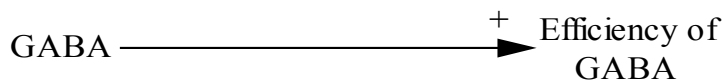
Link 39

</div>

The effectiveness of benzodiazepines to affect GABA depends on the benzodiazepine levels in the brain, efficiency of the site which receives benzodiazepines on the GABA neurons and the amount of the anxiogenic inverse agonist produced in the brain. It means that:

- The more the benzodiazepines, the more the effectiveness of benzodiazepines to affect GABA.

$$\text{Benzodiazepines} \xrightarrow{\quad + \quad} \begin{array}{c}\text{Effectiveness of}\\ \text{Benzodiazepine to Affect}\\ \text{GABA}\end{array}$$
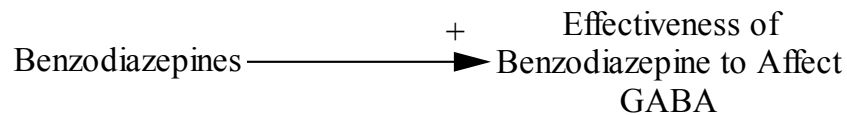
Link 40

- The more the efficiency of benzodiazepine receptor site on GABA, the more the effectiveness of benzodiazepine to affect GABA.

$$\begin{array}{c}\text{Efficiency of Benzodiazepine}\\ \text{Receptor Site (Located on}\\ \text{GABA)}\end{array} \xrightarrow{\quad + \quad} \begin{array}{c}\text{Effectiveness of}\\ \text{Benzodiazepine to Affect}\\ \text{GABA}\end{array}$$

Link 41

- The more the anxiogenic inverse agonist in the brain, the less the efficiency of the benzodiazepine receptor site located on GABA (See Link 42) and, hence, the less the effectiveness of benzodiazepine to affect GABA (See Link 41).

$$\begin{array}{c}\text{Anxiogenic Inverse}\\ \text{Agonist}\end{array} \xrightarrow{\quad - \quad} \begin{array}{c}\text{Efficiency of Benzodiazepine}\\ \text{Receptor Site (Located on}\\ \text{GABA)}\end{array}$$
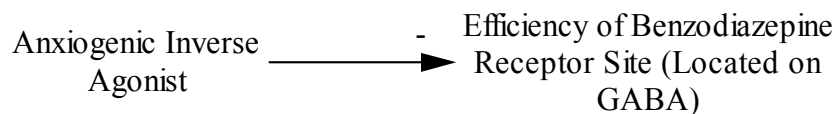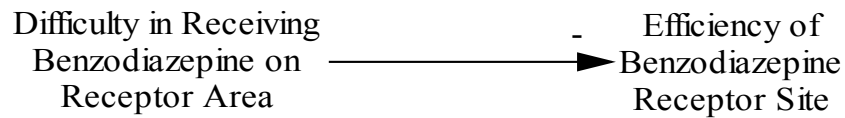
Link 42

The efficiency of benzodiazepine receptor site may be low due to the dysregulation of GABA's benzodiazepine receptor area, difficulty in receiving benzodiazepines on the receptor area and/or the insensitivity of the receptor area to benzodiazepines. It means that:

- The more the dysregulation of the GABA receptor area, the less the efficiency of the benzodiazepine receptor site.

Dysregulation of the
Benzodiazepine Receptor Area ──── ▶ Efficiency of Benzodiazepine
(Located on GABA)   ‾   Receptor Site (Located on
GABA)
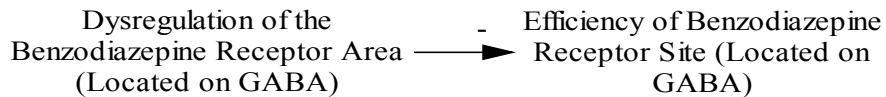
Link 43

- The more the difficulty in receiving benzodiazepines on a GABA neurons' receptor area, the less the efficiency of benzodiazepine receptor site.

Difficulty in Receiving
Benzodiazepine on ──── ▶ Efficiency of
Receptor Area   ‾   Benzodiazepine
Receptor Site

Link 44

- The more sensitive the GABA neurons' benzodiazepine receptor area (to the benzodiazepines), the more the efficiency of the benzodiazepine receptor site.

Sensitivity of Receptor ──── ▶ Efficiency of
Area to Benzodiazepine   +   Benzodiazepine
Receptor Site
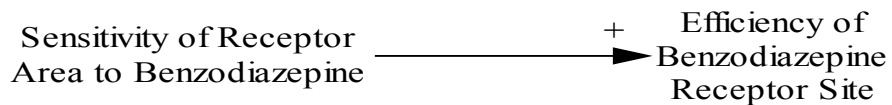
Link 45

Link 46:

Quote:

"Erratic firing of neurons in the BG, a mild seizurelike activity resulting from problems with GABA function, triggers panic attacks." (Wehrenberg and Prinz 2007, 26)

Interpretation:

Out of the blue panic attacks, which seem unrelated to the life events, may be a result of sporadic firings of neurons in the basal ganglia (BG) (Wehrenberg and Prinz 2007, 69). GABA when sufficient and working properly diminishes such firings and, hence, keeps one from such panic attacks (Wehrenberg and Prinz 2007, 127-8). The more the efficiency of GABA, the less the erratic firings of neurons in the BG (See secs. 3.7 and 3.8.3.2 for details).

Link:

Efficiency of ———————— Firings of Neurons
GABA   in BG
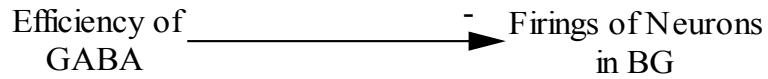
Link 46

Link 36	Efficiency of ———————— + ACG's (Correct) GABA Stress Report
Description	The more the efficiency of GABA, the more effective the ACG's correct stress reporting to the amygdala as compared to what it would otherwise have been.
Source	Wehrenberg and Prinz 2007, 177
Link 37	Efficiency of ———————— - Amygdala's Stress GABA Perception
Description	The more the efficiency of GABA, the less the amygdala's perception of stress.
Source	Wehrenberg and Prinz 2007, 177
Link 38	Effectiveness of Benzodiazepines to Affect ———————— + Efficiency of GABA GABA
Description	The more the effectiveness of benzodiazepines to effect GABA, the more the inhibiting efficiency of GABA over the various brain activities.
Source	Wehrenberg and Prinz 2007, 100-01
Link 39	GABA ———————— + Efficiency of GABA
Description	The more the GABA levels, the more the efficiency of GABA.

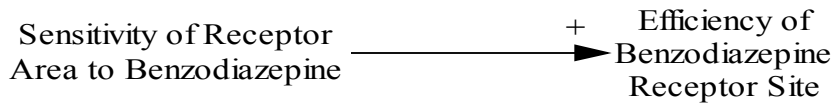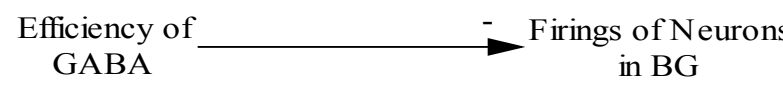| Source	Implied from: Wehrenberg and Prinz 2007, 100-01
Link 40	Benzodiazepines —(+)→ Effectiveness of Benzodiazepine to Affect GABA
Description	The more the benzodiazepines, the more the effectiveness of benzodiazepines to affect GABA.
Source	Wehrenberg and Prinz 2007, 100-01
Link 41	Efficiency of Benzodiazepine Receptor Site (Located on GABA) —(+)→ Effectiveness of Benzodiazepine to Affect GABA
Description	The more the efficiency of benzodiazepine receptor site on GABA, the more the effectiveness of benzodiazepines to affect GABA.
Source	Wehrenberg and Prinz 2007, 100-01
Link 42	Anxiogenic Inverse Agonist —(-)→ Efficiency of Benzodiazepine Receptor Site (Located on GABA)
Description	The more the anxiogenic inverse agonist in the brain, the less the efficiency of the benzodiazepine receptor site located on GABA.
Source	Wehrenberg and Prinz 2007, 100-01
Link 43	Dysregulation of the Benzodiazepine Receptor Area (Located on GABA) —(-)→ Efficiency of Benzodiazepine Receptor Site (Located on GABA)
Description	The more the dysregulation of GABA receptor area, the less the efficiency of benzodiazepine receptor site (located on GABA).
Source	Wehrenberg and Prinz 2007, 100-01
Link 44	Difficulty in Receiving Benzodiazepine on Receptor Area —(-)→ Efficiency of Benzodiazepine Receptor Site

Description	The more the difficulty in receiving benzodiazepines on the GABA neurons' receptor area, the less the efficiency of benzodiazepine receptor site.
Source	Wehrenberg and Prinz 2007, 100-01
Link 45	Sensitivity of Receptor Area to Benzodiazepine $\xrightarrow{\quad + \quad}$ Efficiency of Benzodiazepine Receptor Site
Description	The more sensitive the GABA neurons' benzodiazepine receptor area to the benzodiazepines, the more the efficiency of benzodiazepine receptor site.
Source	Wehrenberg and Prinz 2007, 100-01
Link 46	Efficiency of GABA $\xrightarrow{\quad - \quad}$ Firings of Neurons in BG
Description	The more the inhibiting efficiency of GABA, the less the neuronal firings in the BG.
Source	Wehrenberg and Prinz 2007, 127-8

Table 4.4: Translation of the Role of GABA in Panic

Synthesizing the Links:

Low *efficiency of GABA* neurotransmitter is hypothesised to be an important factor in the etiology of PD. *Benzodiazepines* are the brain chemicals which affect the *GABA's functional efficiency* to relax the nervous system. The *benzodiazepine receptor site* is located on the *GABA* neurons. The more *efficiently* this site works, the more effectively *benzodiazepine* regulates *GABA* (See Fig. 4.5).

The *efficiency of the bezodiazepine receptor site* decreases if it is *dysregulated*, having any difficulty to receive *bezodiazepines* and/or not sufficiently *sensitive to benzodiazepine*. In addition, the presence of any *anxiogenic inverse agonist* also serves to decrease the very *efficiency*.

The more the *effectiveness of benzodiazepines to regulate GABA*, the more the *efficiency of GABA* to:

- Help the *anterior cingylate gyrus (ACG) modulate the amygdala*.

- Calm down the erratic firing of neurons in the *basal ganglia*.

- Help the *amygdala* calm down its *crude stress perception*.

It should be noted here that the *efficiency of GABA* also depends on the *GABA* levels in the brain in a way that the more the *GABA* levels, the more the *efficiency of GABA*. Similarly, the *effectiveness of benzodiazepines to regulate GABA* depends on the *benzodiazepine* levels in the brain; the more the latter the more the former (See Fig. 4.5).

The detailed picture of how *GABA* takes part in the stress response reaction is highlighted in Fig. 4.6. For simplicity, the details of the factors on which the *efficiency of GABA* depends are omitted from this figure. The *firing of neurons in the BG* is directly connected to the *amygdala's perception rate* as, unlike the fear inducing information, this information does not come from the way of thalamus. The more the *firings of neurons in the BG*, the more the *amygdala's stress perception* and, consequently, the stronger the stress response reaction. It is the simplified Fig. 4.6 which is going to be used in the forthcoming stock and flow model. However, the variable *firing of neurons in the BG* will be ignored in the model as the main point of interest of the literature is the "conditioned" panic.
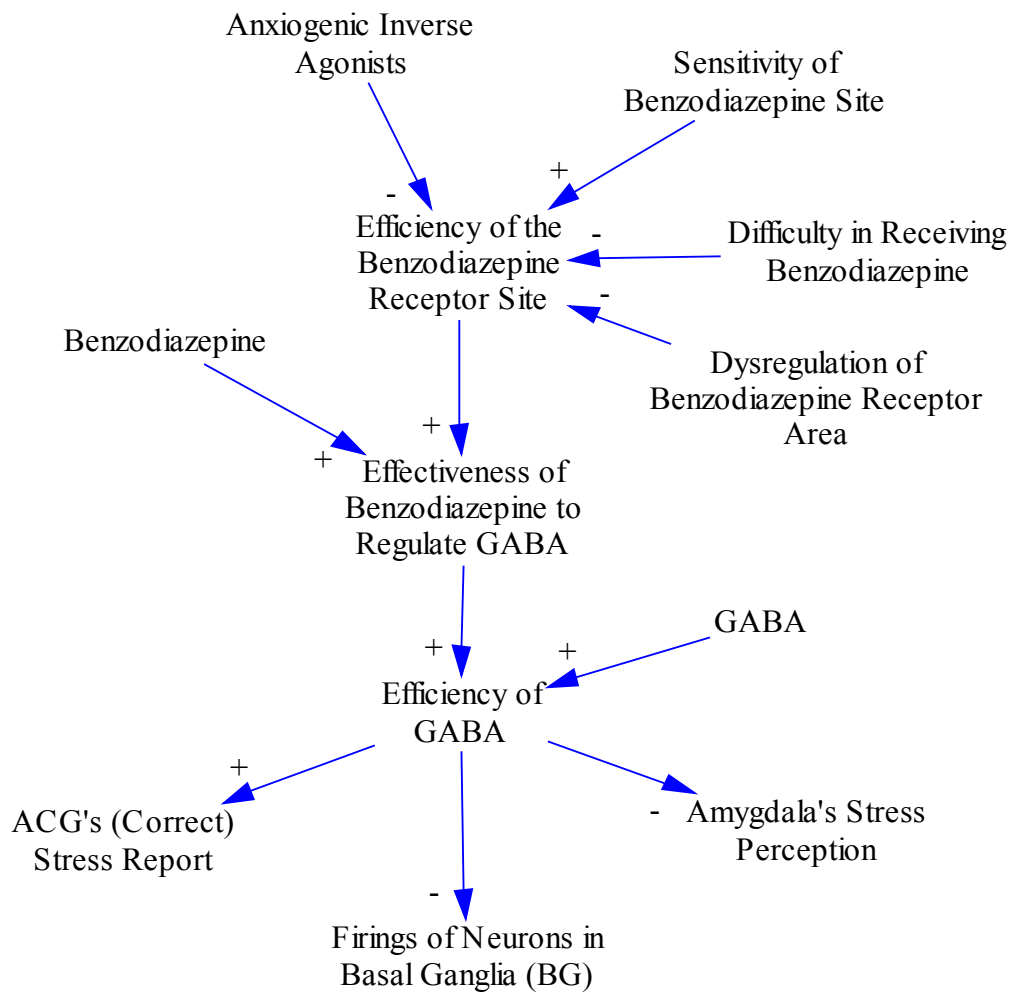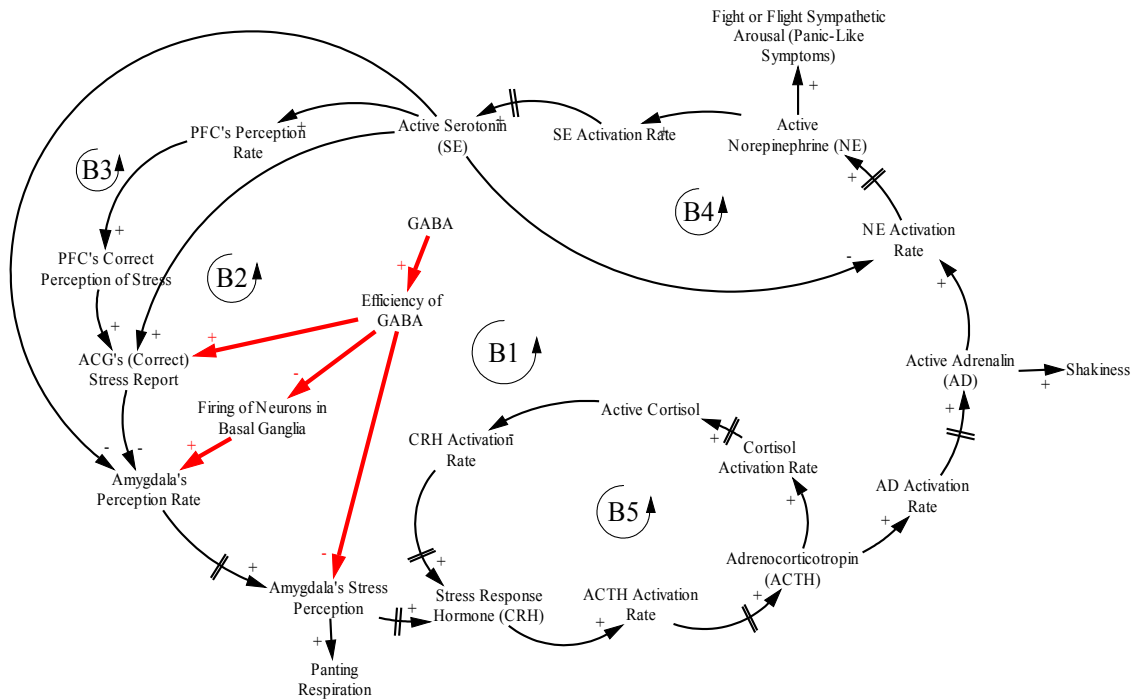
Fig. 4.5: A CLD Showing the Role of GABA in Panic

Fig. 4.6: A CLD Showing the Role of GABA in the Stress Response Reaction

4.7 Translation of the Stress and the Creation of Stimuli Mechanism:
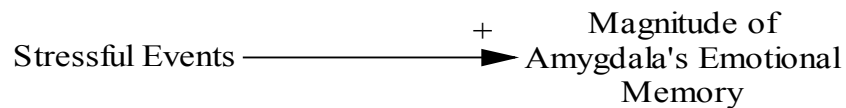
Link 47:

Quote:

"The amygdala learns what is dangerous. It learns from experience if sensory inputs are threatening or not. It very quickly forms associations between specific situations and pain, danger or negative outcome. Therefore, after a frightening experience, and especially after a trauma, the amygdala maintains alertness to all future signals that a similar experience is about to occur... Any aspect of the genuinely frightening experience could be learned by the amygdala as a signal to watch for in the future. Whenever one of those signals is perceived by the amygdala, the person will feel frightened. Even when the sound, smell, or place is not presently dangerous, the amygdala may react as if it is, because the association formed in the amygdala between danger and the stimulus will cause the amygdala to start the fear or panic response." (Wehrenberg and Prinz 2007, 28-9)

Interpretation:

Once a stressful (traumatic or frightening) event takes place, the amygdala remembers that experience by storing some of its information into its emotional memory. It actually

associates that event with the things which happen or are present at the time it occurs because it sees those things as the factors responsible for the stress (irrespective of the fact if they are actually responsible or not). Thus, these things are stored into the amygdala's emotional memory as "dangerous" and whenever they are encountered, the amygdala's stress perception boosts up and it starts energizing the body either to fight or flee from the plausible danger. (Wehrenberg and Prinz 2007, 28-30; LeDoux 1998, 259-60) Such false activation of the fight or flight reaction, without the presence of a real threat or danger, causes PD in some individuals (Wehrenberg and Prinz 2007, 60). To sum up, the more the stressful events in a person's life, the bigger the amygdala's emotional memory in its magnitude.

Link:

Stressful Events ——————⟶ Magnitude of Amygdala's Emotional Memory

<center>+</center>

<center>Link 47</center>

Link 48 - 51:

Quote:

> *"Suppose you are driving down the road and have a terrible accident. The horn gets stuck on. You are in pain and generally traumatized by the experience. Later, when you hear the sound of a horn, both the implicit* (unconscious) *and the explicit* (conscious) *memory systems are activated. The sound of the horn (or a neural representation of it), having become a conditioned fear stimulus, goes straight from the auditory system to the amygdala and implicitly elicits bodily responses that typically occur in situations of danger* (fight or flight activity)*: muscle tension (a vestige of freezing), changes in blood pressure and heart rate, increased perspiration, and so on."* (LeDoux 1998, 200-01)
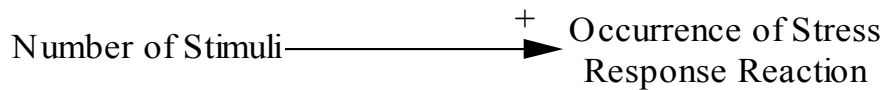
Interpretation and Links:

This means that the amygdala would keep associating more and more things with stress whenever it would occur and, consequently, the emotional memories would keep growing and so as the number of stress stimuli. For example, if a person somehow undergoes a panic attack while having a cup of coffee, the amygdala may easily associate the panic with the coffee – referring to the coffee as a dangerous enemy responsible for the panic attack. Next time, as it would see the cup, taste or smell of the coffee as an enemy (the stress stimulus), which causes the stress, its stress perception would immediately boost

and it would straightaway start to prepare the body for a fight or flight response. (Wehrenberg and Prinz 2007, 64-66) See Sec. 3.5.2. In short, the more the amygdala's emotional memory in magnitude, the more the number of stress stimuli.

Magnitude of
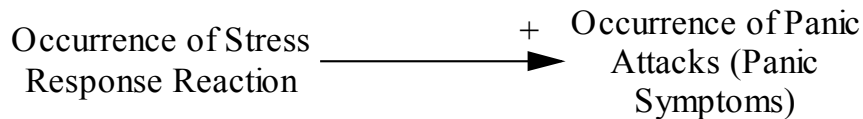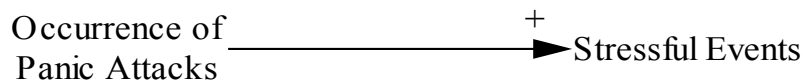Amygdala's Emotional ————————▶ Number of Stimuli
Memory
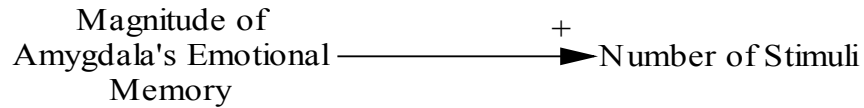
Link 48

The more the number of stimuli (things associated with danger), the more the occurrences of the stress response reaction (See Link 49) leading to frequent panic attacks (See Link 50). A panic attack itself is a terrifying, traumatic and highly stressful experience, therefore, it can be inferred from the above quotation (LeDoux 1998, 200-01) that the more the occurrences of panic attacks, the more the number of stressful (traumatic) life events in a sufferer's life (See Link 51) (Also see: Wehrenberg and Prinz 2007, 64-66).

Number of Stimuli ————————▶ Occurrence of Stress
Response Reaction

Link 49

Occurrence of Stress ————————▶ Occurrence of Panic
Response Reaction   Attacks (Panic
Symptoms)

Link 50

Occurrence of ————————▶ Stressful Events
Panic Attacks

Link 51

Link 47	Stressful Events ————————▶ Magnitude of Amygdala's Emotional Memory
Description	The more the stressful events in a person's life, the more things would

	be stored as dangerous in the amygdala's emotional memory.
Source	Wehrenberg and Prinz 2007, 28-30; LeDoux 1998, 259-60
Link 48	Magnitude of Amygdala's Emotional Memory ⟶+ Number of Stimuli
Description	The amygdala remembers what is dangerous. The more things it would remember as dangerous, the more the number of stimuli.
Source	Wehrenberg and Prinz 2007, 64-66
Link 49	Number of Stimuli ⟶+ Occurrence of Stress Response Reaction
Description	The more the number of stimuli, the more frequently the amygdala would arouse the stress response reaction.
Source	LeDoux 1998, 200-01; Wehrenberg and Prinz 2007, 64-66
Link 50	Occurrence of Stress Response Reaction ⟶+ Occurrence of Panic Attacks (Panic Symptoms)
Description	The more the frequency of the stress response reaction, the more the occurrence of panic attacks.
Source	LeDoux 1998, 200-01; Wehrenberg and Prinz 2007, 64-66
Link 51	Occurrence of Panic Attacks ⟶+ Stressful Events
Description	The more the frequency of panic attacks, the more the stressful events in a panic patient's life.
Source	LeDoux 1998, 200-01; Wehrenberg and Prinz 2007, 64-66

Table 4.5: The Translation of the Stress and Stimuli Relationship

Synthesizing the Links:

The more the *stressful (traumatic) events* in an individual's life, the more the *magnitude*

of the amygdala's emotional memory as the amygdala learns what is dangerous by associating specific situations with pain, danger or negative outcome. The more things the amygdala would associate with pain, danger or negative outcome in its *emotional memory*, the more *stimuli* would be created which would repeatedly serve to generate the *fear emotion* eventually leading to the frequent *panic attacks*. As a *panic attack* itself is a *stressful event*, its occurrence adds to the number of *stressful events* in an individual's life paving way to the vicious cycle illustrated in Fig. 4.7. This cycle reinforces each of its variables with time and, thus, forms a reinforcing loop.
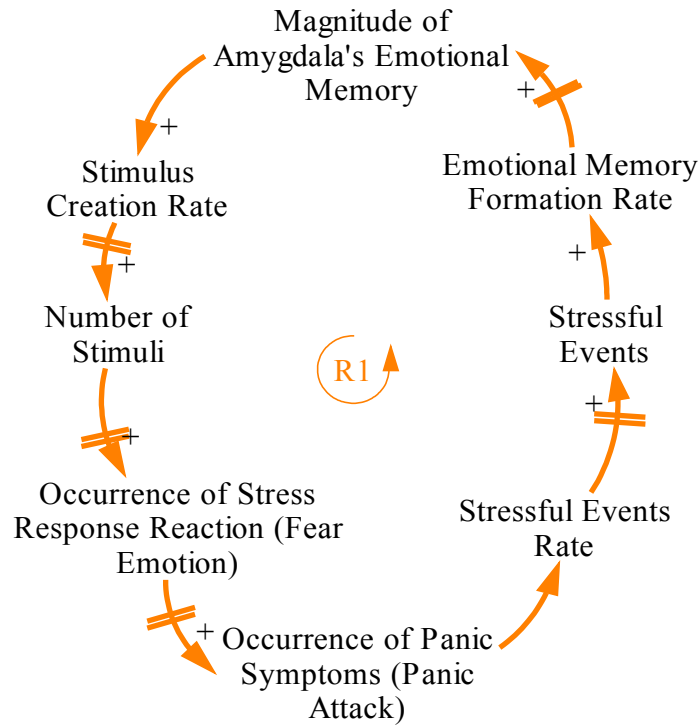
Fig. 4.7: A CLD of the Stress and Stimuli Feedback Relationship

Simplified Syntheses:

Some variables in the stress and stimuli feedback relationship, shown in Fig. 4.7, are omitted from the diagram shown in Fig. 4.7a. This is expected to simplify the forthcoming stock and flow model by limiting its level of aggregation.
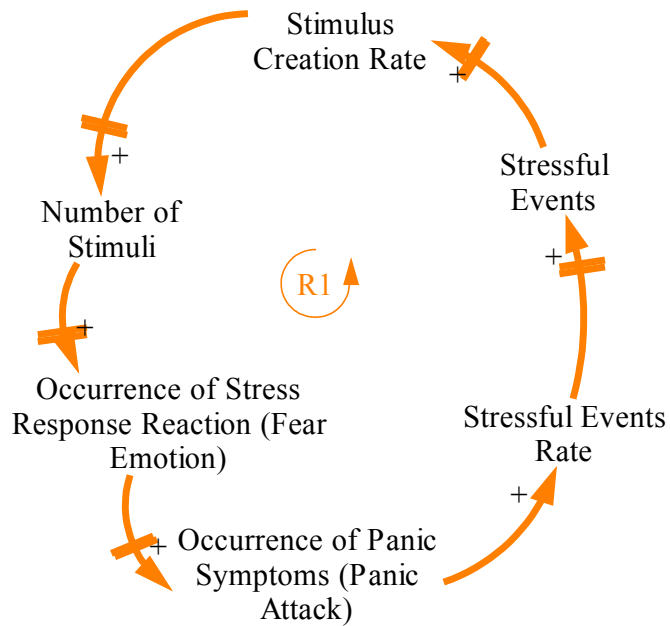
Fig. 4.7a: A Simplified CLD of the Stress and Stimuli Feedback Relationship

4.8 Translation of the Circular Nature of a Panic Attack (Cognitive Error and Kindling):

Link 52 - 59:

Quote:

"The erroneous thoughts (develop during a panic attack) *that the person is dying, losing control, or going crazy maintain the mindless fear of another panic attack. In other words, people react to the sensations without using logical thought to examine their frightened, reactive cognitions.*

The more often the brain goes into a panic attack, the more easily a panic attack can be set off the next time, regardless of why the panic started. This process is called kindling. The faulty cognitions that develop during a panic attack do not disappear when the rapid heart rate goes down. Fear causes hypervigilant attention to physiological arousal and magnifies every small tingle or twitch. The fear that those sensations will develop into panic will actually create panic (Casey, Newcombe, & Oei, 2005)... The inner dialogue may go something like this:

'I have felt panic before. I have a physical sensation. I wonder if it is panic. I'd better pay attention. I will hypervigilantly monitor my physical sensations. Uh, oh! I feel every sensation getting faster – heart rate, breathing. Yes, I am sure this is panic! Oh, no! I hate this. Now my heart is really fast and my breathing is shallow.'

Sure enough, the panic attack comes on full swing, as self-talk made all the sensations worse. This circular interaction between physiology and thinking is easily begun." (Wehrenberg and Prinz 2007, 55-6)

Interpretation and Links:

The more often one undergoes panic sensations (pounding heart, increased blood pressure, sweating, flushing, shaking, chest pain, choking etc.), the more cognitive error or erroneous thoughts (like dying, losing control or going crazy etc.) one develops and/or reinforces one's already developed erroneous thoughts (See Link 52). The panic sensations themselves develop as a result of the panic symptoms. This issue will be discussed later in this section. The cognitive error, developed in response to the panicky sensations, then lead the one to maintain the "conscious" fear[29] of another panic attack (See Link 53).

Panicky Sensations $\xrightarrow{\;\;+\;\;}$ Cognitive Error

Link 52

Cognitive Error $\xrightarrow{\;\;+\;\;}$ Fear of Another Panic Attack

Link 53
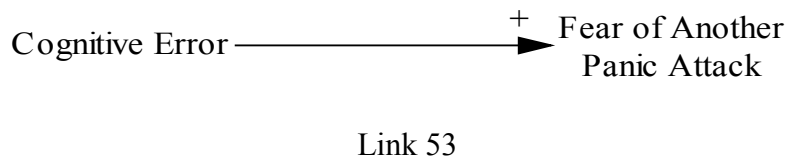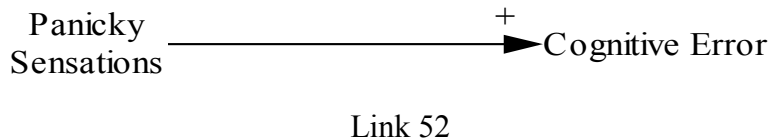
This fear then leads to a state of hypervigilance in which the one constantly keeps a close eye on each and every panic-like sensation in the anticipation of another panic attack.

Fear of Another Panic Attack $\xrightarrow{\;\;+\;\;}$ Hypervigilance to Panic-Like Sensations

Link 54
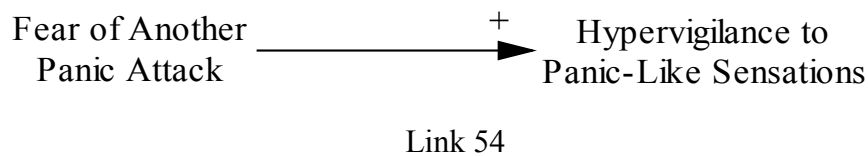
In such a state, even a minor increase in heart or breathing rate etc. (any panic-like symptom) would bring about panicky sensations which are conditioned with these symptoms. These sensations then make the one fear about the possibility of another panic attack. LeDoux (1999, 259-60) illustrates this process as follows:

"...an elevation of blood pressure that occurs in response to hyperventilation might become a conditioned fear stimulus. If blood pressure happens to increase for some

---

29 This type of fear is different from the "fear emotion" and is referred to as the "feeling of fear" in the introduction (See Sec. 1.5 for details).

other reason, such as talking to a superior or being in some other socially tense situation, the noxious sensations previously elicited by hyperventilation, having been conditioned to increases in blood pressure levels, are now brought on. These sensations are then noticed and interpreted as indicative of the onset of a panic attack."

In fact, a panic-like symptom (for example, pounding heart) first initiates the fight or flight activity by activating the amygdala. When this activity is initiated, the other panic-like symptoms (for example, shallow breathing, tremor, shakiness, flushing etc.) are manifested. It is the manifestation of these symptoms which actually gives rise to the panicky sensations that further stimulate the fear of another panic attack (LeDoux 1999, 260-1). However, to keep it simple, it will not be taken into account here how panic symptoms are brought on but only that these symptoms, once brought on, stimulate the panicky sensations. To sum up, panic symptoms give rise to panicky sensations which further stimulate fear of another panic attack.

Panic Symptom(s) ⟶ + Panicky Sensations

Link 55

Panicky Sensations ⟶ + Fear of Another Panic Attack

Link 56
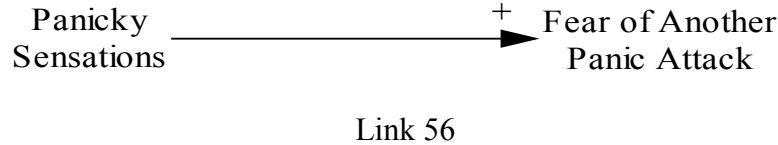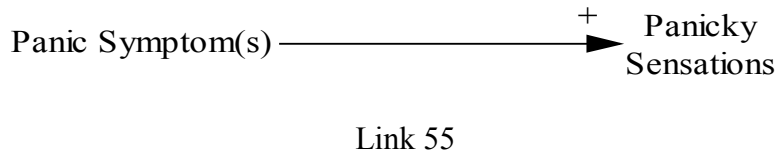
The hypervigilant monitoring of one's physical sensations would further increase these sensations which would serve to activate the stress response reaction giving rise to a panic attack (the symptoms of shallow breathing, sweating, shakiness, pounding heart etc.) without any real stress, threat or danger. See Sec. 3.5.3 for details.

Hypervigilance to Panic-Like Sensations ⟶ + Panicky Sensations

Link 57

Panicky Sensations $\xrightarrow{\quad + \quad}$ Stress Response Reaction (Emotion of Fear)

Link 58

Stress Response Reaction $\xrightarrow{\quad + \quad}$ Panic Symptoms
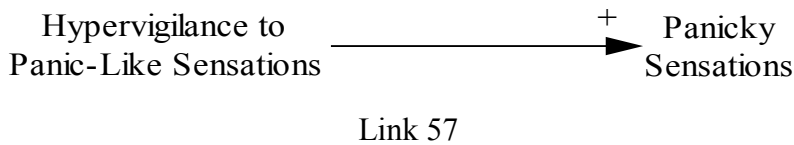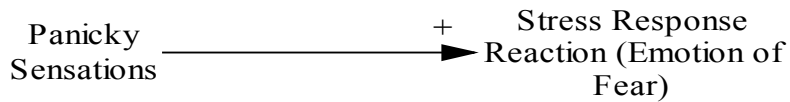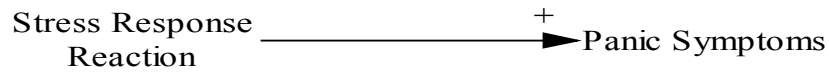
Link 59

Link 52	Panicky Sensations $\xrightarrow{\quad + \quad}$ Cognitive Error
Description	The more frequently panicky sensations would manifest (because of panic attacks), the more cognitive error a sufferer would develop.
Source	Wehrenberg and Prinz 2007, 55-6
Link 53	Cognitive Error $\xrightarrow{\quad + \quad}$ Fear of Another Panic Attack
Description	The more the cognitive error, the more the fear of another panic attack.
Source	Wehrenberg and Prinz 2007, 55-6
Link 54	Fear of Another Panic Attack $\xrightarrow{\quad + \quad}$ Hypervigilance to Panic-Like Sensations
Description	The more the fear of another panic attack, the more the hypervigilance to the panic-like sensations.
Source	Wehrenberg and Prinz 2007, 55-6
Link 55	Panic Symptom(s) $\xrightarrow{\quad + \quad}$ Panicky Sensations
Description	The panic symptoms would give rise to the panicky sensations.

Source	Wehrenberg and Prinz 2007, 55-6; LeDoux 1999, 260-1
Link 56	Panicky Sensations $\xrightarrow{+}$ Fear of Another Panic Attack
Description	The more intense the panicky sensations, the more the fear of another panic attack.
Source	Wehrenberg and Prinz 2007, 55-6; LeDoux 1999, 260-1
Link 57	Hypervigilance to Panic-Like Sensations $\xrightarrow{+}$ Panicky Sensations
Description	The more the hypervigilance to the panicky sensations, the more intense the panicky sensations.
Source	Wehrenberg and Prinz 2007, 55-6
Link 58	Panicky Sensations $\xrightarrow{+}$ Stress Response Reaction (Emotion of Fear)
Description	The more intense the panicky sensations, the more intense the stress response reaction.
Source	Wehrenberg and Prinz 2007, 55-6
Link 59	Stress Response Reaction $\xrightarrow{+}$ Panic Symptoms
Description	The more intense the stress response reaction, the more intense the panic symptoms.
Source	Wehrenberg and Prinz 2007, 55-6

Table 4.6: The Translation of the Circular Nature of Panic (Cognitive Error and Kindling)

Synthesizing the Links:

The *panicky sensations*, developed as a result of the *panic symptoms*, lead an individual to a state of *cognitive error* in which the individual forms erroneous thoughts of dying, losing control or going crazy. These thoughts maintain the *conscious feelings of fear of another panic attack* which leads to a state of *hypervigilance*. In such a state the individual maintains a high awareness of his heart and breathing rate, sweating, stomach distress, choking, chest pain etc. in the anticipation of another panic attack. The *hypervigilance* magnifies the sensations of the beating of the heart, shortness of breath, stomach distress or chest pain etc. even though, in reality, the change in the heart or breathing rate, stomach distress or chest pain etc. may be negligible (See Loop 'R3', Fig. 4.8). This unnecessary increase in the *panicky sensations* would activate the amygdala and, through it, the stress response reaction (emotion of fear). The very reaction would lead to the *panic symptoms* which would give rise to the *panicky sensations*, and again, contribute to develop a state of *cognitive error*.

See Loop 'R1'; there is a circular interaction between the *panic symptoms* and *panicky sensations*. The *panic symptoms* may be weak to begin with but they reinforce themselves through the *panicky sensations* which initiate the stress response reaction. This reinforcement eventually gives rise to a full blown panic attack with strong *panic symptoms*.

Note that the *panicky sensations*, once developed, reinforce themselves by means of the *fear of another panic attack* and *hypervigilance* (See Loop 'R2', Fig. 4.8). When these *sensations* become strong enough, through this circular reinforcement, only then they trigger the stress response reaction effectively enough to generate the *panic symptoms* on some scale (See Loop 'R1').
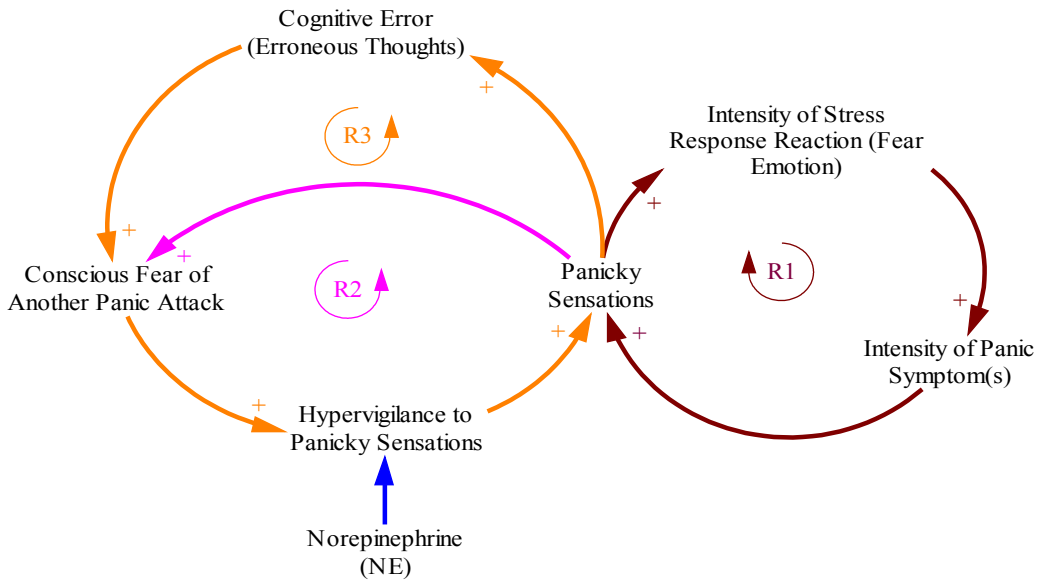
Fig. 4.8: The Cognitive Error and Kindling Feedback Structure

Note that the *panicky sensations* effect the stress response reaction in another way which may be better understood in context of Fig. 4.7a. The occurrence of *panicky sensations* itself is a stressful event for the sufferer and, hence, it would tend to increase the *number of stimuli* which would result in increasing the frequency of the occurrences of the stress response reaction. Every time a *stress response reaction* would take place, it would obviously give rise to the *panicky sensations* and, hence, a circular interaction would take place between these variables which is highlighted in Fig. 4.7b with the help of Loop 'R2'.
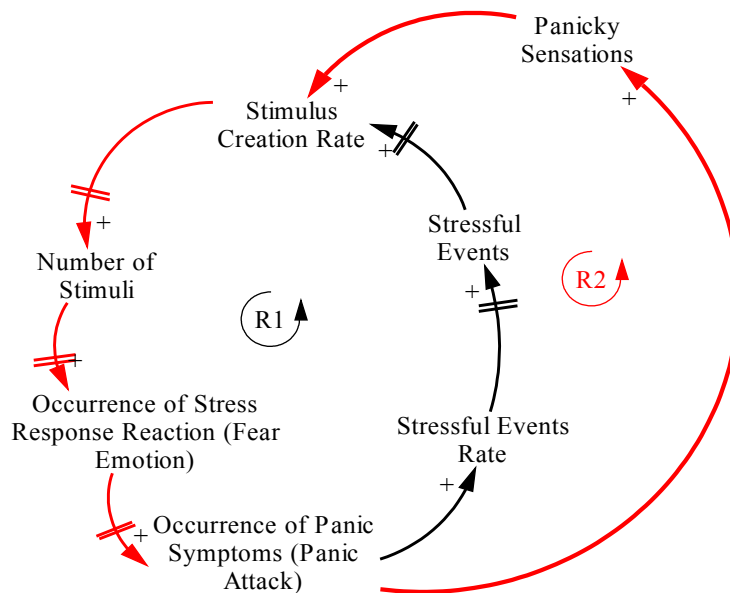

Fig. 4.7b: A Simplified CLD Highlighting the Role of Panicky Sensations in the Stress

Fig. 4.9 elaborates the Loops 'R1' and 'R2' of Fig. 4.8 in more detail. In this figure, the variable *intensity of panic symptoms* (of Fig. 4.8) is replaced by the individual panic symptoms. Also, the variable *amygdala's stress perception* is included in this figure to highlight the importance of the amygdala in generating panic. The variable *stress response reaction* in Figs. 4.8 and 4.9 refers to the stress response reaction at the chemical level (also known as the fear emotion) shown in the Fig. 4.3 in detail. Here the whole fear emotion is condensed in one variable so that the reader's focus remain on the concepts of cognitive error and kindling.
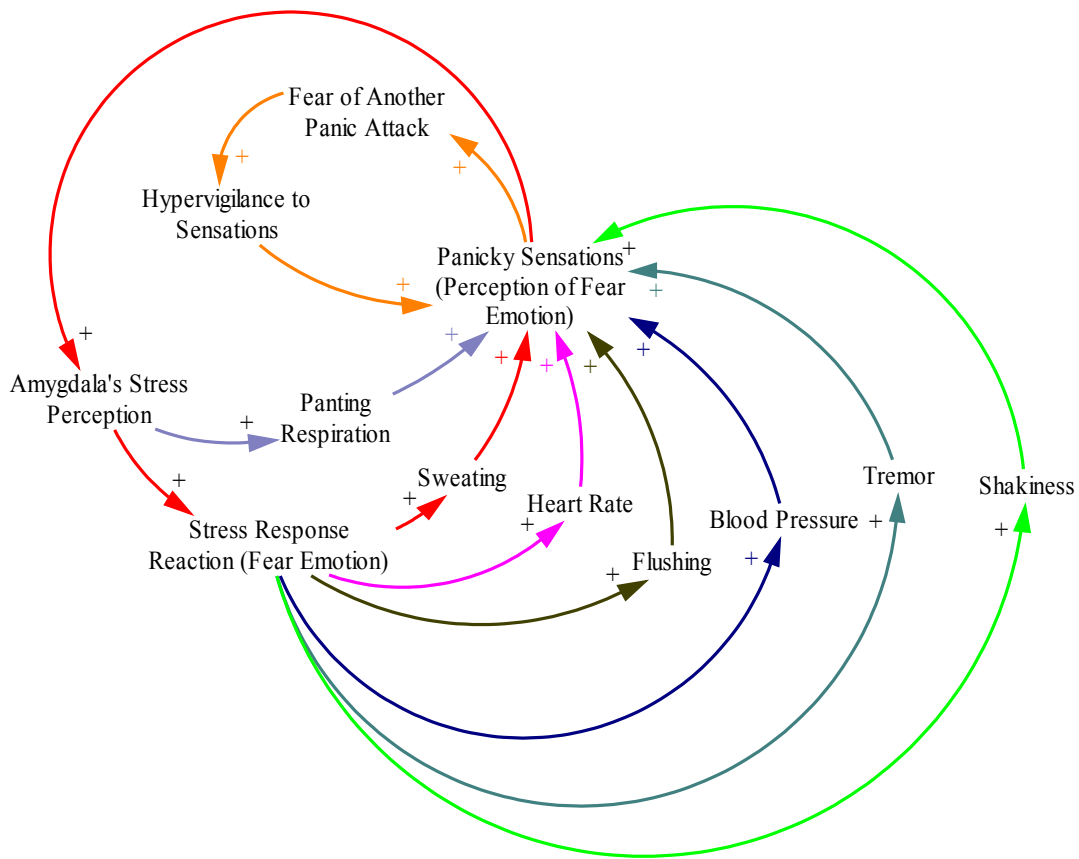

Fig. 4.9: The Cognitive Error and Kindling Feedback Structure (Elaborating Loops "R1" and "R2" of Fig. 4.8)

Simplified Syntheses:

To lower the level of aggregation, the diagram shown in Fig. 4.8 is simplified in the Fig. 4.8a. In the latter figure, *norepinephrine* is directly connected to the *panicky sensations* bypassing the *hypervigilance to panicky sensations*. The variable *cognitive error* is also bypassed. Note that the *intensity of stress response reaction* (Fig. 4.8) represents the overall intensity of the whole fear emotion (starting through a stimulus and leading to the
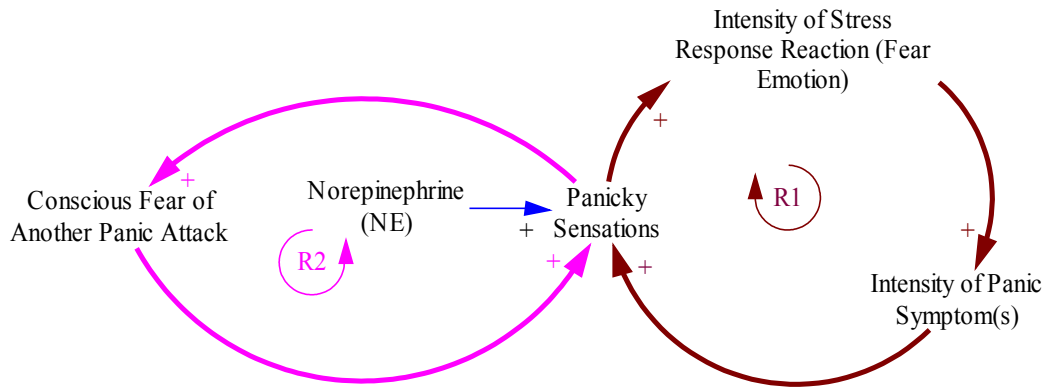
panic symptoms).

Fig. 4.8a: A Simplified Diagram of the Cognitive Error and Kindling Feedback Structure

5. Stock and Flow Model

In this section, the causal loop diagrams (CLDs) developed in the previous section are translated into the stock and flow model (See Appendix B for a quick introduction of system dynamics based stock and flow models). The section moves step by step taking one CLD at a time – translating and incorporating it into the body of the model. Note that, unlike a word by word translation, it is not necessary that each and every bit of a CLD be translated as it is. Sometimes the reader may find tiny deviations in the stock and flow structure as compared to the CLD it is emerging from. This is because the concepts concisely represented in a CLD are made detailed in the stock and flow model. However, on the whole, the concepts represented by a CLD and its corresponding stock and flow structure should be consistent. All the stock-and-flow-model equations are presented at the end in Appendix C.

5.1 Modelling the Amygdala and Prefrontal Cortex (PFC) Circuitry:

As a quick reminder, the CLD which represents the amygdala and PFC circuitry is being reproduced here (See Fig. 4.1). The details of how this CLD emerged from the literature may be seen in Section 4.1.
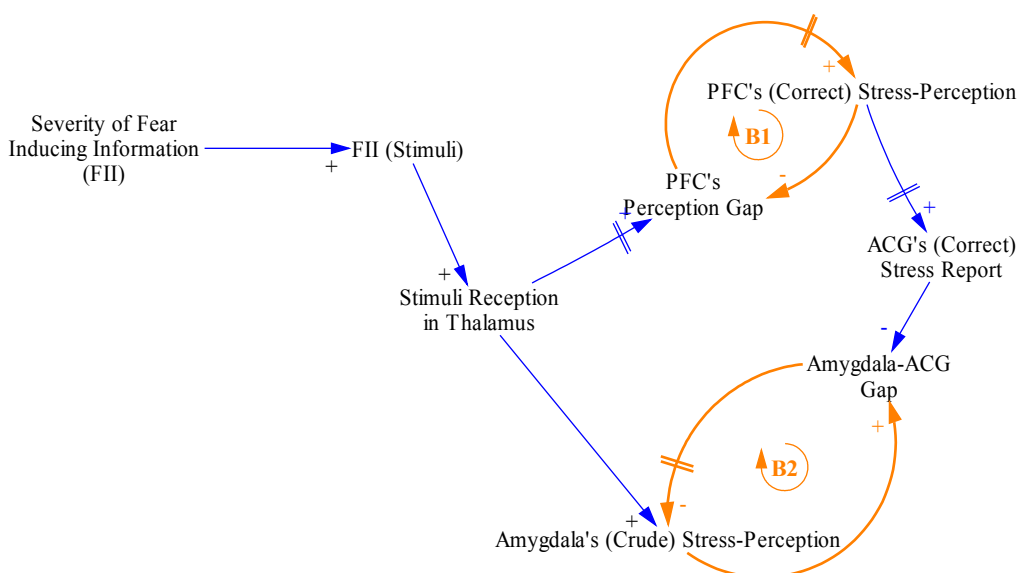

Fig. 4.1 (Reproduced): A CLD Showing the *Fear Inducing Information* (FII), *Amygdala* and *PFC* Connections

Amygdala's crude stress perception, *PFC's correct stress perception* and *ACG's correct stress report*[30] give a feel of stocks as they respond to the information that flows into them and create delays. In addition, they generate the information on which their mutual

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30 For reader's convenience, all the variable names used in the model are italicized in this section.

and other variables' actions are based upon (See Sterman 2000, 192). *Amygdala's crude stress perception* and *PFC's correct stress perception* respond to the *fear inducing information (FII)* with a slight delay, whereas, *ACG's correct stress report* adjusts to *PFC's correct stress perception* with a delay. *ACG's correct stress report* is based on the information generated by *PFC's correct stress perception*. The a*mygdala's crude stress perception*, in addition to *fear inducing information*, is based on the information generated by *ACG's correct stress report*. Similarly, the activation of the whole stress response reaction is based on the information generated by the *amygdala's crude stress perception.* Fig. 5.1 shows the PFC, ACG and amygdala as stocks.
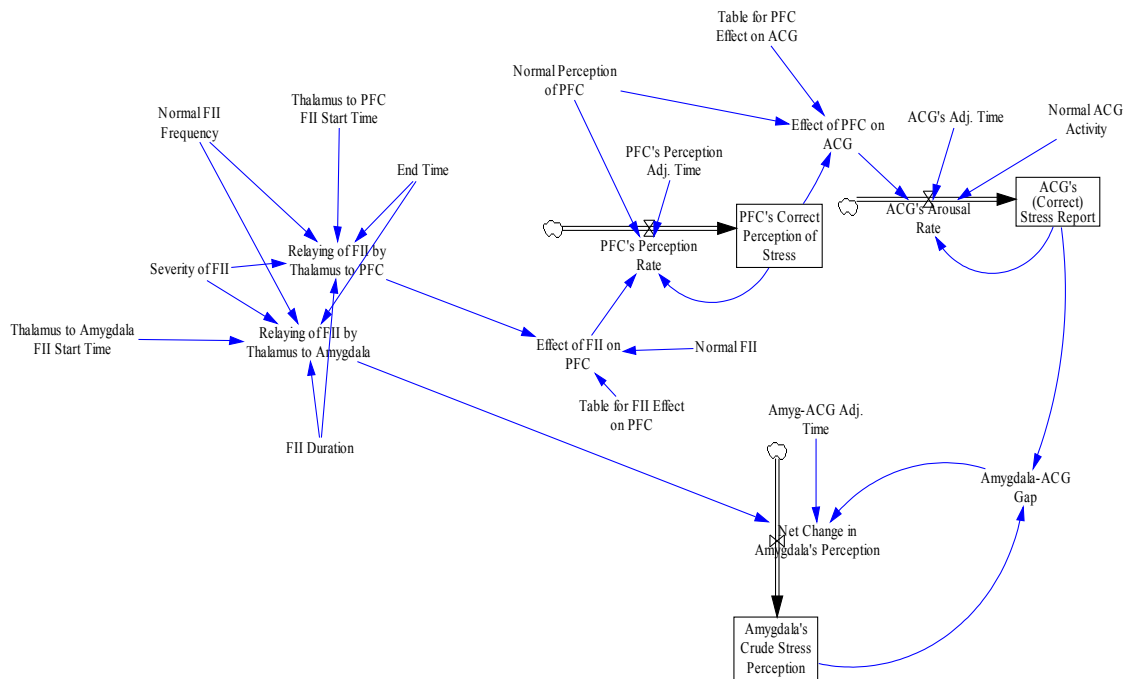

Fig.5.1: A Stock and Flow Model of the *Amygdala-PFC* Circuitry

All of these three stocks are measured in neurons/second. The real world interpretation of this unit is the number of neurons firing per second; the more the neurons fire, the higher the activity level in the brain. In reality, thousands and millions of neurons may fire in one second but these values are scaled in the model for simplicity.

Severity of fear inducing information may be set anywhere between 0 (lowest) and 500 (highest) neurons/second/second in the model shown in Fig. 5.1. The two variables *relaying of fear inducing information (FII) by thalamus to PFC* and *relaying of fear inducing information (FII) by thalamus to amygdala* contain pulse inputs[31] which actually

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31 Precisely, the PULSE TRAIN function is used whose syntax and working are as follows: *"PULSE TRAIN(start,width,tbetween,end) returns 1.0, starting at time start, and lasting for interval width and*

represent the *FII* entering into the brain from the external world. The only difference between the two variables is that the former relays the same pulse input with a 2 second delay as compared to the latter. This is because the *FII* is received in the *amygdala* far early than the *PFC*. (See and compare the equations of *relaying of FII by thalamus to PFC* and *relaying of FII by thalamus to amygdala* presented in Appendix C, Sec. C.1) Fig. 5.2 compares the behaviour of the two pulse functions when the *severity of fear inducing information* is at its maximum, i.e. 500.
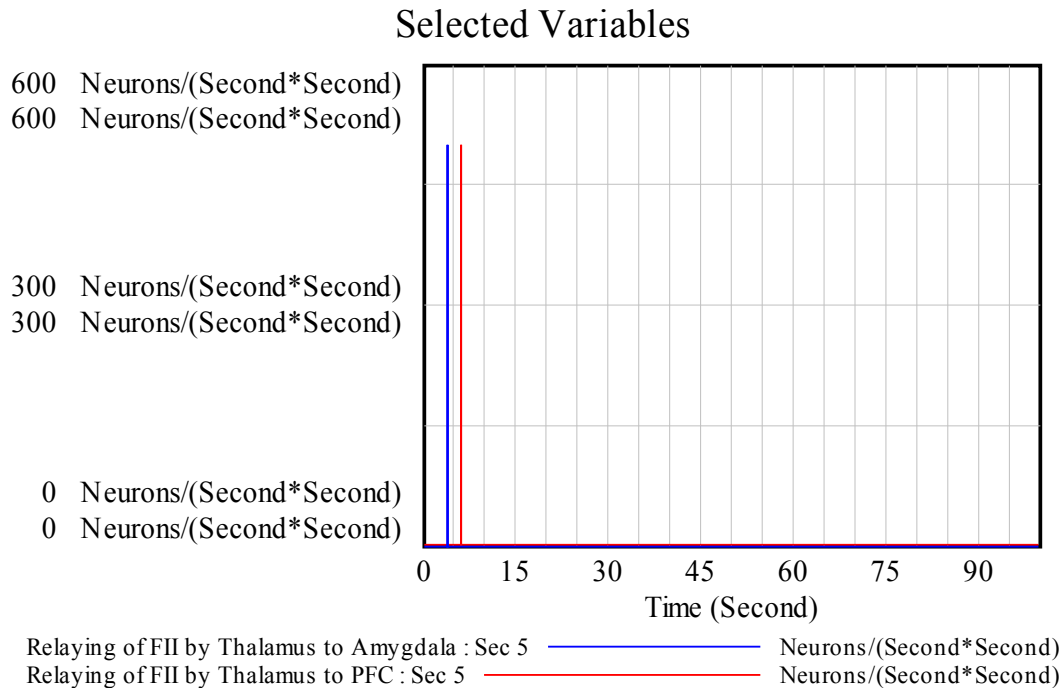
Selected Variables

Relaying of FII by Thalamus to Amygdala : Sec 5 ———————— Neurons/(Second*Second)
Relaying of FII by Thalamus to PFC : Sec 5 ———————— Neurons/(Second*Second)

Fig. 5.2 Comparison of the Step Functions (Representing *Fear Inducing Information*) for *Amgdala* and *PFC*

When the *FII* reaches the *amygdala*, its *perception of stress* immediately starts rising in a "stair-step" fashion. This stair-step can be seen by cutting the loop[32] which adjusts the *amygdala* to the *ACG* (See Fig. 5.3).

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then repeats this pattern every tbetween time; 0.0 is returned at all other times. If the value of tbetween is smaller than width then 1 will be returned between start and end. If width is less than or equal to TIME STEP* the pulses will only last one TIME STEP. The value returned by PULSE TRAIN depends only on the arguments passed to it. Normally, this function is called with Constants. However, you can call it with dynamic variables or expressions in which case the actual output pattern may not be regular." (Vensim from Ventana Systems, Inc.)

*For understanding the concept of TIME STEP, see John D. Sterman, Business Dynamics: S*ystem Thinking and Modeling for a Complex World* (Irwin McGraw-Hill 2000), 903-911.

32 In the present case, the loop is cut by multiplying the equation of *amygdala-ACG gap* by '0'.

Amygdala's Crude Stress Perception
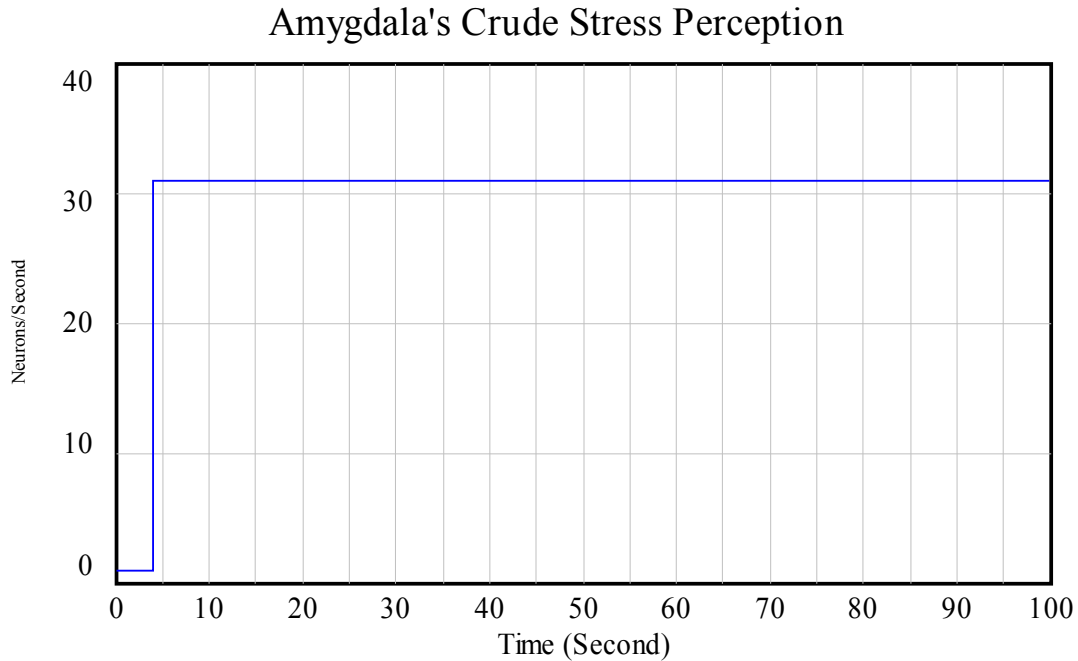
Amygdala's Crude Stress Perception : Cutting the Amygdala-ACG Loop

Fig. 5.3 The Behaviour of *Amygdala's Crude Stress Perception* in the Absence of *ACG's Correct Stress Reporting*

It is the *ACG's correct stress reporting* stock that the *amygdala* adjusts to for lowering its *stress perception* back to normal (See the equation of the *net change in amygdala's perception* in Appendix C, C.1). The normal value for the *amygdala*, *PFC* and *ACG* stocks is assumed to be 1. *ACG's correct stress report* adjusts to *PFC's correct perception of stress* by means of a linear effect[33], i.e., the more/less the *PFC's correct perception of stress*, the more/less the *ACG's correct stress report* (See the equation of *table for PFC effect on ACG* in Appendix C, C.1). PFC, as mentioned earlier, receives the *FII* 2 seconds after the amygdala has received it. However, unlike the *amygdala*, as its *stress perception* is *correct*, it is quickly able to pull its *perception* down to the normal level (See Fig 5.4.).

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33 Such effects are implemented in the model using *table functions*. See John D. Sterman, *Business Dynamics: System Thinking and Modeling for a Complex World* (Irwin McGraw-Hill 2000), 552-595 for a detailed study of the table functions.

PFC's Correct Perception of Stress
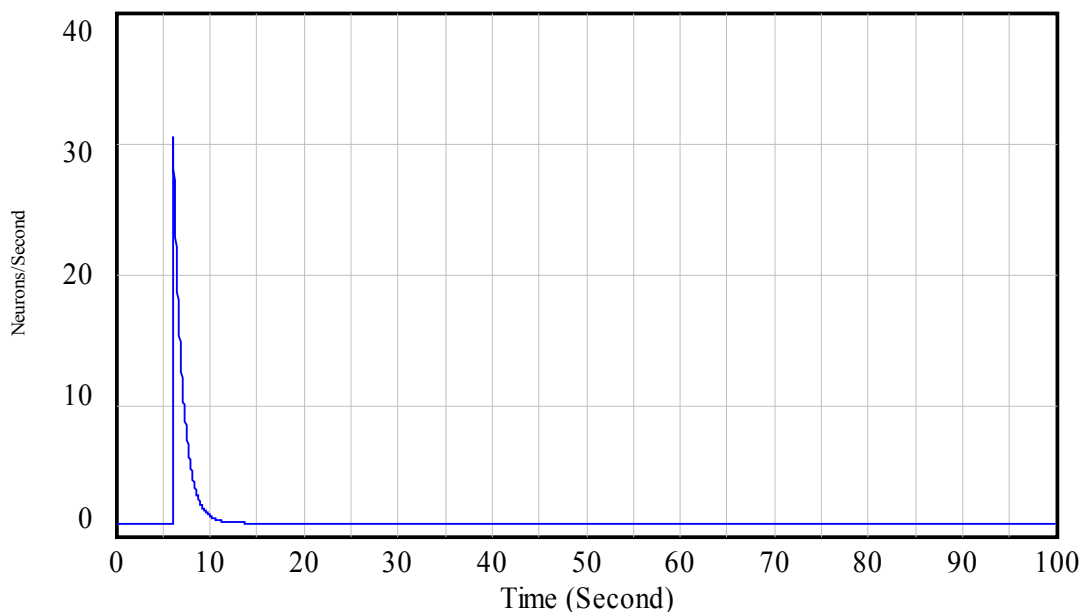
PFC's Correct Perception of Stress : Cutting the Amygdala-ACG Loop ⎯⎯⎯⎯⎯

Fig. 5.4 The Behaviour of *PFC's Correct Perception of Stress* upon Receiving the *FII*

The *effect of FII on PFC* is linear which means that the *PFC* adjusts itself "correctly" to the *FII* (See Appendix C, Sec. C.1 for the PFC related equations). To understand why it is correct, it is helpful to compare the *PFC's stress perception* with that of the *amygdala's*. The latter boosts up and stays high in response to the *FII* until it is adjusted by the ACG (or indirectly by the *PFC*), whereas, the former also boosts but is able to very quickly adjust itself back to its normal or initial level (See and Compare Figs. 5.3 and 5.4). Note here that the *FII* is typically fake in panic disorder (PD) and, hence, its correct perception is the ability to see that it is fake. The *PFC* exhibits this ability by adjusting its *stress perception* quickly down to normal, whereas, the *amygdala* remains unable to do so without the intervene of *ACG's correct stress report* which actually is a result of *PFC's correct perception of stress*. The comparative behaviour of the three stocks is shown in Fig. 5.5. It is apparent from the figure that the *amygdala* stock is adjusting to the *ACG* stock and the *ACG* stock is following the *PFC* stock.
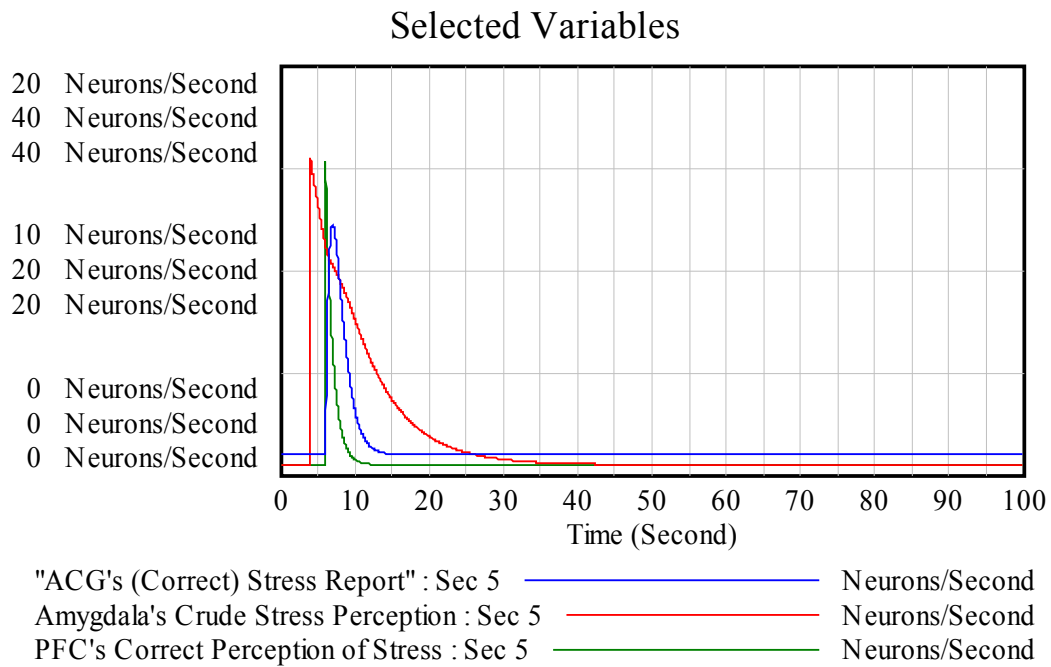
Selected Variables

20 Neurons/Second		
40 Neurons/Second		
40 Neurons/Second		
10 Neurons/Second		
20 Neurons/Second		
20 Neurons/Second		
0 Neurons/Second		
0 Neurons/Second		
0 Neurons/Second		

Time (Second)

"ACG's (Correct) Stress Report" : Sec 5 ———————— Neurons/Second
Amygdala's Crude Stress Perception : Sec 5 ———————— Neurons/Second
PFC's Correct Perception of Stress : Sec 5 ———————— Neurons/Second

Fig. 5.5 The Comparative Behaviour of the Three Stocks where *Amygdala* Follows *ACG* and *ACG* follows *PFC*

Amygdala-ACG adjustment time determines how quickly the amygdala would adjust to the *ACG*. Its value is kept far high than the *PFC* and *ACG* stocks' adjustment times which shows that there is a good delay before the *amygdala* could fully adjust to the *ACG* or indirectly to the *PFC* stock (See Secs. 3.5.1). It should be noted here that the literature does not pinpoint each and everything like it is modelled, however, all the inputs, relationships and behaviours shown so far are a close estimation of what the literature suggests about the functioning of the amygdala, PFC and ACG after receiving the FII.

5.2 Modelling the Norepinephrine (NE) and Serotonin (SE) Feedback System:

The CLD to be translated into the stock and flow model in this section is that of the NE and SE feedback system (See Fig. 4.2a).
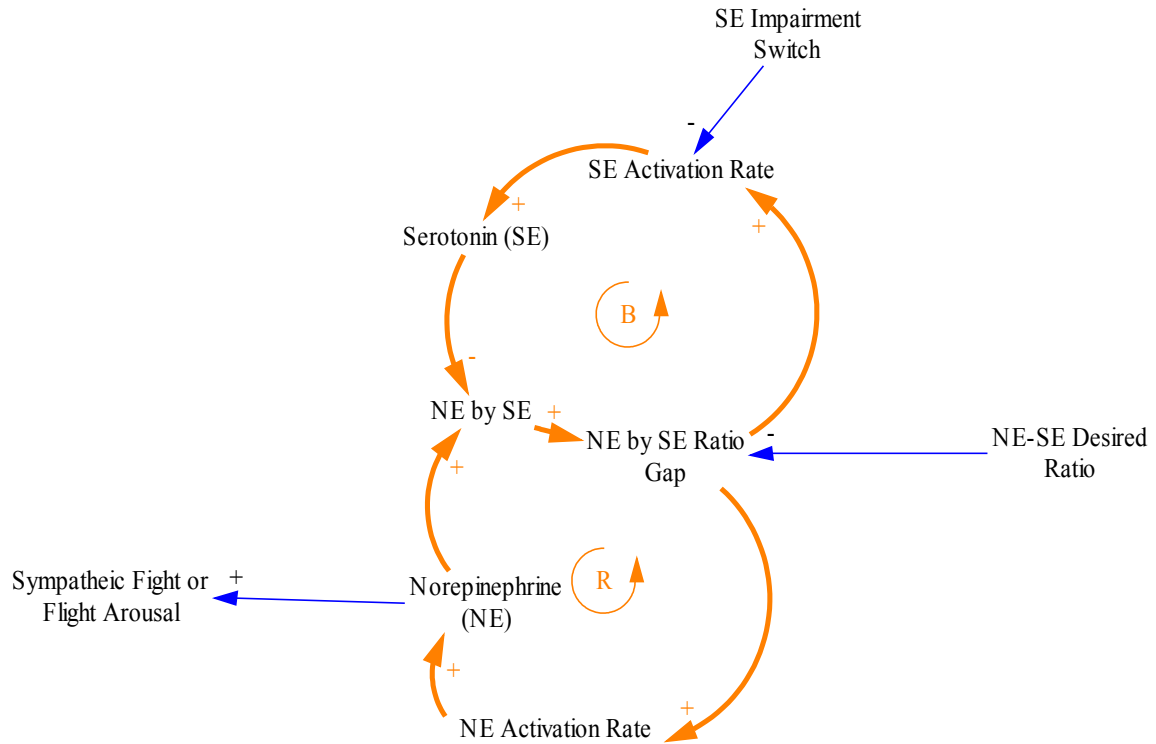
Fig. 4.2a (Reproduced): A CLD showing the NE and SE Feedback System

The *NE* and *SE* variables are stocks which mutually adjust to the *desired NE-SE ratio*. Fig. 5.6 shows these stocks which are measured in molecules. The label "active" preceding *NE* and *SE* means that these stocks only contain the "currently" active *NE* and *SE* molecules out of all the *NE* and *SE* molecules present in the brain. There seems to be a normal NE and SE ratio in the brain which is not explicitly mentioned in the literature, therefore, the desired NE and SE ratio is normalized to 1. This means that the *NE* and *SE* stocks would tend to balance towards the same levels. *NE-SE desired ratio* is divided by the actual *NE by SE* value to obtain the *NE/SE ratio gap* through which both the NE and SE stocks adjust to the *desired NE/SE ratio*.
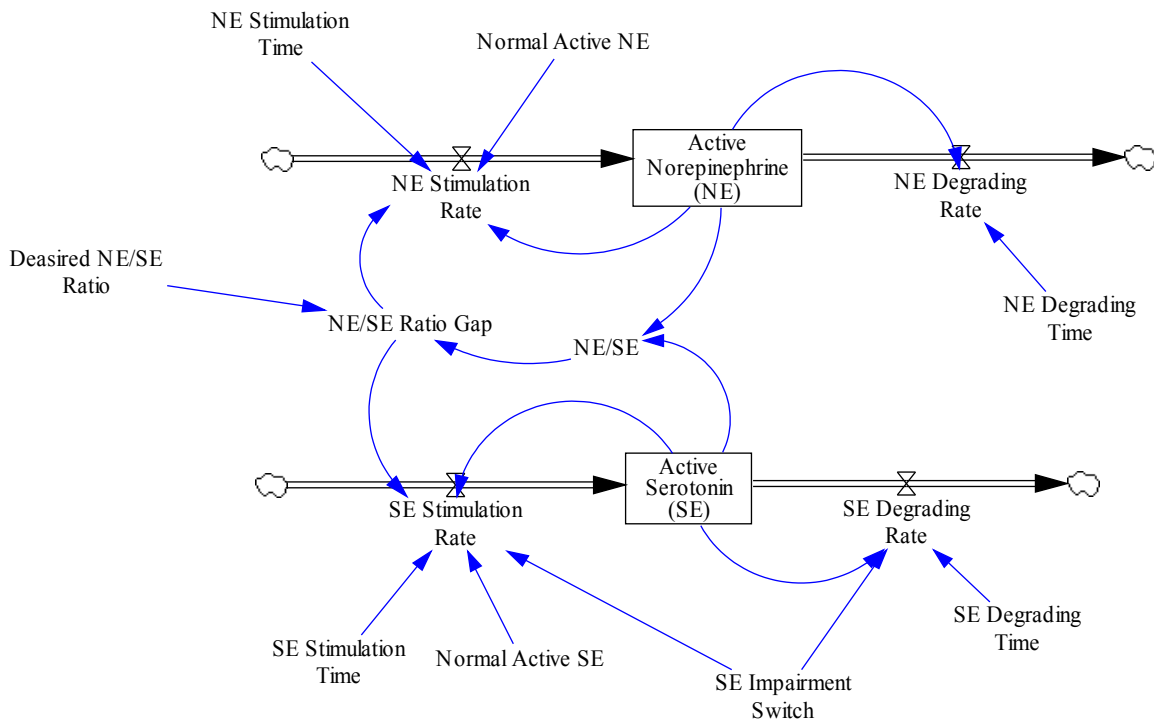
Fig. 5.6: A Stock and Flow Model of the *NE/SE* Feedback System

NE and *SE* stimulation times are kept short and degrading times quite long to imitate the biological chemistry of the body and brain which allows a quick activation but, relatively, very slow deactivation of chemicals and hormones. (See Appendix C, Sec. C.2 for the complete equations of the model shown in Fig. 5.6).

The *SE impairment switch*, as apparent form its name, works like an on/off switch: when it is '0' (on), it suggests that the *SE impairment* exists and when '1' (off); the contrary. It is multiplied by the value in the *SE stimulation rate*. When the switch is on, i.e., *SE impairment = 0,* the *SE stimulation rate* becomes zero which means that the a*ctive SE* stock cannot rise any longer, however, it will keep falling down to its minimum possible levels through the *SE degrading rate*. This is exactly what happens when SE is impaired in the brain; the feedback between NE and SE becomes void; NE keeps rising in order to boost SE but the SE levels keep falling and, all of a sudden, happen to be extremely low (See Sec. 3.8.1.1). However, there lies a problem in this case which is that it is highly unlikely that the NE levels would keep rising dramatically. There needs to be some other feedback mechanism (in the absence of the NE-SE feedback) that somehow helps NE fall back to its normal levels. Otherwise, the NE levels would reach and remain at very high levels for a long period of time which means that they would keep the sympathetic fight or flight arousal activated for a long period of time, consequently, producing the long lasting panic attacks. However, panic attacks are not known to last for more than several minutes. The model crashes down in the SE impairment case as the *NE* levels

dramatically become too high to be calculated any longer. As it is the appropriate behaviour to which no answer is found in the literature, the NE-SE feedback mechanism will not be included in the final model[34]. Otherwise, it will make the simulation impossible in all the cases including the low SE levels due to the impaired SE.

The variable *sympathetic fight or flight arousal* (See the CLD shown in Fig. 4.2a) represents the arousal of specific symptoms like the pounding heart, shallow breathing and shaking etc. This arousal will be later represented in the stock and flow terms by means of translating one of these symptoms (as the rest are alike), i.e., the activity of the heart during the stress response reaction.

Now, the model will be simulated over a period of 10 seconds so that the behaviour of the *NE* and *SE* stocks may be manifested. The parameters used are as follows:

Active Serotonin (SE) = 100 molecules
Active Norepinephrine (NE) = 1000 molecules
SE Impairment Switch = 1 (Indicating that the SE impairment does not exist)

Fig. 5.7 shows the behaviour of the *NE* stock, whereas, Fig. 5.8 of the *SE* stock. As evident from the figures, both of these stocks very quickly adjust towards the *desired NE/ SE ratio* which is assumed to be 1.
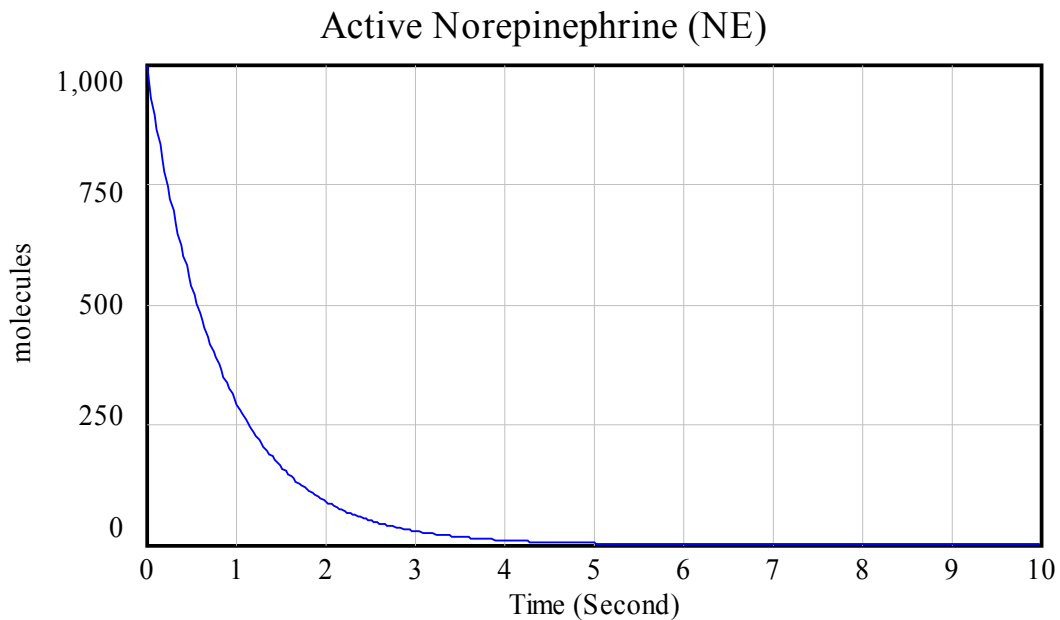
Fig. 5.7: Behaviour of the NE Stock whilst Adjusting towards the *Desired NE/SE Ratio*

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34 However, NE and SE will be included as a stock and converter respectively.
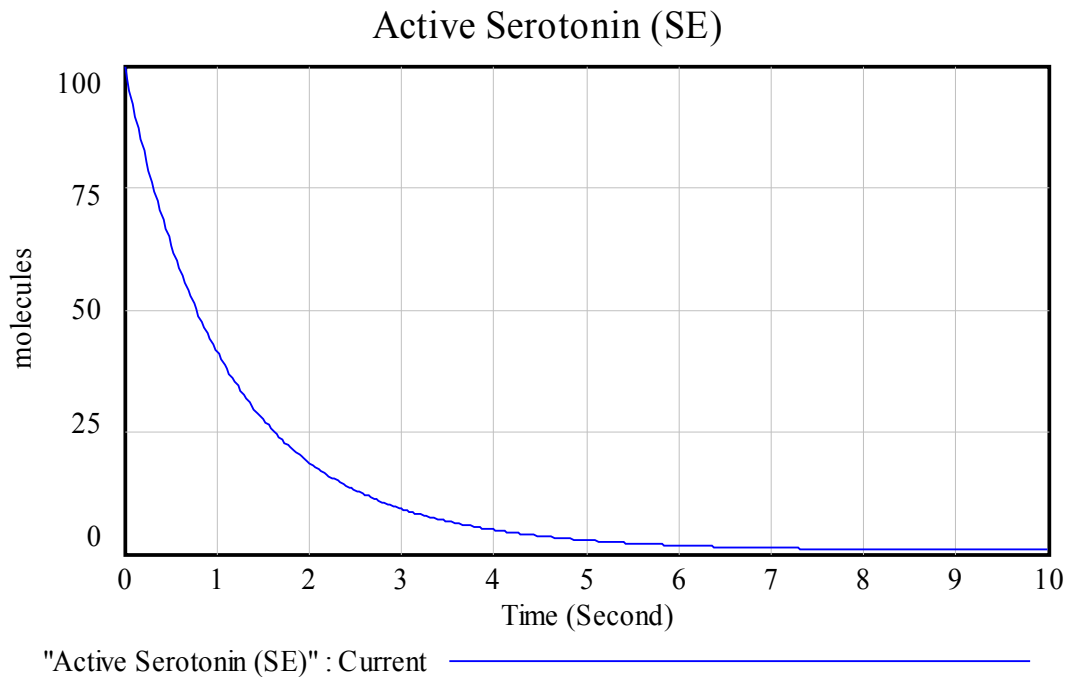
Active Serotonin (SE)

Fig. 5.8: Behaviour of the SE Stock whilst Adjusting towards the *Desired NE/SE Ratio*

5.3 Modelling the Stress Response Reaction (Fear Emotion) and the Impact of NE on PD:

The next CLDs to be translated are reproduced in Fig. 4.3a and 4.4a. These two CLDs may easily be combined together. The resultant CLD would look like Fig. 4.3/4a.
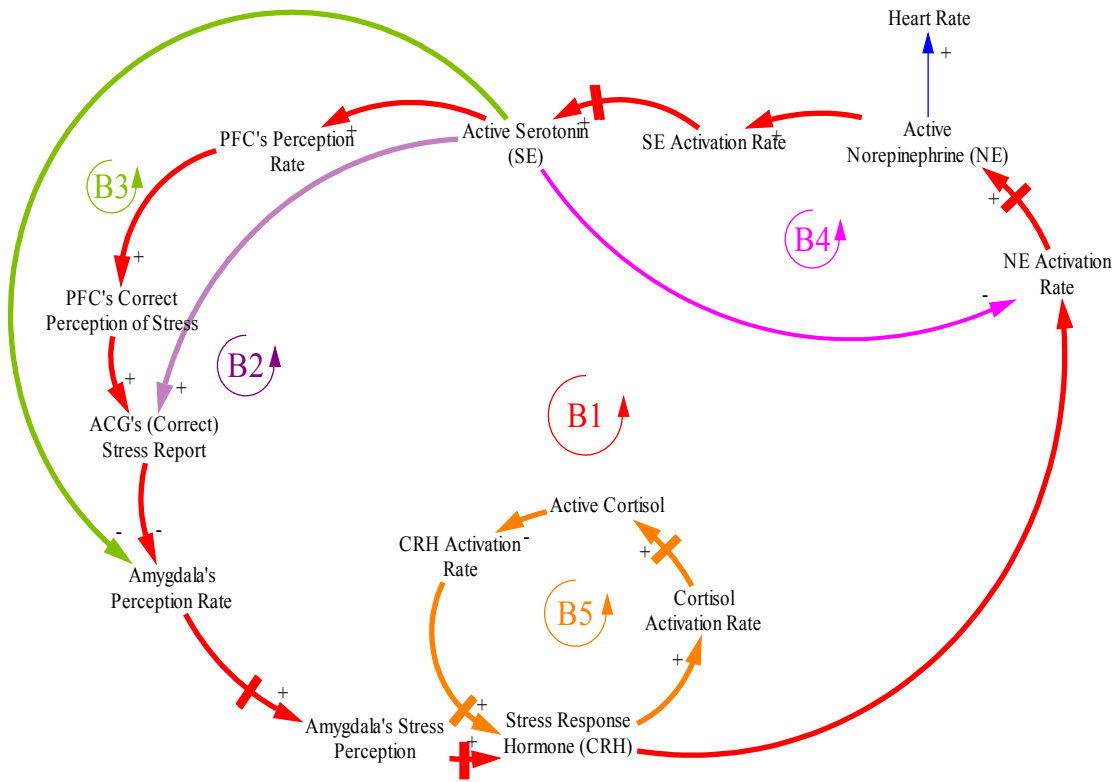
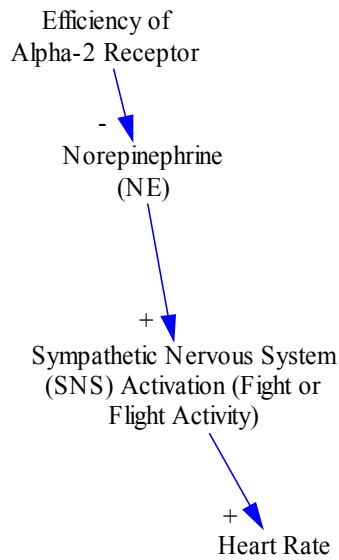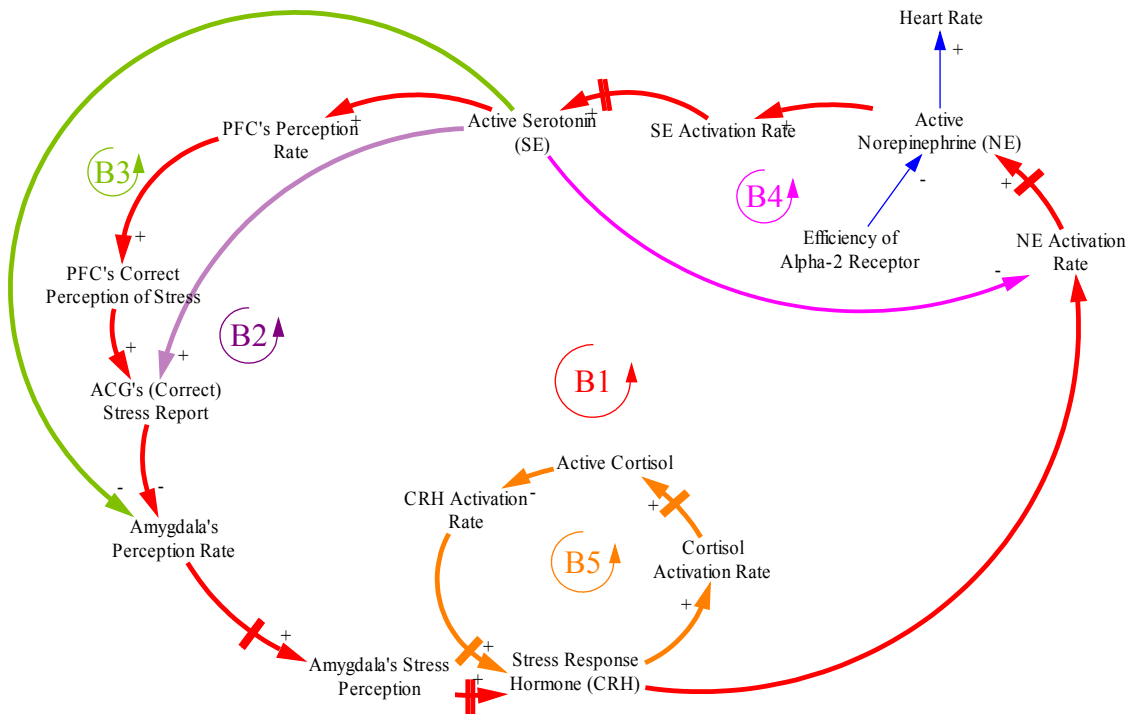Fig. 4.3a (Reproduced): A CLD of the Stress Response Cycle

Fig. 4.4a (Reproduced): A Part of CLD Reflecting the Role of *Efficiency of Alpha-2 Receptor* and *NE* in PD

ig. 4.3/4a: A CLD of the Stress Response Cycle including the *Impact of the Efficiency of Alpha-2 Receptor*

Note that the *amygdala/PFC* circuitry and *SE/NE* feedback system shown in Fig. 4.3/4a have already been translated into the stock and flow models in Sections 5.1 and 5.2. The *stress response hormone* and *active cortisol* (See Loop 'B5', Fig. 4.3/4a) are stocks as they represent the accumulation of chemicals and are responsible for the momentum or sluggishness in the stress response system (See Ford 1999, 16). *Heart rate*, if represented in average, would also be a stock showing the average rise and fall of the heart rate over time. *Efficiency of alpha-2 receptor* gives a "stock feeling" as well for it changes less rapidly as compared to the other variables (See Ford 1999, 16) and maintains its current level if frozen with a "snapshot" (See Sterman 2000, 199). However, for simplicity, it will be modelled as a constant parameter whose values may be set (before simulation) between '0' and '100' percent. All these neurochemical stocks will be measured in molecules, whereas, the *average heart rate* will be measured in (heart)beats per second. Fig. 5.9 (Pg. 104) shows *active cortisol*, the *stress response hormone* and *average heart rate* as interrelated stocks and the *efficiency of alpha-2 receptor* as a constant and combines them with the models developed in Sections 5.1 and 5.2 in the light of the CLD shown in Fig. 4.3/4a.

The NE and SE feedback mechanism, however, is not incorporated in this model due to a critical problem thoroughly discussed in Sec. 5.1. Although SE clearly is a stock in concept but it is included as a converter (constant) in this model because without the

intervene of NE, it cannot vary throughout the simulation time period. It is worth noticing here that in case of impaired SE, the NE-SE feedback system does not work in anyway, therefore, SE would behave like a converter in that case, i.e., it would remain low and unchanged throughout the simulation time period (See Sec. 3.8.1.1). Like the NE stock, the SE converter is also measured in molecules whose value may be set between '0' and '100'. '100' molecules represent the normal SE levels in a healthy brain, whereas, below that all values represent SE impairment cases.
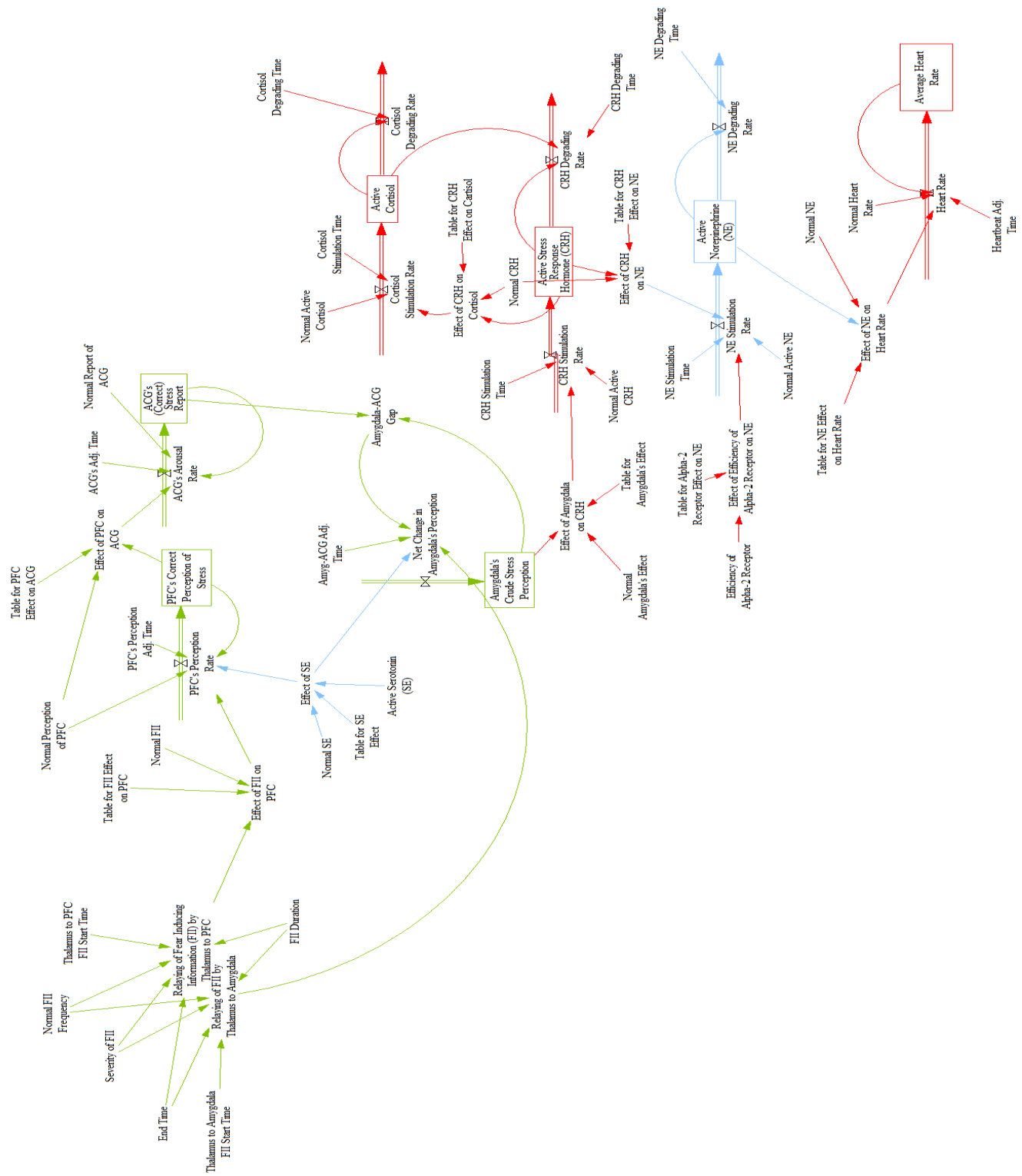
Fig. 5.9 (Pg. 104): A Stock and Flow Model of the Stress Response Reaction including the *Amygdala-PFC* Circuitry, *NE/SE* Feedback System and *Heart Rate* – the Last Mentioned being a Representative of the PD or Fight/Flight Symptoms

The model developed in Section 5.1 is connected with the rest of the structure through the *effect of amygdala on CRH*. The table function for this effect is almost s-shaped which means that its output (the *effect of amygdala on CRH*) grows rapidly at first with its input (the *amygdala's crude stress perception*) but then gradually slows until it reaches its maximum value. The *effect of amygdala on CRH* positively effects the *CRH* production, i.e., the more the effect, the more the *CRH* stimulation and, hence, levels in the brain (See *CRH stimulation rate* equation in Appendix C, Sec. C.3). The literature does not provide any detailed picture of how the amygdala precisely effects CRH (See Sec. 3.3) but the relationship it suggests would, more or less, be the same function as shown in Fig. 5.10. This is true for the rest of the "effect of" relationships incorporated in the model as well.
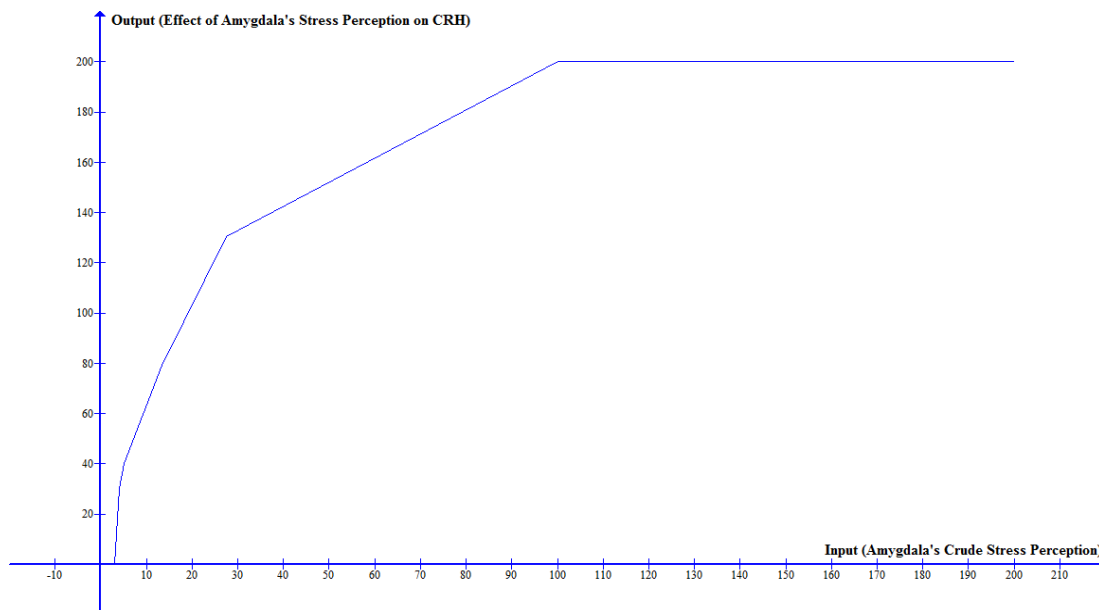

Fig. 5.10: Table Function for the *Effect of Amygdala's Crude Stress Perception on CRH*

After receiving the *fear inducing information (FII)*, the *amygdala* stimulates *CRH* which further stimulates *cortisol* and *NE* in a way that the more/less *CRH,* the more/less *cortisol* and *NE*. These *CRH-cortisol* and *CRH-NE* relationships are modelled with the help of table functions. As *cortisol* rises after being stimulated by *CRH*, it speeds up the *CRH degrading rate* through which *CRH* falls back to its initial level that it maintained before being stimulated by the *amygdala*. When *NE* rises, it positively effects the *average heart rate*. This effect, as it is modelled, is shown in Fig. 5.11.
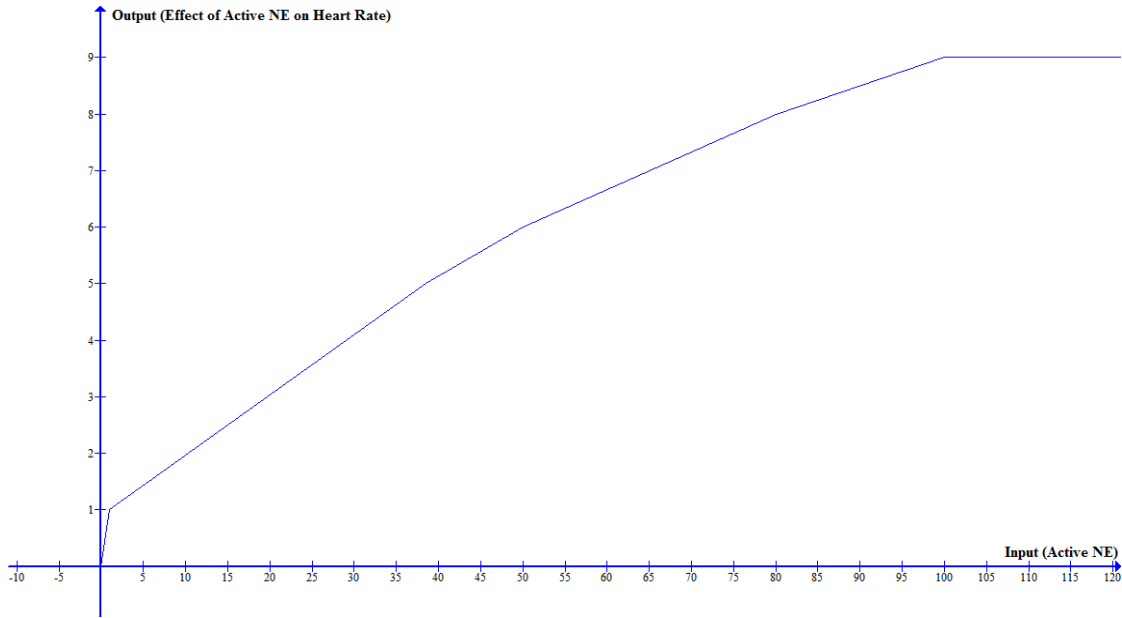
Fig. 5.11: Table Function for the *Effect of NE on Average Heart Rate*

The *degrading times* for *CRH*, *cortisol*, *NE* and *SE* are kept quite long and their *stimulation times* short to imitate the real life scenario in which these chemicals quickly activate but take a relatively longer time to degrade back to their initial levels.

For simplicity, instead of modelling all the panic symptoms separately to represent a panic attack, the *average heart rate* is considered to be the sole representative of a panic attack in this model. Note that, more or less, all the panic symptoms (most of which are stimulated by *NE*) like rise in average breathing rate, average blood pressure and average flushing etc. would give rise to the same stock and flow structure as that of the *average heart rate*.

High levels of *SE*[35] will have a counteracting effect on the *PFC's perception rate* and *net change in amygdala's perception*. Note that this counteracting effect on the *PFC's perception rate* is a positive mechanism as it would not allow the *PFC's stress perception* to rise exceedingly. As the *SE-amygdala* and *SE-PFC* relationships are identical, the same table function is used to represent them (See Fig. 5.12). The output of this function (i.e. the *effect of SE*) is divided by the corresponding values in the two inflows it is effecting which means that it serves to cut short whatever the value of these inflows is. For the complete model equations, see Appendix C, Sec. C.3.

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35 Set, before simulation, through the SE converter which may take on any value between '0' and '100' molecules.
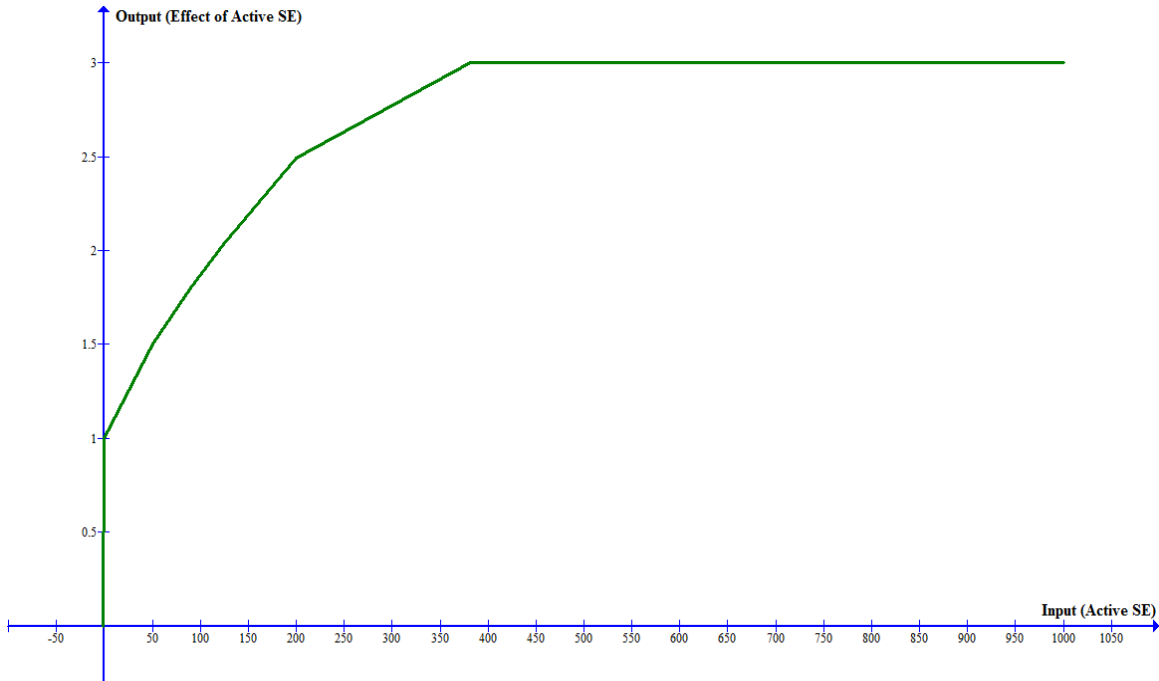
Fig. 5.12: Table Function for the *Effect of SE (*on the *PFC* and *Amygdala* Inflows)

Now, the model will be simulated over a period of 1000 seconds (16 minutes) so that the behaviour of the key variables may be manifested. The parameters used are as follows:

Efficiency of alpha-2 receptor = 100 (Highest, , i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 1 (Extremely Low, i.e., abnormal)

After receiving the *FII* from the thalamus, the *amygdala* and *PFC* stocks' comparative behaviour will be as shown in Fig. 5.13. It is clear from the figure that the *amygdala* stock is adjusting to the *ACG* stock except for the first few seconds when the *ACG* stock itself has not received any input from the *PFC* stock (See Sec. 5.1 for details).

Selected Variables

"ACG's (Correct) Stress Report" : High severity of FII, High Efficiency of alpha-2 receptor, Low SE ——————— Neurons/Second
Amygdala's Crude Stress Perception : High severity of FII, High Efficiency of alpha-2 receptor, Low SE ——————— Neurons/Second
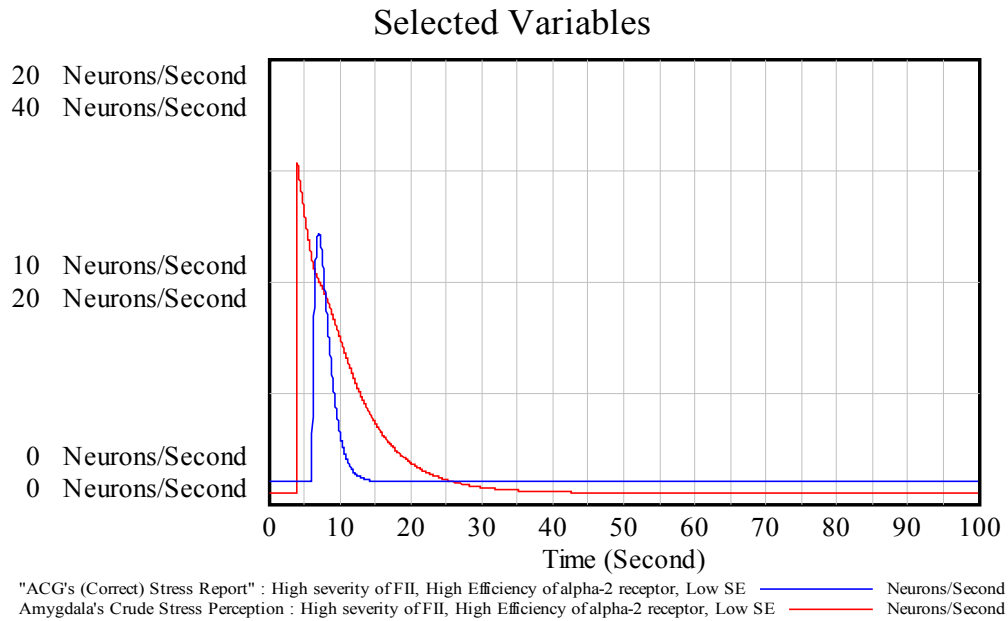
Fig. 5.13: Comparative Behaviour of the *Amygdala* and *ACG* Stocks

After being stimulated by the *amygdala*, the comparative behaviour of the *CRH* and *NE* stocks will be as shown in Fig. 5.14. The *NE* stock follows the *CRH* stock although its peak touches a higher value as compared to that of the *CRH's* because the NE-CRH relation is such that comparatively lower *CRH* levels are able to stimulate higher *NE* levels.

Selected Variables

"Active Norepinephrine (NE)" : High severity of FII, High Efficiency of alpha-2 receptor, Low SE ——————— Molecules
"Active Stress Response Hormone (CRH)" : High severity of FII, High Efficiency of alpha-2 receptor, Low SE ——————— Molecules
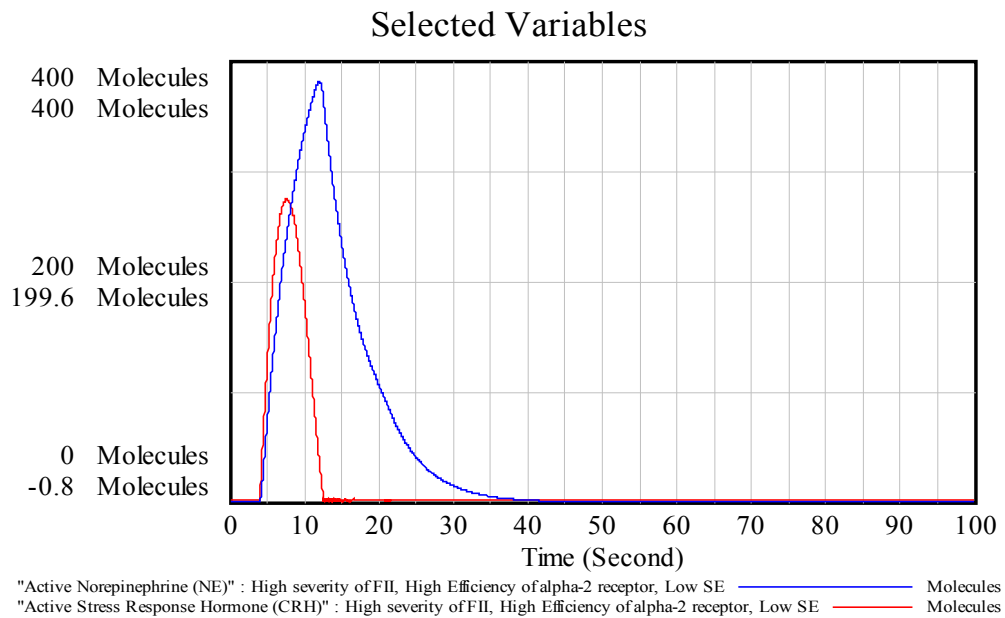
Fig. 5.14: Comparative Behaviour of the *CRH* and *NE* Stocks

The behaviour of the *SE* converter is shown in Fig. 5.15. It constantly remains on 1 throughout the simulation.

Active Serotonin (SE)

"Active Serotonin (SE)" : High severity of FII, High Efficiency of alpha-2 receptor, Low SE ————————
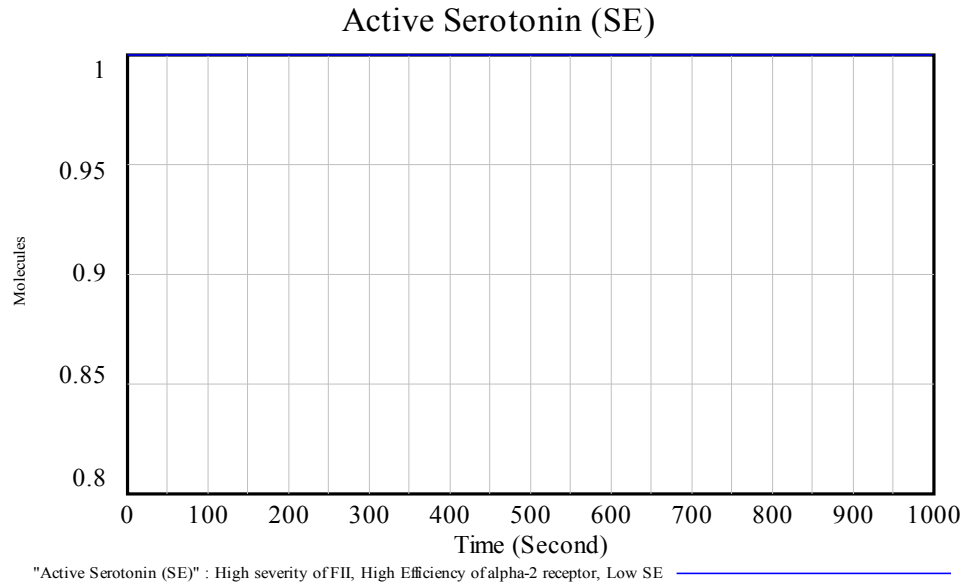
Fig. 5.15: Behaviour of the SE Converter

Fig. 5.16 shows the behaviour of the *average heart rate* stock after being effected by the *NE* stock. The spike in the average heart rate lasting for about 14 minutes actually indicates the presence of a panic attack during which the heart beats faster than normal – the normal being 1.2 beats per second or around 72 beats per minute.
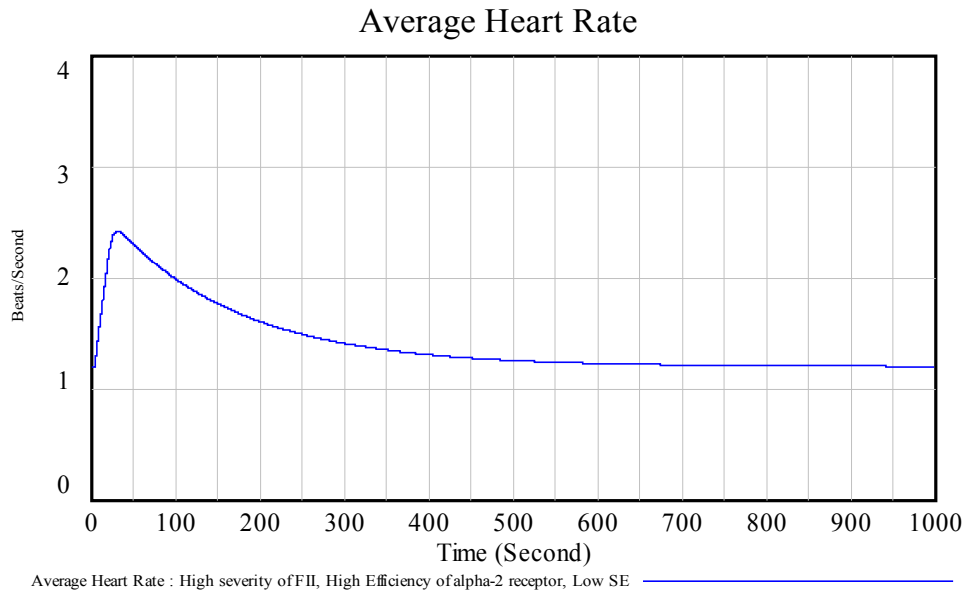
Average Heart Rate

Average Heart Rate : High severity of FII, High Efficiency of alpha-2 receptor, Low SE

Fig. 5.16: Behaviour of the *Average Heart Rate* Stock after being Effected by *NE*

5.4 Modelling the Impact of Over-reactive Stress Response on PD:

The over-reactive stress response reaction may be represented within the model developed in the previous section (See Fig. 5.9). For that, the *effect of amygdala's crude stress perception on CRH* needs to be modified in a way that even a low-intensity stimulus (*FII*), once perceived in the *amygdala*, can produce a good amount of *CRH*. Such an *amygdala-CRH* relationship may be achieved by increasing the output (the *effect of amygdala's crude stress perception on CRH)* of the table function shown in Fig. 5.10. What this increase implies is that the same input (the *amygdala's crude stress perception*) would produce a bigger effect which would result in stimulating more *CRH* molecules than normal – paving way for the initiation of the stress response reaction (fear emotion) in relation to a minor stimulus. Fig. 5.17 shows the table function which would be used in the model to represent an over-reactive stress response system (Compare Figs. 5.10 and 5.17).
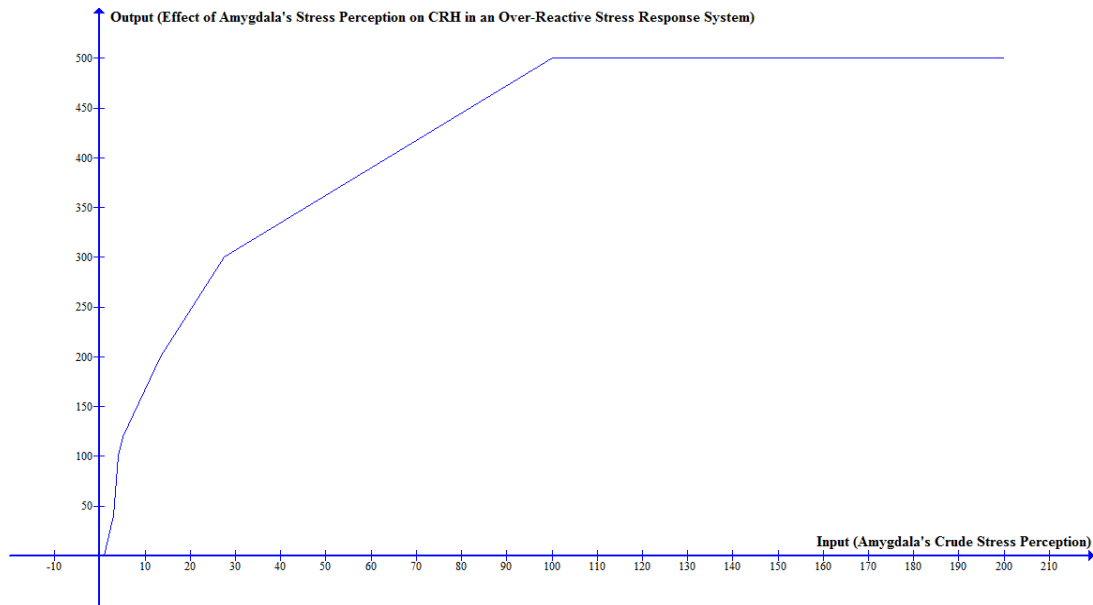
Fig. 5.17: Table Function for the *Effect of Amygdala's Crude Stress Perception on CRH* in an Over-reactive Stress Response System

When the model is simulated over a period of 1000 seconds, the comparative effect of the normal and over-reactive stress response systems on the *CRH* stock is as shown in Fig. 5.18. In the simulated model, only the *effect of amygdala's crude stress perception on CRH* is changed (in the over-reactive case) as per Fig. 5.17. Rest of the parameters remain the same as the last simulation in Sec. 5.3.

Active Stress Response Hormone (CRH)

"Active Stress Response Hormone (CRH)" : Normal stress response system
"Active Stress Response Hormone (CRH)" : Over-reactive stress response system
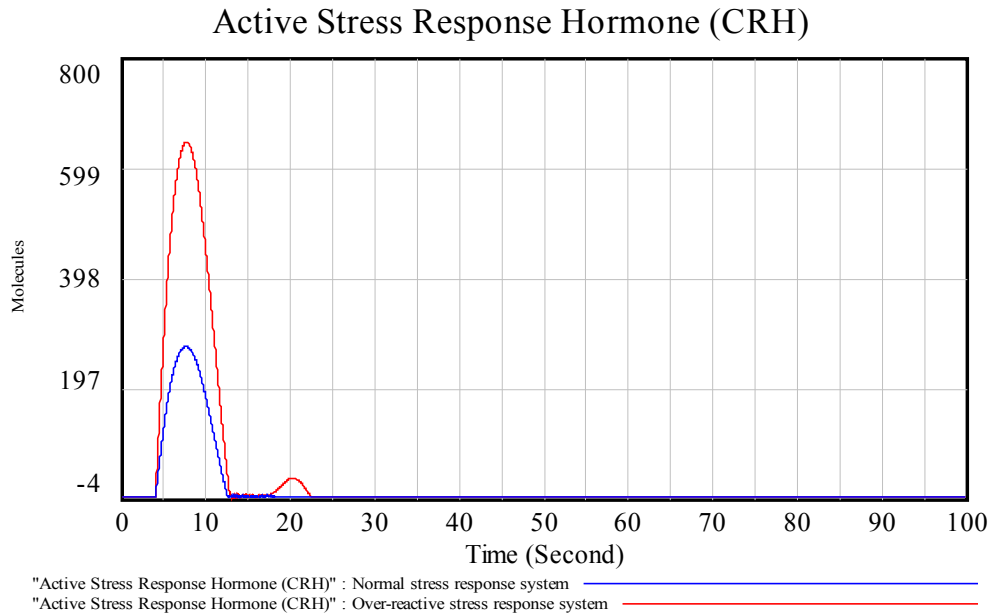
Fig. 5.18: Comparative Behaviour of the *CRH* Stock Whilst Normal and Over-Reactive Stress Response Systems

It is evident from Fig. 5.18 that, in case of an over-reactive stress response system, a greater amount of *CRH* will be activated which will result in a stronger stress response reaction (fear emotion) eventually leading to a severer panic attack (See Fig. 5.17).

Average Heart Rate

Average Heart Rate : Normal stress response system
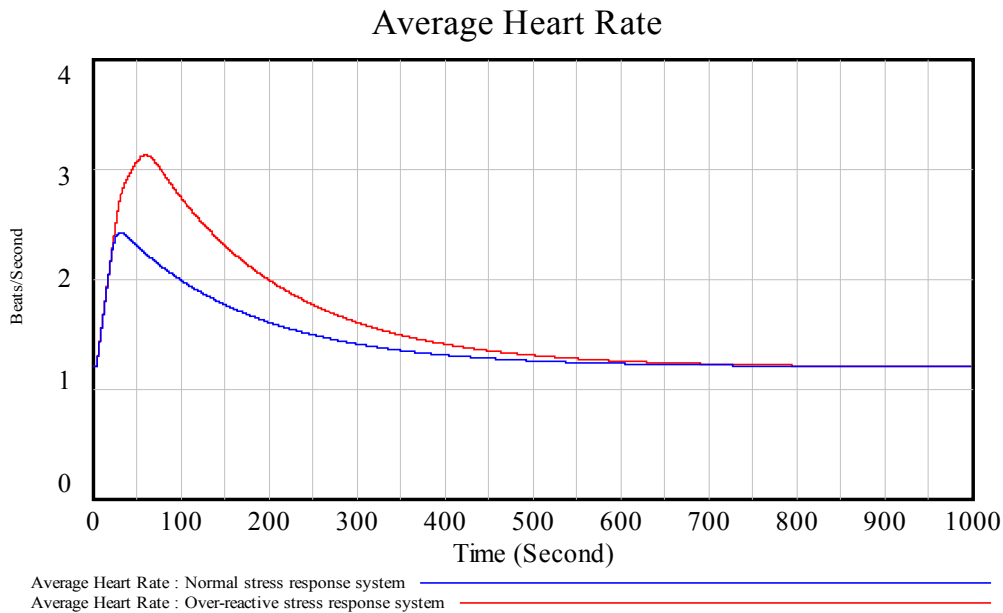Average Heart Rate : Over-reactive stress response system

Fig. 5.19: Comparative Behaviour of the *Average Heart Rate* Stock Whilst Normal and Over-Reactive Stress Response Systems

5.5 Modelling the Impact of GABA on PD:

The next CLD to be translated is shown in Fig. 4.6.
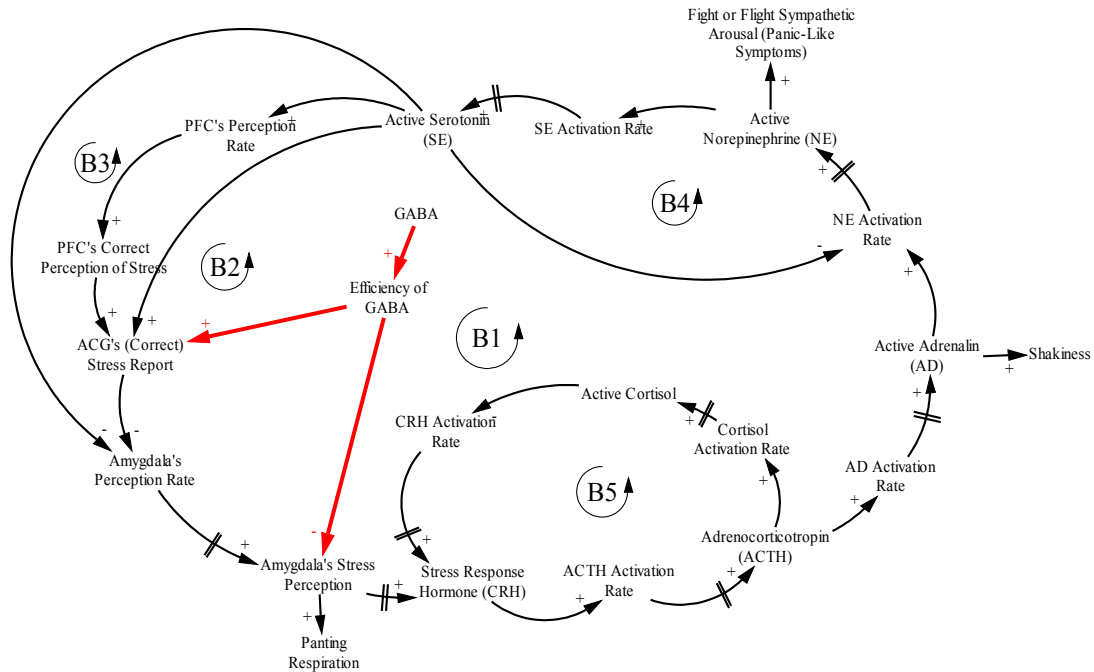
Fig. 4.6 (Reproduced without the *Firing of Neurons in Basal Ganglia*): A CLD of the Role of *GABA* in the Stress Response Reaction

It is straightforward to see that *GABA*, like all other chemicals, is a stock but it would be modelled as a constant as it is intended to keep the stock and flow model simple by excluding the factors on which the *GABA* levels depend. Also, it is highly unlikely that the *GABA* levels would significantly fluctuate over the model's simulation time frame. Fig. 5.20 (Pg. 114) includes the *GABA* converter into the body of the model developed so far.

Fig. 5.20 (Pg. 114): The Stock and Flow Model Highlighting the *Effect of GABA* on the Stress Response Reaction

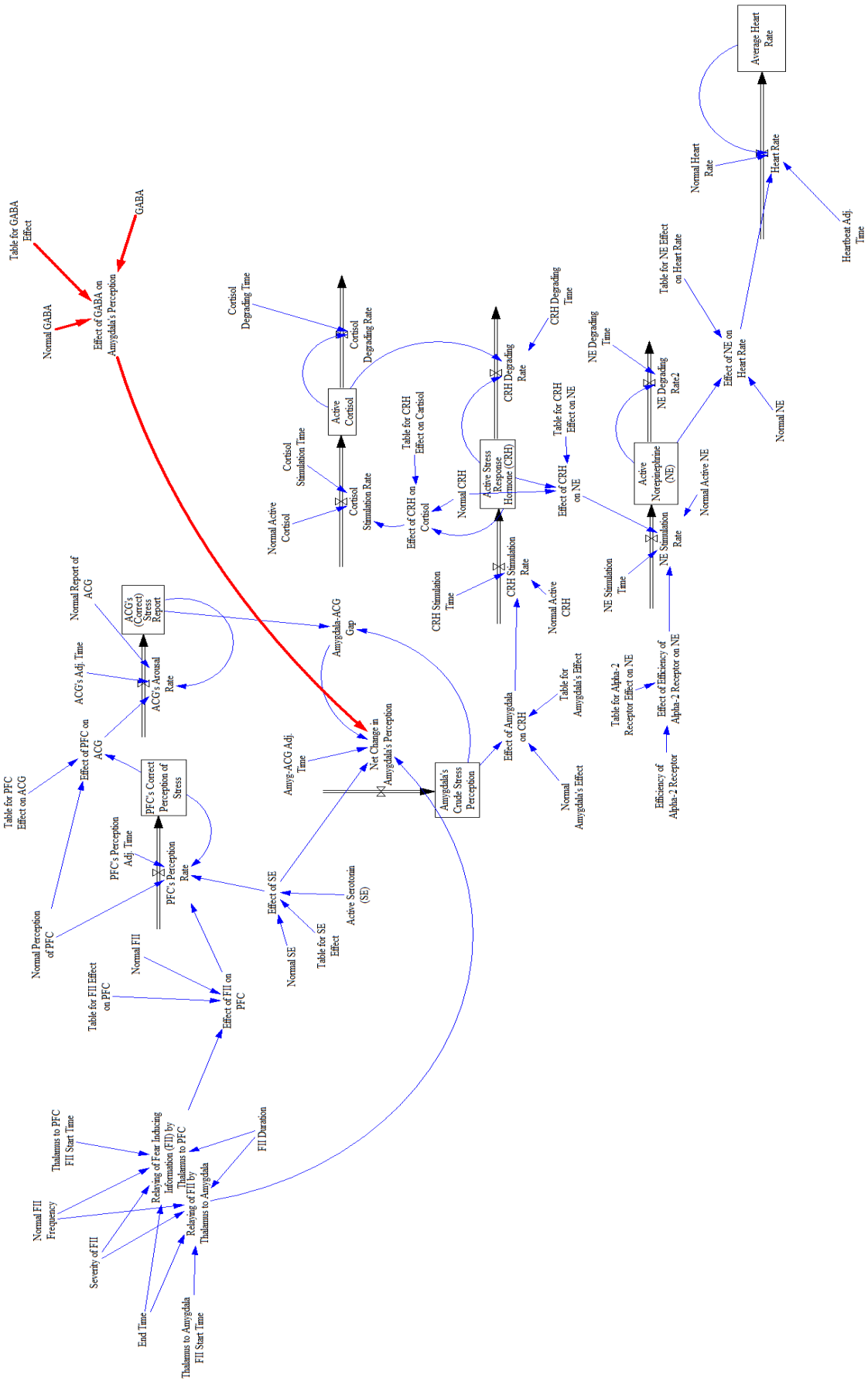The value of the *GABA* constant may be set anywhere between '0' and '500' molecules where '0' depicts the minimum GABA levels in the brain, whereas, '500' maximum. As evident from Fig. 4.6, *GABA* negatively effects the *amygdala's stress perception* directly as well as through enhancing the *ACG's* modulating effect onto the amygdala through the *ACG's correct stress reporting*. Both of these factors are entertained by introducing the *effect of GABA on the amygdala's perception* into the equation of the *net change in amygdala's perception*. The equation is as follows:

*(Relaying of FII by Thalamus to Amygdala / (Effect of SE * Effect of GABA on Amygdala's Perception)) + ("Amygdala-ACG Gap" * Effect of SE * Effect of GABA on Amygdala's Perception / "Amyg-ACG Adj. Time")*

The table function for the *effect of GABA on the amygdala's perception* is shown in Fig. 5.21.
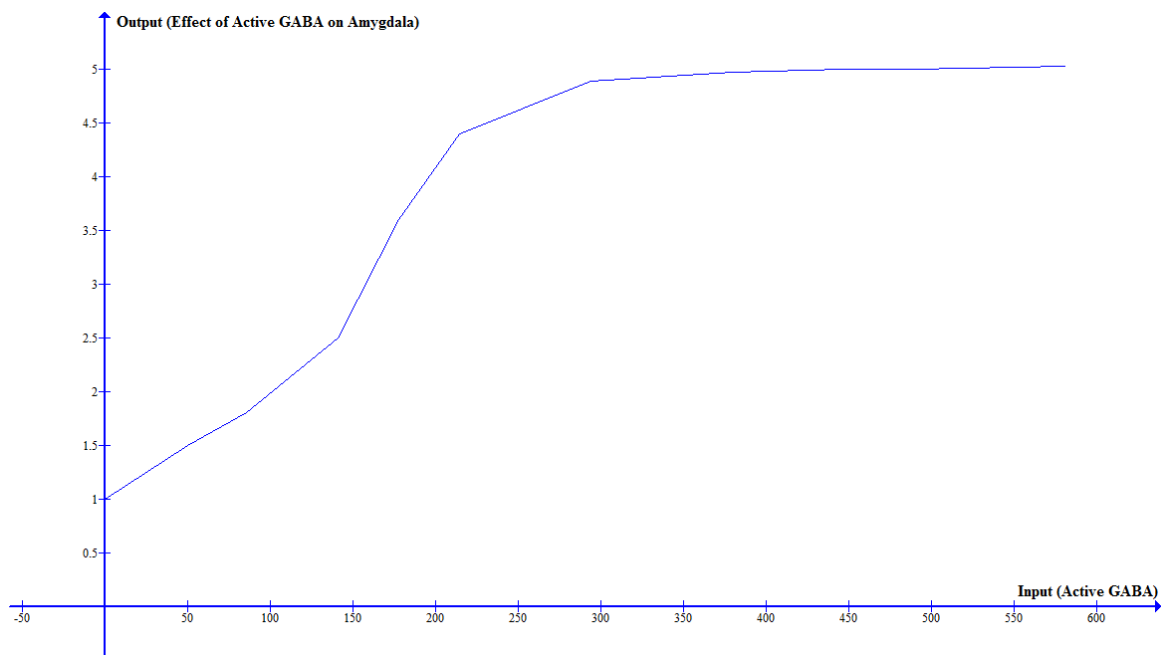
Fig. 5.21: Table Function for the *Effect of GABA on the Amygdala's Perception*

Now, the model will be simulated over a period of 30 seconds to see the impact of the low and high values of *GABA* on the *amygdala's stress perception* stock. Fig. 5.22 shows the comparative behaviour of the *amygdala* stock when the model is simulated with high (i.e., 500 molecules) and low (i.e., 150 molecules) values of GABA whilst all other variables are kept constant.
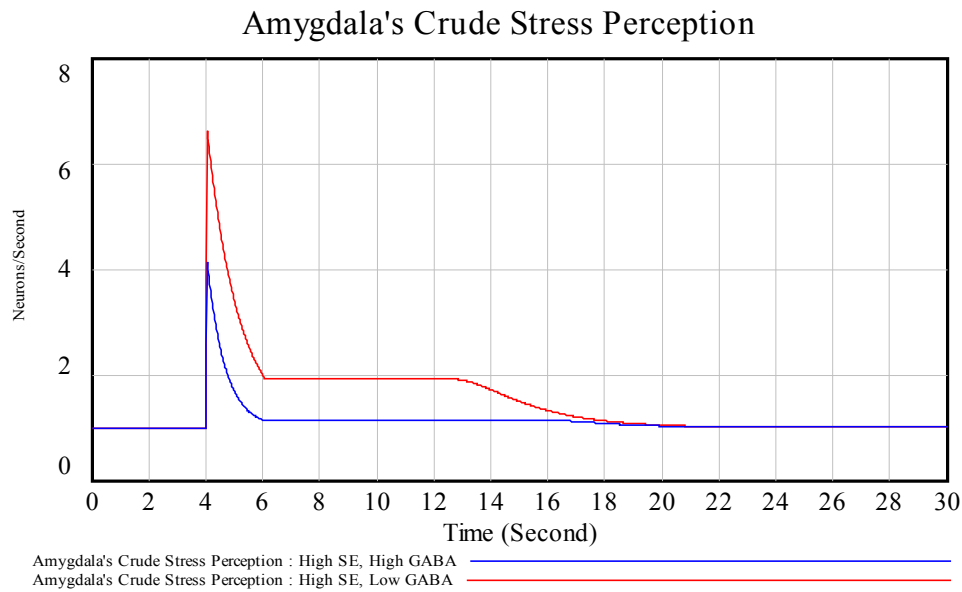
Fig. 5.22: Behaviour of the *Amygdala's Stress Perception* Stock Whilst Low and High GABA Values

It is evident from Fig. 5.22 that when *GABA* is high, it significantly helps reducing the magnitude of the *amygdala's stress perception*.

5.6 Modelling the Stress and the Creation of Stimuli Mechanism:

The next CLD to be translated is the one that represents the stress and stimuli feedback relationship. See Fig. 4.7a.

Fig. 4.7a (Reproduced): A CLD representing the Stress and Stimuli Feedback Relationship

Stressful events is an obvious stock whose inflow is dependent on the *occurrence of panic symptoms* (which are represented by the *average heart rate* in the stock and flow model developed). It is also straightforward to see that the *number of stimuli* is a stock whose inflow is dependent on the *stressful events*. There would be no outflow for the *stressful events* and *stimuli* stocks as they do not decline within the simulation time span of the model – it is time consuming and difficult to get rid of the stressful (traumatic) events and panic-causing stimuli stored in the brain. Fig. 5.23 (Pg. 118) highlights the *stressful events* and *stimuli* stocks and connects them with the rest of the model developed so far. The *stressful events* stock is measured in "events" and the *stimuli* stocks in "stimuli".
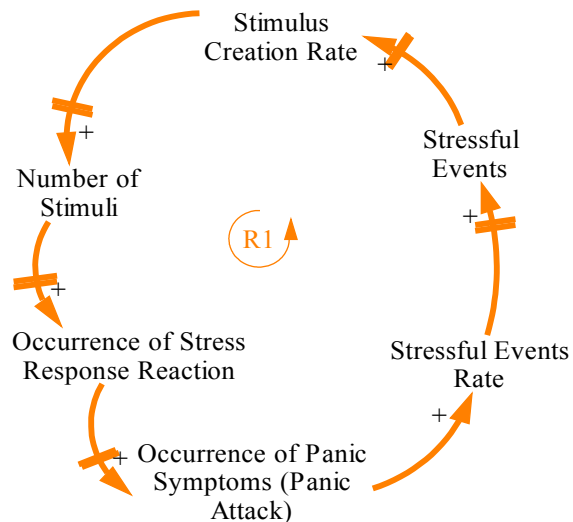
As mentioned earlier, all the panic symptoms are represented by the *average heart rate* in the stock and flow model developed, therefore, the variable *occurrence of panic symptoms* (Fig. 4.7a) is actually representing the occurrence of the changes in the *average heart rate*. The variable *occurrence of stress response reaction* (Fig. 4.7a) represents the whole stress response reaction starting from the amygdala, activating the stress response hormone (CRH), cortisol, norepinephrine (NE), serotonin (SE) and, eventually, leading to the panic symptoms (represented by the *average heart rate* in the model). The stock and flow model shown in Fig. 5.9 is a good portray of the whole stress response reaction.
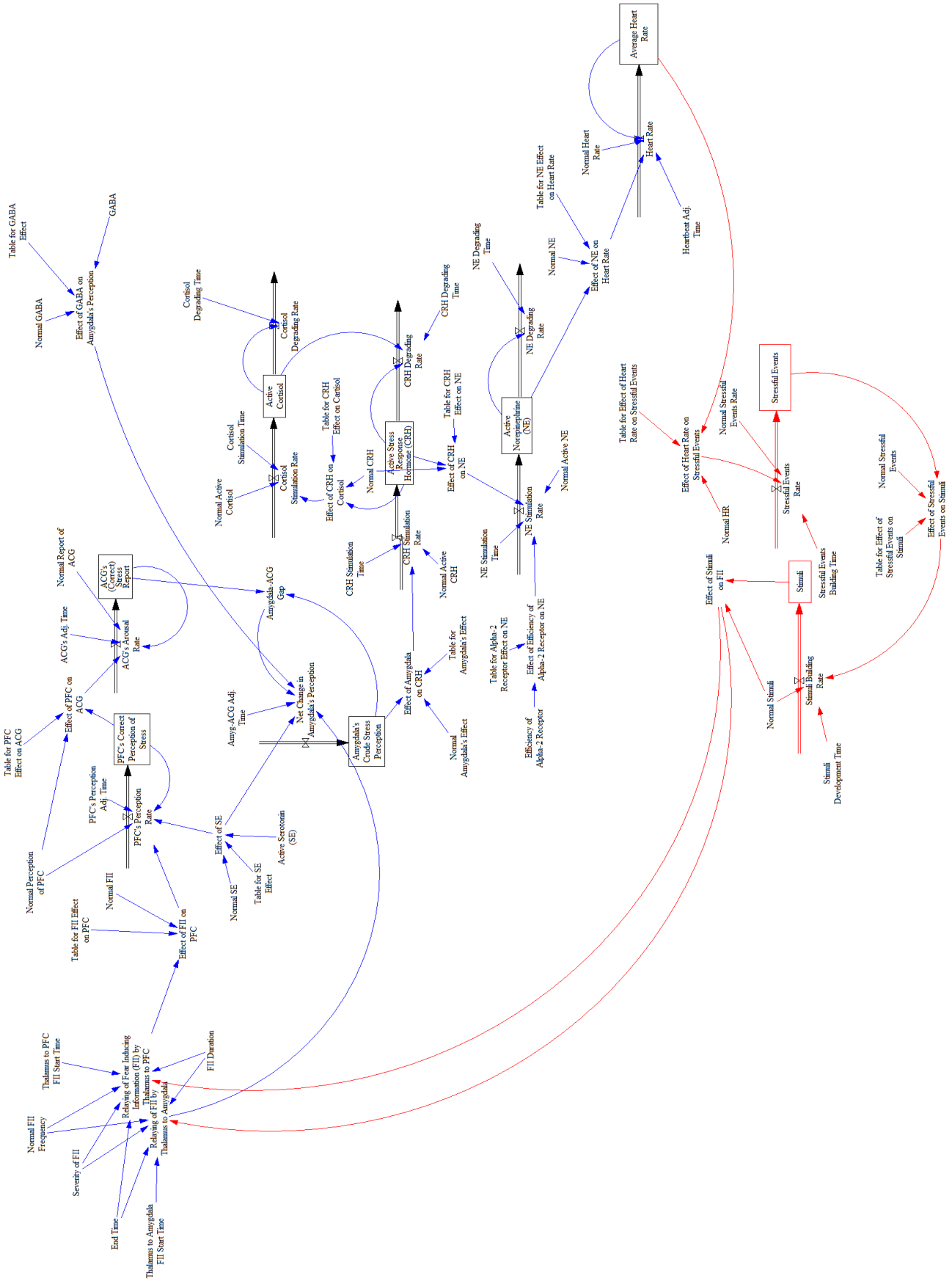
118

Fig. 5.23 (Pg. 118): The Stock and Flow Model Highlighting the Stress and the Creation of Stimuli Mechanism

In the model shown in Fig. 5.21, the effect of *average heart rate on stressful events* is implemented by a table function which ensures that the more the *average heart rate*, the more the effect which, consequently, positively influences the *stressful events rate*. Similarly, the *effect of stressful events on stimuli* is also implemented by a table function which ensures that the more the *stressful events*, the more the *effect* and, hence, the *stimuli building rate*.

The *stimuli* stock when rises, tends to increase the frequency of the *fear inducing information (FII)* entering into the brain. This may be better understood by a real-life example. During the occurrence of stressful (traumatic) events (like panic attacks), the brain starts associating stress or danger with the things it encounters. If a panic attack occurs while the sufferer is in an elevator, the sufferer's brain would associate the elevator with danger and, hence, the elevator would be a new "stimulus". As and when the sufferer would see an elevator the next time, the brain would start relaying the fear inducing information to the amygdala which may start initiating the whole stress response reaction resulting in a panic attack. In the model, this mechanism is implemented by associating the frequency of the pulse train functions (of the variables: *Relaying of FII by thalamus to PFC* and *relaying of FII by thalamus to amygdala*) with the *stimuli* stock in a way that the more the number of stimuli in the *stimuli* stock, the more the frequency of the pulse train functions representing the *FII*. For the full model equations, see Appendix C.6.

Now, the model will be simulated over a period of 20,000 seconds so that the behaviour of the key variables of this section may be manifested. The parameters used are as follows:

Efficiency of alpha-2 receptor = 100 (Highest, , i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.24 shows the behaviour of *relaying of FII by thalamus to amygdala*[36]. Several spikes, over time, are a result of increasing number of stimuli (in the *stimuli* stock) which tend to increase the frequency of FII. Each of these spikes will, eventually, cause a panic attack in the *average heart rate* stock (See Fig. 5.25) after stimulating the whole fear emotion circuitry.

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36 The behaviour of *relaying of FII by thalamus to PFC* will also be the same as shown in Fig. 5.24 except that each spike will occur in it with a 2 second delay (as compared to Fig. 5.24).
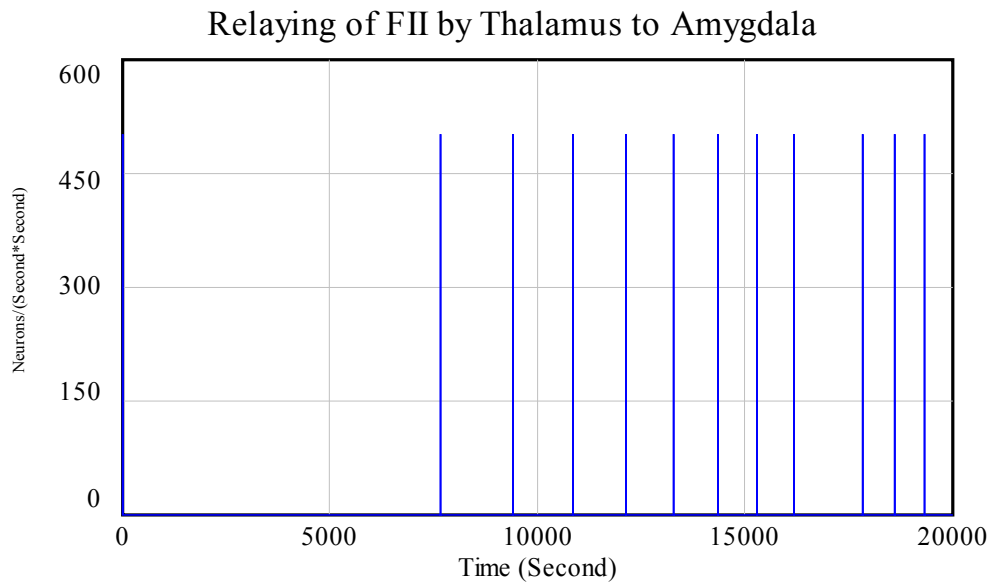
Relaying of FII by Thalamus to Amygdala

Fig. 5.24: Behaviour of *Relaying of FII by Thalamus to Amygdala* – Each Spike Represents an Episode of Fear Inducing Information
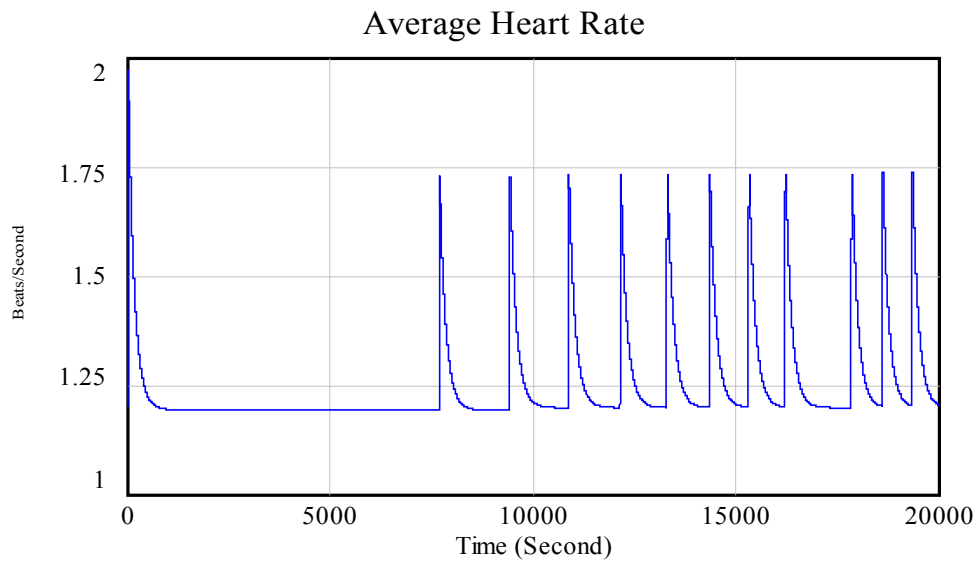
Average Heart Rate

Fig. 5.25: Behaviour of the *Average Heart Rate* Stock – Each Spike Represents a Panic Attack

Fig. 5.26 shows the behaviour of the *stressful events* stock which is directly effected by the *average heart rate* stock. It grows bigger and bigger with each panic attack in the *average heart rate* stock.
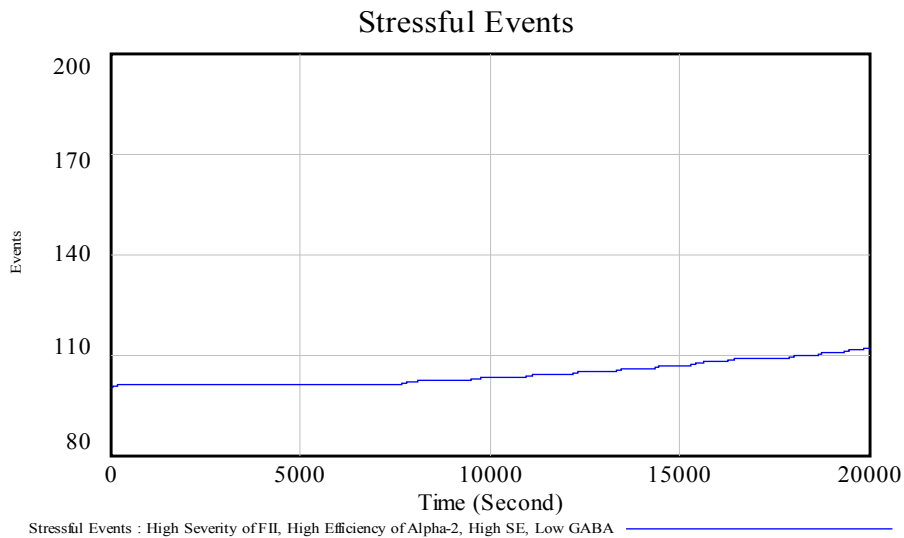
Fig. 5.26: Behaviour of the *Stressful Events* Stock – the Stock is Positively Growing with Each Panic Attack

The s*tressful events* stock directly effects the *stimuli* stock which grows higher and higher as the stressful events increase (See Fig. 5.27). The increase in the number of stimuli result in increasing the frequency of FII (See Fig. 5.22) and, consequently, the occurrence of panic attacks within the *average heart rate* stock (See Fig. 5.23).
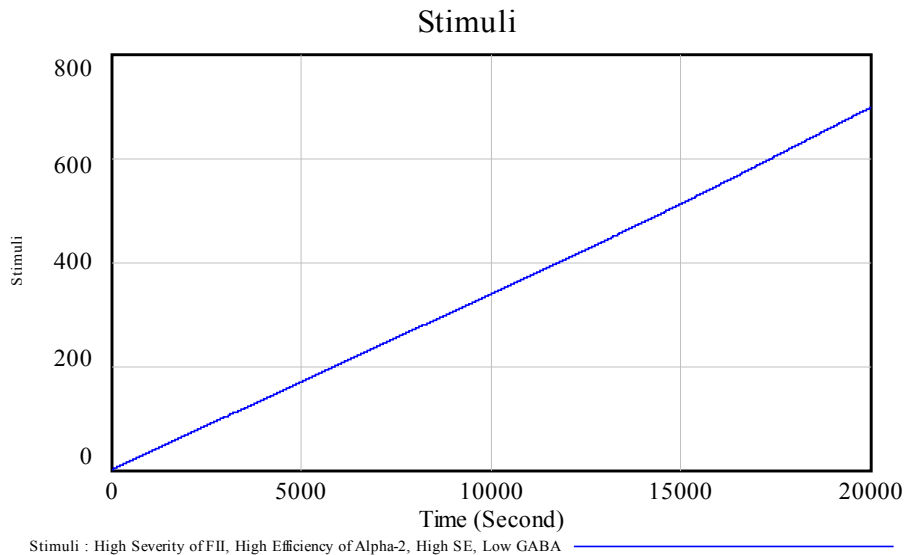
Fig. 5.27: Behaviour of the *Stimuli* Stock – the Stock is Positively Growing with the Increase in the *Stressful Events*

5.7 Modelling the Cognitive Error and Kindling:

The next CLDs to be translated are reproduced in Fig. 4.8a and 4.7b below:
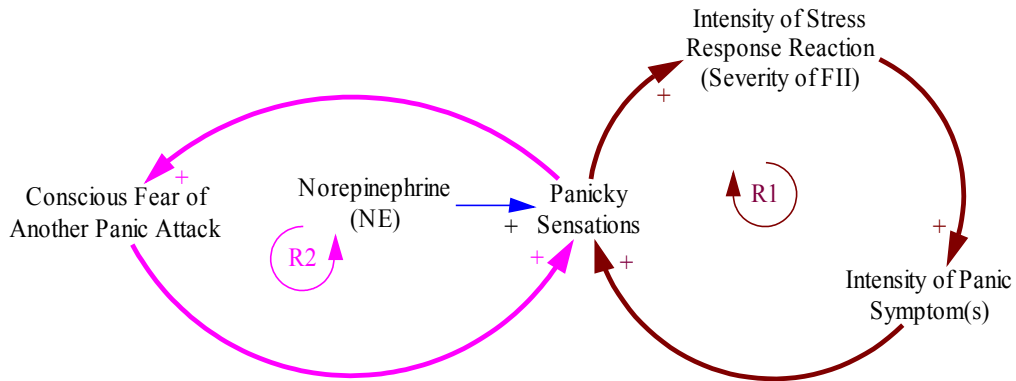
Fig. 4.8a (Reproduced): A CLD of the Cognitive Error and Kindling Feedback Mechanism
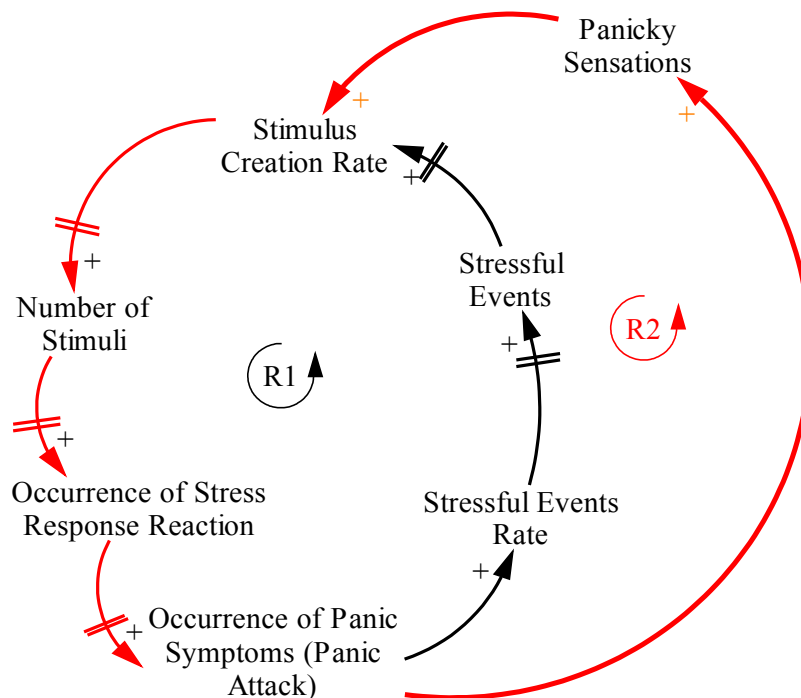
Fig. 4.7b (Reproduced): A Simplified CLD Highlighting the Role of *Panicky Sensations* in the Stress and Stimuli Feedback Relationship

The *panicky sensations* effect the stress response reaction in two ways. One is highlighted in Fig. 4.8a, whereas, the other in Fig. 4.7b. As it is intended to keep the stock and flow model as simple as possible, therefore, only the latter effect (shown in Fig. 4.7b, see Loop 'R2') of the *panicky sensations* would be modelled in this study, whereas, the former effect (shown in Fig. 4.8a, see Loop 'R1') would be left for the future studies.

The *panicky sensations* variable gives a feel of a stock as it creates delays in responding to the information that flows into it and generates the information on which the actions of the other variables are based (See Sterman 2000, 192). The *conscious fear of another panic attack* (See Fig. 4.8a, Loop 'R2') also gives a "stock feeling" as it tends to maintain its current level if the stress response scene is frozen with a snapshot (See Sterman 2000, 199). Both of these variables (the *panicky sensations* and *conscious fear of another panic attack*) are inter-dependent, as apparent from Fig. 4.8a, which means that they would effect each other's flows. In addition, the *panicky sensations* would also be effected by *norepinephrine (NE)*. As per Fig. 4.7b, the *panicky sensations* effect the *stimuli* stock and are effected back by the *panic symptoms*, i.e., the *average heart rate*. Fig. 5.28 (Pg. 124) includes the *panicky sensations* and *conscious fear of another panic attack* as "average of" stocks in the model and highlights their role in the stress response system responsible for Panic Disorder (PD). Both of these stocks are measured in "sensations/second".

Fig. 5.28 (Pg. 124): The Stock and Flow Model Highlighting the Role of *Panicky Sensations* and *Conscious Fear of Another Panic Attack* in the Stress Response System

In the above model (shown in Fig. 5.28), the *average panicky sensations* stock adjusts to the effect of *NE*, *average heart rate* and *average fear of another panic attack* stocks on it. All these "effects" are implemented with the help of table functions which depict the relation that the more the input (*NE*, *average heart rate* and *average fear of another panic attack*), the more the output (the *effect of NE*, *average heart rate* and *average fear of another panic attack*).
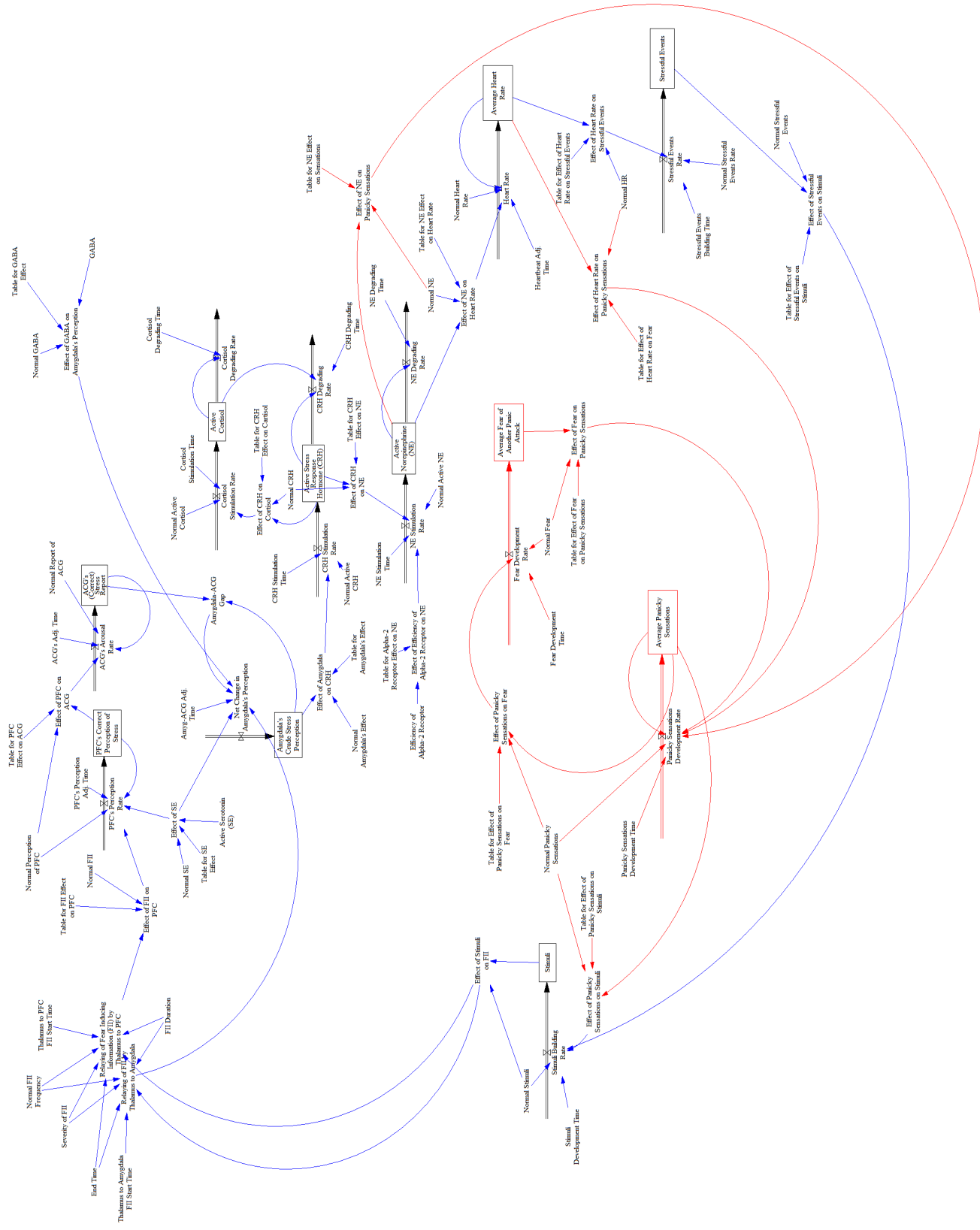
The *average panicky sensations* stock effects the *average fear of another panic attack* stock with an almost s-shaped table function and the latter develops more and more with time as and when the *average panicky sensations* stock rises (courtesy the rise in the *NE* and *average heart rate* stocks) on the activation of the stress response reaction. There is no outflow to the *average fear of another panic attack* stock as nothing flows out of it during the whole simulation time period of the model. The fear of having another panic attack, once developed, takes a lot of time and effort to ward off.

The *average panicky sensations* stock, along with the *stressful events* stock, plays a very important role in PD (repeated panic attacks with increasing frequency) by positively effecting the *stimuli building rate*. The effect of *panicky sensations on stimuli* is implemented with the help of a table function which sends one stimulus to the *stimuli* stock whenever the *panicky sensations* stock has a value more than or equal to 100 sensations/second. There is no information in the literature about how many stimuli are formed per minute as a result of rise in the *panicky sensations*, therefore, the relation is implemented on the "best guess" basis. Nonetheless, it should be noted that the very relation – the more the *average panicky sensations*, the more the *stimuli* – would remain the same even if the precise values are somewhat changed. For the complete model equations, see Appendix C.7.

Now, the model will be simulated over a period of 20,000 seconds so that the behaviour of the key variables of this section may be manifested. The parameters used for the simulation are as follows:

Efficiency of alpha-2 receptor = 100 (Highest, , i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 120 (Low, i.e., abnormal)

After being effected by the *NE, average heart rate* and *average fear of another panic attack* stocks, the behaviour of the *average panicky sensations* stock will be as shown in Fig. 5.29.

Average Panicky Sensations
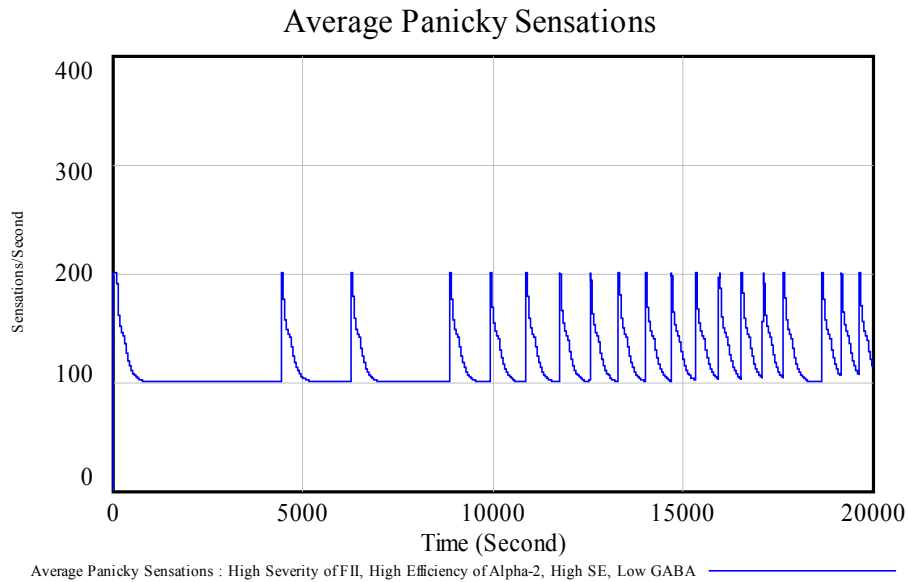
Fig. 5.29: Behaviour of the *Average Panicky Sensations* Stock – Each Spike Shows the Panicky Sensations During a Panic Attack

The *panicky sensations* will rise and fall following the rise and fall of the *NE* and *average heart rate* stocks. The comparative behaviour of the *average panicky sensations* and *average heart rate* stocks is shown in Fig. 5.30.

Selected Variables
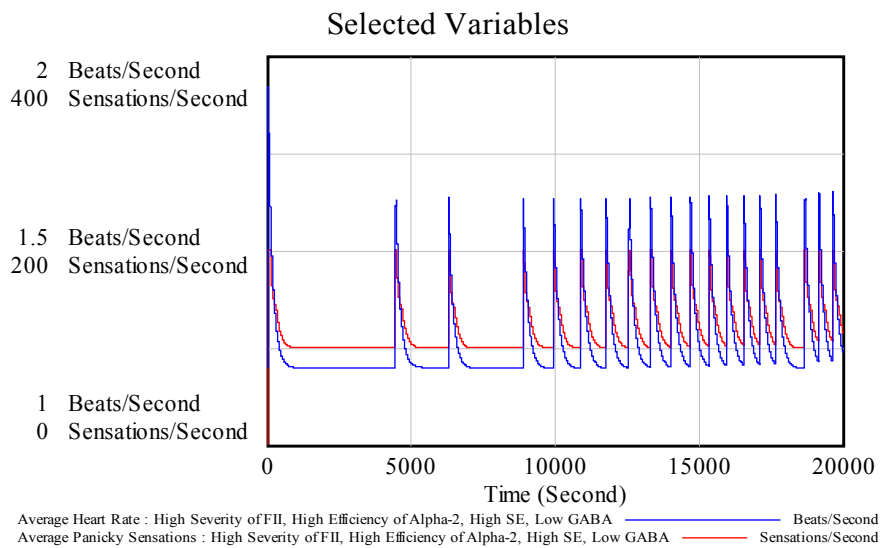
Fig. 5.30: Comparative Behaviour of the *Average Panicky Sensations* and *Average Heart Rate* Stocks

It is evident from Fig. 5.30 that the panicky sensations, in their rise and fall, are following

the panic attacks of the *average heart rate* stock. Whenever these panicky sensations will rise with the panic attacks, they will serve to increase the *stimuli* stock. With the increase in the *stimuli* stock, the frequency of panic attacks will increase as the very stock serves to increase the frequency of the *fear inducing information (FII)* (See Sec. 5.6). The *average panicky sensations* and *average fear of another panic attack* stocks reinforce each other. The behaviour of the latter stock after being reinforced by the spikes in the former is shown in Fig. 5.31.

Average Fear of Another Panic Attack

Average Fear of Another Panic Attack : High Severity of FII, High Efficiency of Alpha-2, High SE, Low GABA ——————
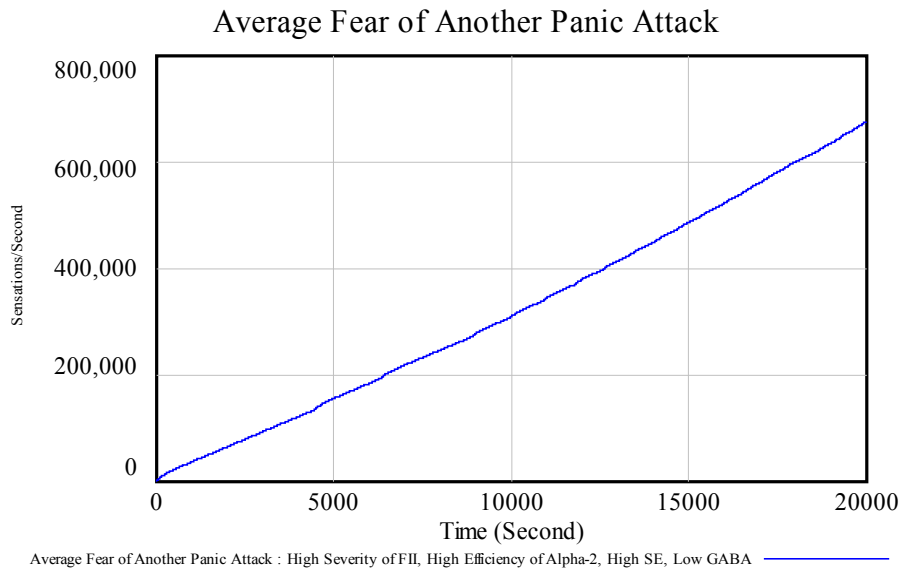
Fig. 5.31: Behaviour of the *Average Fear of Another Panic Attack* Stock

The effect of this reinforcing mechanism in the *average panicky sensations* stock may be highlighted by cutting the fear/sensations loop, i.e., eliminating the effect of *average fear of another panic attack* on the *average panicky sensations*[37]. The resultant behaviour is compared with the normal behaviour in Fig. 5.30.

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37 In the present case, the fear/sensations loop is cut by multiplying the *effect of fear on panicky sensations* by '0' in the *panicky sensations development rate's* equation.
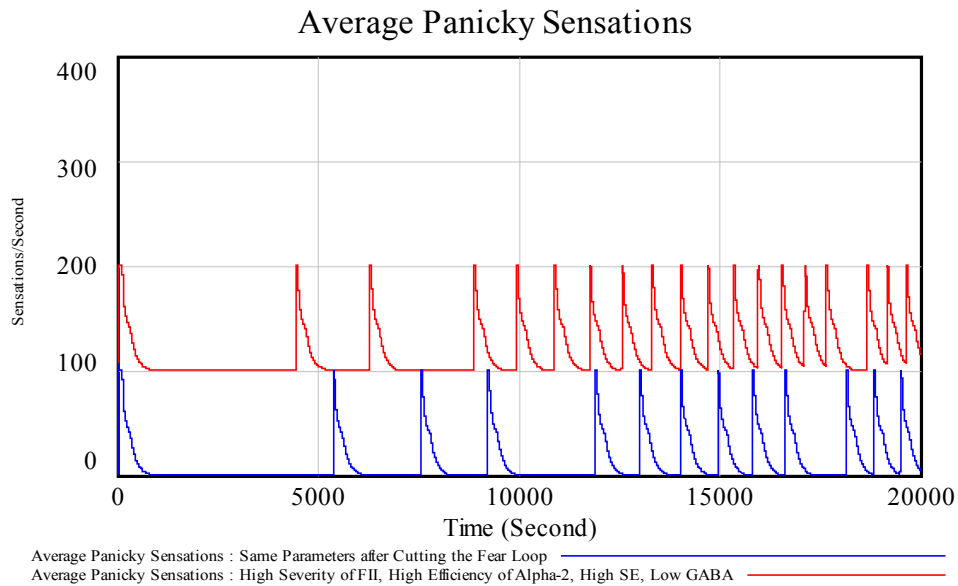
Fig. 5.32: Behaviour of the *Average Panicky Sensations* Stock with and without the Effect of the *Average Fear of Another Panic Attack*

As evident from Fig. 5.30, the rising *fear of another panic attack* will keep the *average panicky sensations* on a constantly high level.

5.8 Simulating the Model:

In this section, the following important scenarios will be simulated to reveal the behaviour of the model:

- High *Efficiency of Alpha-2 Receptor Site*, High *Severity of FII*:

    (1) Low *SE*, High *GABA*

    (2) Low *SE*, Low *GABA*

    (3) High *SE*, Low *GABA*

    (4) High *SE*, High *GABA*

- Low *Efficiency of Alpha-2 Receptor Site*, High *Severity of FII*:

    (5) Low *SE*, High *GABA*

    (6) Low *SE*, Low *GABA*

(7) High *SE*, Low *GABA*

(8) High *SE*, High *GABA*

- High *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, High *SE*, High *GABA*:

    (9) Over-reactive Stress Response System

- Low *Severity of FII*:

    (10) High *Efficiency of Alpha-2 Receptor*, High *SE*, High *GABA*

    (11) High *Efficiency of Alpha-2* Receptor, Low *SE*, Low *GABA*

    (12) Low *Efficiency of Alpha-2 Receptor*, Low *SE*, Low *GABA*

For each of the scenarios mentioned above, the behaviour of the *average heart rate* stock will be shown, for over a period of 20,000 seconds, as the very stock is the indicator if there is a panic attack, panic disorder (PD) or nothing of these two. Note that the time line, i.e., 20,000 seconds or 5.5 hours should not be seen "critically". Simulating the model over 2 or 3 days is time consuming and it would show the same behaviour, over time, as shown in the forthcoming *heart rate* graphs. Therefore, an attempt is made to condense this behaviour within 20,000 seconds to save simulation time and it should be seen accordingly. If PD is left untreated, the panic attacks may become chronic and last for years (Rachman and De Silva 2004, 27). However, with the help of the most common of the treatment methods, i.e., medication and psychotherapy, these attacks can easily be stopped. These treatment methods work to:

- Restore the depleted GABA and SE levels in the brain.

- Help the patient get rid of the cognitive error and fear of another panic attack.

- Resolve the known stimuli (if any) which trigger panic attacks.

- Relax the patient. (Wehrenberg and Prinz 2007, 78, 79; Berman 2005, 51-8)

5.8.1 High *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, Low *SE*, High *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 100 (Highest, i.e., normal)

Severity of FII = 500 (Highest)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 500 (Highest, i.e., normal)

Fig. 5.33 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour of the model is in harmony with the literature which hypothesises the low *SE* levels to be a cause of PD.

Average Heart Rate

Average Heart Rate : Low SE, High GABA

Fig. 5.33: Behaviour of the *Average Heart Rate* Stock Whilst Low *SE* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.2 High *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, Low *SE*, Low *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 100 (Highest, , i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.34 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of

PD. The behaviour of the model is in harmony with the literature which hypothesises the low *SE* and GABA levels to be one of the causes of PD. If Figs. 5.33 and 5.34 are compared, the spikes of the latter figure are bigger than that of the former indicating that PD is severe in the case when both *SE* and *GABA* are on the lower side.

Average Heart Rate

Average Heart Rate : Low SE, Low GABA

Fig. 5.34: Behaviour of the *Average Heart Rate* Stock Whilst Low *SE* and Low *GABA* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.3 High *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, High *SE*, Low *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 100 (Highest, i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.35 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour of the model is in harmony with the literature which hypothesises the low *GABA* levels to be one of the causes of PD. If Figs. 5.34 (representing PD whilst low GABA and low SE) and 5.35 are compared, the spikes of the latter figure are smaller in magnitude than that of the former indicating that PD is less severe in the present case when only *GABA* is on the lower side. It is worth noticing here that it is not a good idea to

compare Fig. 5.35 with Fig. 5.33 (representing low SE) as the literature does not suggest anything about the comparative severity of panic attacks whilst low SE and low GABA. The model is showing severer PD in Fig. 5.35 (as compared to Fig. 5.33) which is a mere assumption and should be seen accordingly.

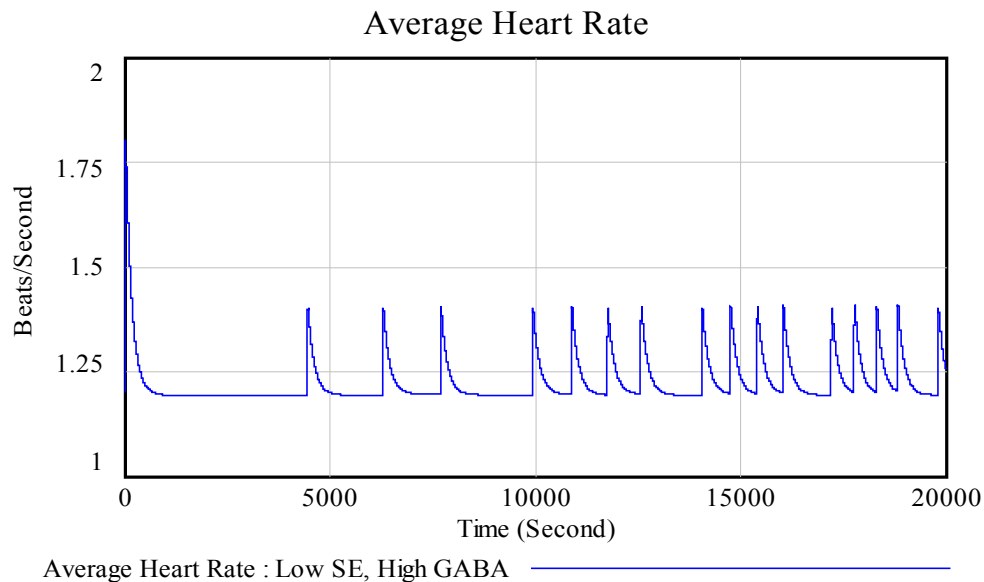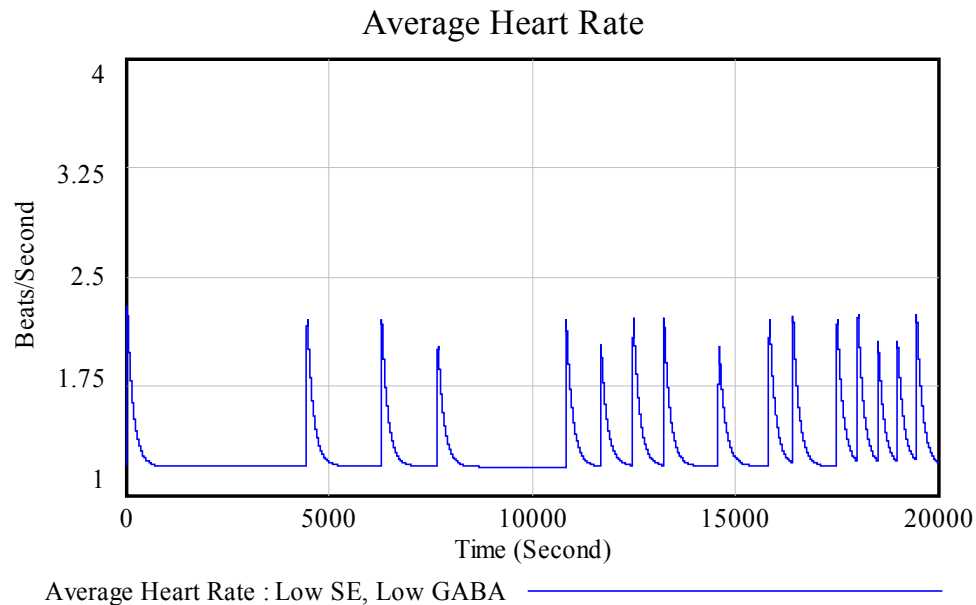Average Heart Rate : High SE, Low GABA ————————
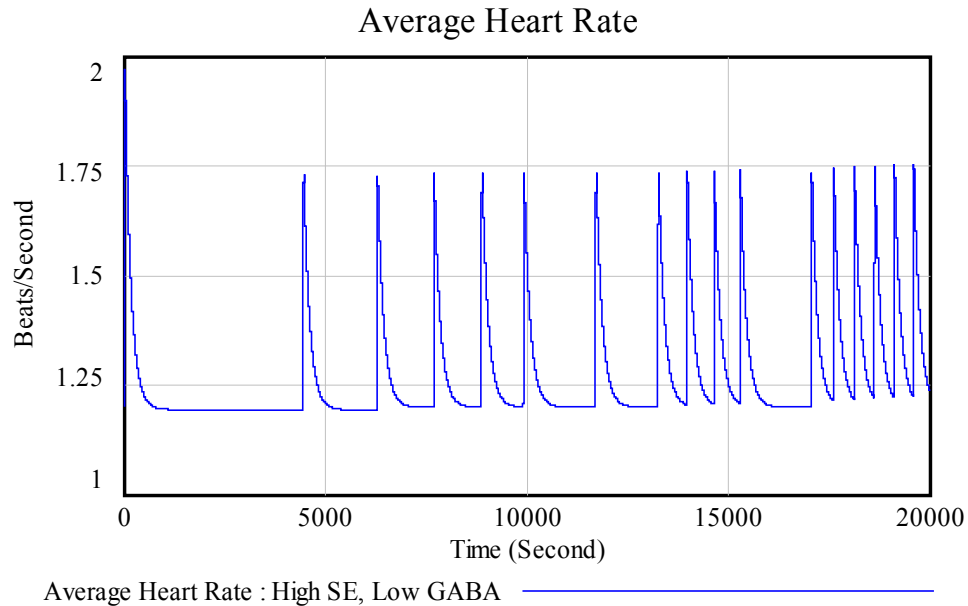
Fig. 5.35: Behaviour of the Average Heart Rate Stock Whilst Low *GABA* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.4 High *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, High *SE*, High *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 100 (Highest, i.e., normal))
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 500 (Highest, i.e., normal)

Fig. 5.36 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Only one small spike in the graph indicates that only one mild panic attack occurred and it did not turn into PD i.e., a number of spikes with an increasing frequency. The behaviour of the model is in harmony with the literature which suggests that there should be no PD when GABA and SE are working properly in the brain whilst there is no access NE due to low alpha-2 efficiency.

Average Heart Rate

Average Heart Rate : High SE, High GABA ─────────────
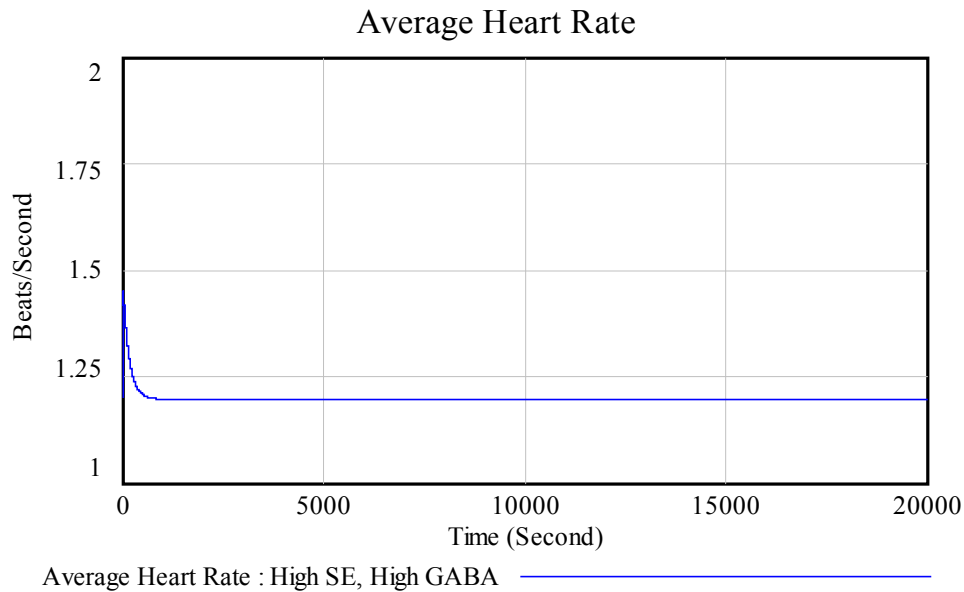
Fig. 5.36: Behaviour of the *Average Heart Rate* Stock Whilst High *SE* and High *GABA* Indicating the Presence of a Panic Attack (A Single Spike) but No PD (A Number of Spikes with an Increasing Frequency)

5.8.5 Low *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, Low *SE*, High *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 10 (Low, i.e., abnormal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 500 (Highest, i.e., normal)

Fig. 5.37 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour of the model is in harmony with the literature which hypothesises the low *SE* levels and low *efficiency of alpha-2 receptor* (resulting in an excess release of *NE*) to be a cause of PD. It is also noteworthy that when both *SE* and the *efficiency of alpha-2 receptor* are on the lower side, the panic spikes are bigger in magnitude as compared to the spikes the model manifested when *SE* alone was on the lower side (Compare Figs. 5.33 and 5.37).

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Average Heart Rate

Average Heart Rate : Low Efficiency of Alpha-2 Receptor, High Severity of FII, Low SE, High GABA ———

Fig. 5.37: Behaviour of the *Average Heart Rate* Stock Whilst Low *Efficiency of Alpha-2* and Low *SE* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

Fig. 5.38 compares the behaviour of *NE* stock in the first (high *efficiency of alpha-2 receptor*) and the present scenario (low *efficiency of alpha-2 receptor*). When the *efficiency of alpha-2 receptor* is low, there is an excess release of *NE* which results in bigger panic spikes as shown in Fig. 5.37.

Active Norepinephrine (NE)

"Active Norepinephrine (NE)" : High Efficiency of Alpha-2 Receptor, High Severity of FII, Low SE, High GABA ———
"Active Norepinephrine (NE)" : Low Efficiency of Alpha-2 Receptor, High Severity of FII, Low SE, High GABA ———
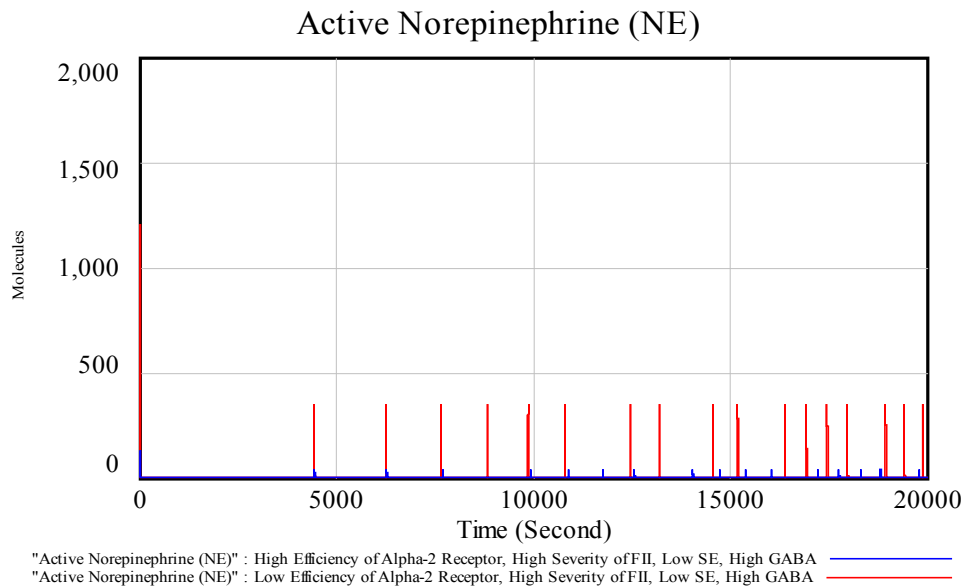
Fig. 5.38: Comparative Behaviour of the *NE* Stock Whilst High and Low *Efficiency of Alpha-2 Receptor*

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5.8.6 Low *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, Low *SE*, Low *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 10 (Low, i.e., abnormal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.39 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour of the model is in harmony with the literature which hypothesises the low *SE*, low *GABA* and low *efficiency of alpha-2 receptor site* to be the contributing factors to the etiology of PD. Note that as there are more contributing factors, the spikes (panic attacks) on the graph are bigger in comparison with the previous scenarios.

Average Heart Rate : Low Efficiency of Alpha-2 Receptor, High Severity of FII, Low SE, Low GABA ⎯⎯⎯⎯

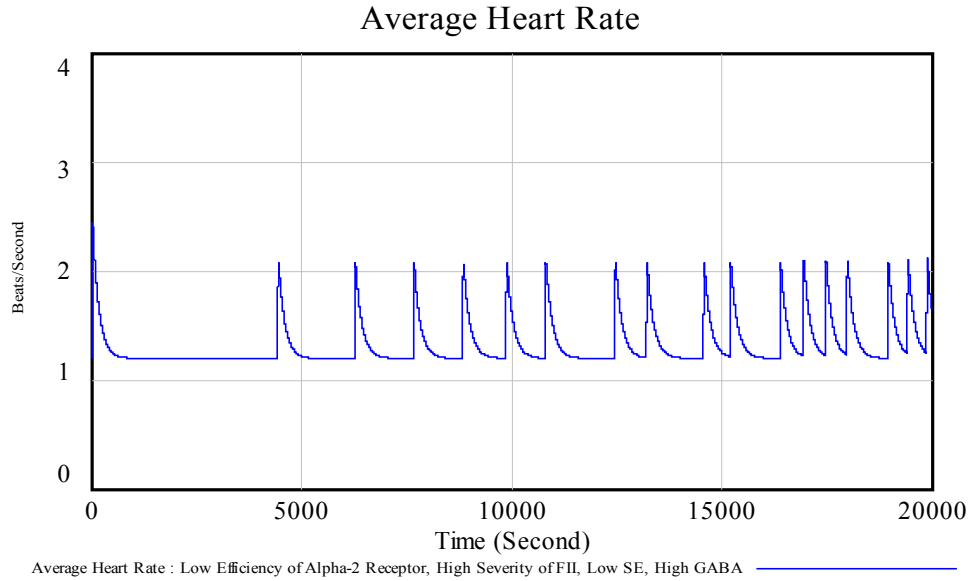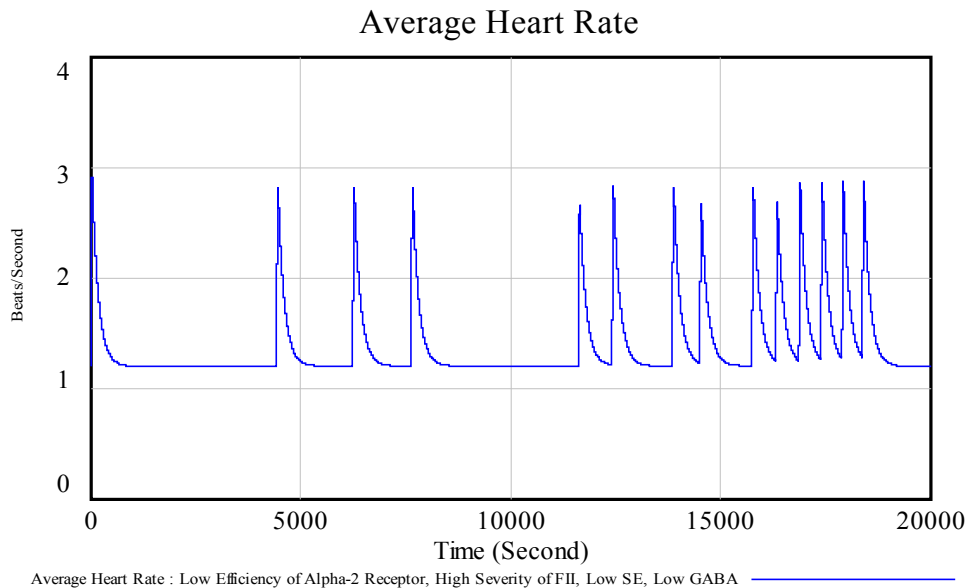Fig. 5.39: Behaviour of the *Average Heart Rate* Stock Whilst Low *SE* and Low *GABA* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.7 Low *Efficiency of Alpha-2 Receptor*, High *Severity of FII*, High *SE*, Low *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 10 (Low, i.e., abnormal)

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Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.40 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour of the model is in harmony with the literature which hypothesises the low *GABA levels* and low *efficiency of alpha-2 receptor* to be one of the various scenarios supportive to the development of PD. As compared to Fig. 5.39 of the previous scenario (5.8.6), the spikes of Fig. 5.40 are smaller which indicates that when there is one less contributing factor, i.e., normal SE, the panic attacks are less severe.

Average Heart Rate

Average Heart Rate : Low Efficiency of Alpha-2 Receptor, High Severity of FII, High SE, Low GABA
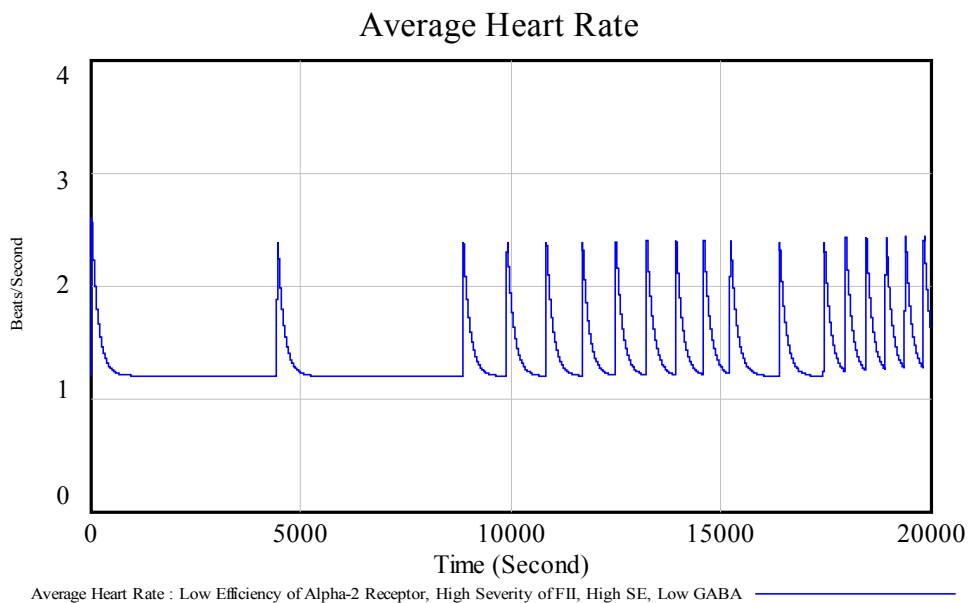
Fig. 5.40: Behaviour of the *Average Heart Rate* Stock Whilst Low *Efficiency of Alpha-2 Receptor Site* and Low *GABA* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.8 Low *Efficiency of Alpha-2 Receptor,* High *Severity of FII*, High *SE*, High *GABA*:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 10 (Low, i.e., abnormal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 500 (Highest, i.e., normal)

Fig. 5.41 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Only one spike in the graph indicates that only one panic attack occurred and it did not turn into PD i.e., a number of spikes with increasing frequency. When both *GABA* and *SE* are high, they would chop off the intensity of the *FII* in the *amygdala* and would not allow it to cross the threshold value necessary to stimulate the stress response reaction (through the *stress response hormone - CRH*). This is an interesting observation which should stimulate a debate whether there should be PD solely on the basis of low *efficiency of alpha-2 receptor* whilst *GABA* and *SE* are working properly in the brain!

Average Heart Rate

Average Heart Rate : Low Efficiency of Alpha-2 Receptor, High Severity of FII, High SE, High GABA
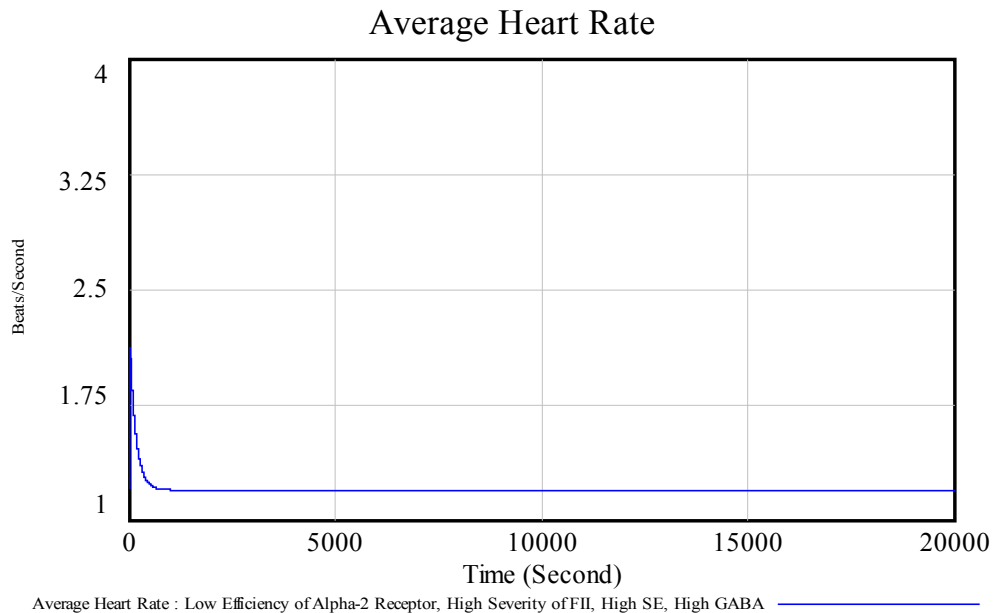
Fig. 5.41: Behaviour of the *Average Heart Rate* Stock Whilst Low *Efficiency of Alph-2 Receptor*, High *SE* and High *GABA* Indicating the Presence of a Panic Attack (A Single Spike) but No PD (A Number of Spikes with the Increasing Frequency)

5.8.9 High *Efficiency of Alpha-2 Receptor,* High *Severity of FII*, High *SE*, High *GABA,* Over-reactive Stress Response System:

In this section, the model is simulated with the following parameters:

Efficiency of alpha-2 receptor = 100 (High, i.e., normal)
Severity of FII = 500 (Highest)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 500 (Highest, i.e., normal)
Table for Amygdala's Effect (on CRH) = As shown in Fig. 5.17 (Represents the over-reactive stress response system)

Fig. 5.42 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Each spike in the graph is an indicator of a panic attack and the several spikes increasing in frequency, over time, indicate the presence of PD. The behaviour is in harmony with the literature which hypothesises the inborn over-reactive stress response system to be one of the contributing factors to PD.
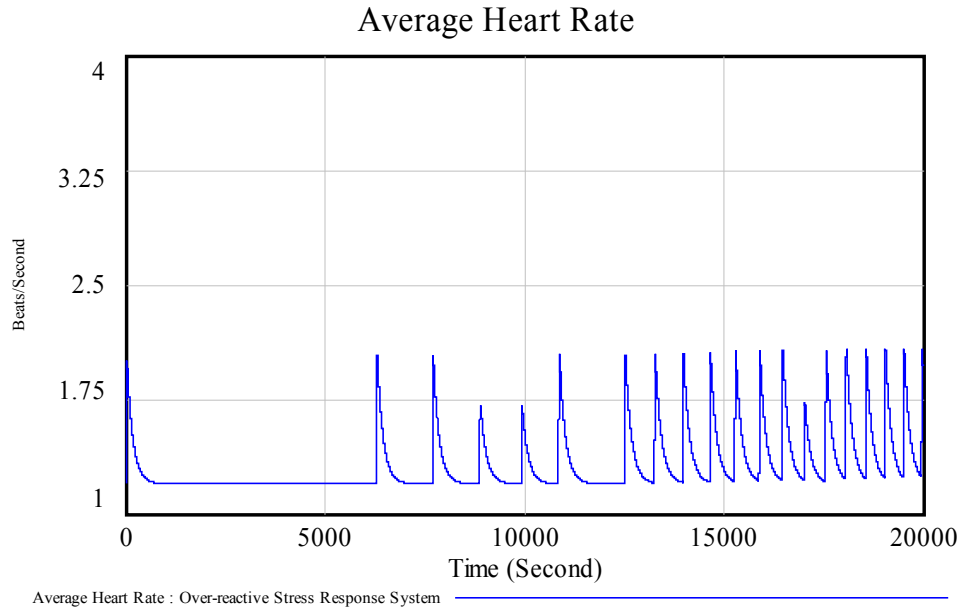
Fig. 5.42: Behaviour of the *Average Heart Rate* Stock Whilst the *Over-reactive Stress Response System* Indicating the Presence of PD (A Number of Spikes with the Increasing Frequency)

5.8.10 Low *Severity of FII*, High *Efficiency of Alpha-2 Receptor,* High *SE*, High *GABA*:

In this section, the model is simulated with the following parameters:

Severity of FII = 100 (Low)
Efficiency of alpha-2 receptor = 100 (High, i.e., normal)
Serotonin (SE) = 100 (Highest, i.e., normal)
GABA = 500 (Highest, i.e., normal)

Fig. 5.43 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. The straight horizontal line in the graph shows that neither any panic attack occurred nor it turned into PD. The behaviour makes sense as there should be no panic attack whilst the *severity of FII* is low. More so, the *efficiency of alpha-2 receptors* is high (i.e., normal) and *GABA* and *SE* systems are working properly in the brain which would further weaken the chances of PD.

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Average Heart Rate

Average Heart Rate : Low Severity of FII (Fear Inducing Information), High Efficiency of Alpha-2 Receptor, High SE, High GABA ·

Fig. 5.43: Behaviour of the *Average Heart Rate* Stock Whilst Low *Severity of FII*, High *Efficiency of Alph-2 Receptor*, High *SE* and High *GABA* Indicating that no Panic Attack Occurred

5.8.11 Low *Severity of FII*, High *Efficiency of Alpha-2 Receptor*, Low *SE*, Low *GABA*:

In this section, the model is simulated with the following parameters:

Severity of FII = 100 (Low)
Efficiency of alpha-2 receptor = 100 (High, i.e., normal)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.44 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Only one small spike in the graph indicates that only one mild panic attack occurred and it did not turn into PD. This behaviour is quite reasonable as the low *severity of FII* though succeeded to generate a mild panic attack, in the absence of sufficient *SE* and *GABA* levels, but was just not enough to induce more panic attacks which could give rise to PD. Note that, in this scenario, it would not have been unreasonable either had the model shown the presence of PD as it is also reasonable to think that, in spite of *low severity of FII*, a panic attack may turn into PD while there is an *SE* and *GABA* dysfunction. Therefore, the behaviour, Fig. 5.44 shows, is expected to stimulate further research on whether PD can take place in the present scenario.

Average Heart Rate

Average Heart Rate : Low Severity of FII, High Efficiency of Alpha-2 Receptor, Low SE, Low GABA

Fig. 5.44: Behaviour of the *Average Heart Rate* Stock Whilst Low *Severity of FII*, High *Efficiency of Alph-2 Receptor*, Low *SE* and Low *GABA* Indicating the Presence of a Mild Panic Attack

5.8.12 Low *Severity of FII*, Low *Efficiency of Alpha-2 Receptor,* Low *SE*, Low *GABA*:

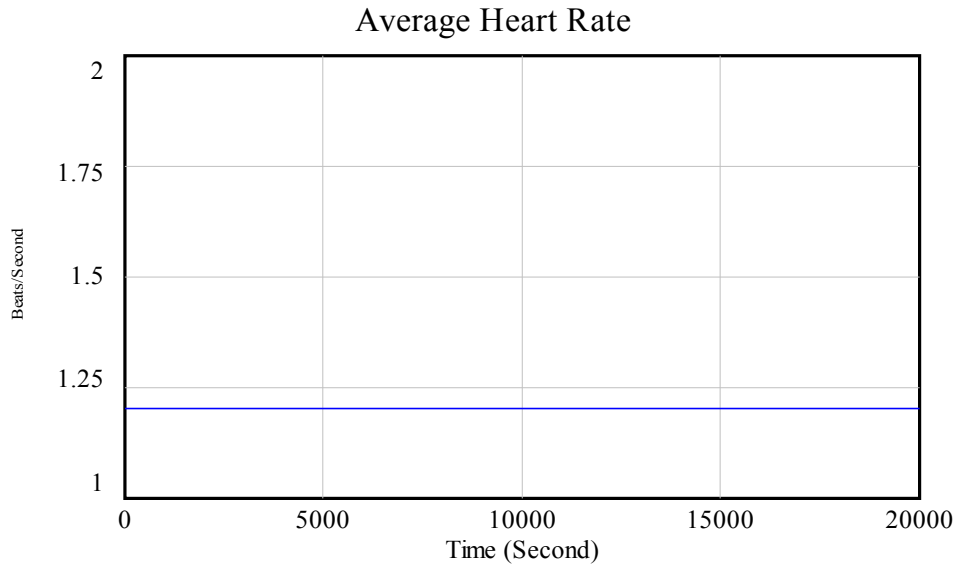In this section, the model is simulated with the following parameters:

Severity of FII = 100 (Low)
Efficiency of alpha-2 receptor = 10 (Low, i.e., abnormal)
Serotonin (SE) = 10 (Low, i.e., abnormal)
GABA = 100 (Low, i.e., abnormal)

Fig. 5.45 shows the behaviour of the *average heart rate* stock when the model is simulated as per the above parameters. Only one spike in the graph indicates that only one panic attack occurred and it did not turn into PD. Like the behaviour the model exhibited in the last scenario, this behaviour is quite reasonable as well but there should be more research on whether a *low-in-severity FII* can cause PD when either one or all of the following are on the lower side: *Efficiency of alpha-2 receptor, SE* and *GABA*.

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Average Heart Rate

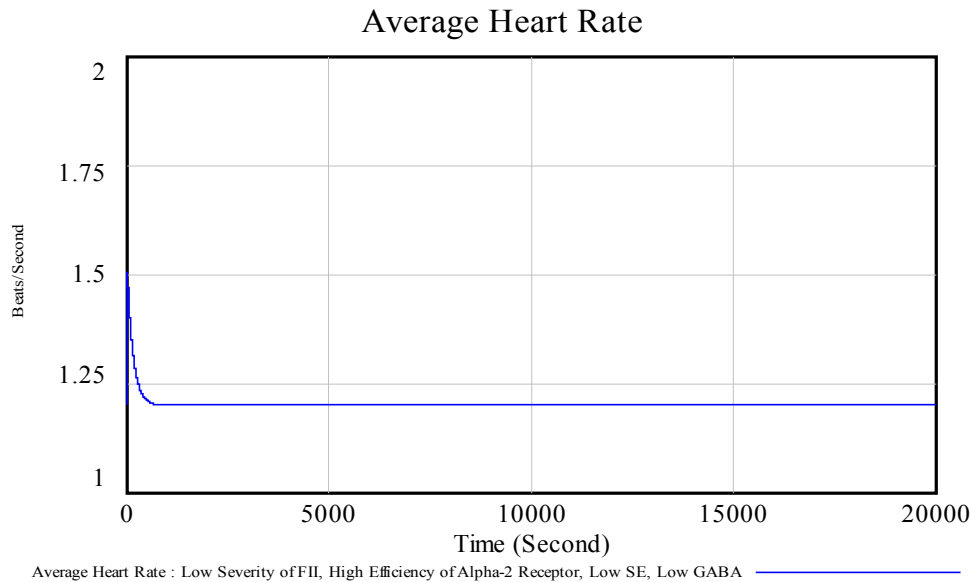Average Heart Rate : Low Severity of FII, Low Efficiency of Alpha-2 Receptor, Low SE, Low GABA ———————
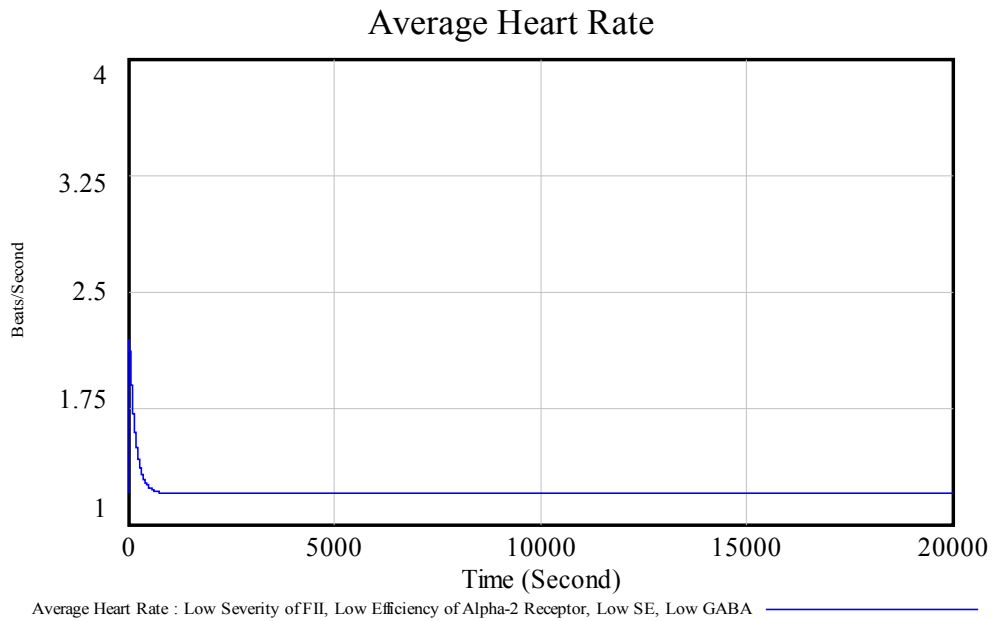
Fig. 5.45: Behaviour of the *Average Heart Rate* Stock Whilst Low *Severity of FII*, Low *Efficiency of Alph-2 Receptor*, Low *SE* and Low *GABA* Indicating the Presence of a Single Panic Attack

6. Conclusion, Recommendations and Future Directions

In this section, the end result of the present research, its limitations and future research directions are discussed.

6.1 Pros and Cons of the Contemporary PD Conceptualizations:

The stock and flow model replicates the reference mode shown in Fig. 1.2 (reproduced below for the reader's ease) in the scenarios that are hypothesised in the literature to cause Panic Disorder (PD). In addition, it is able to produce the panic episodes with the increasing frequency which is an important observation in PD. (See Sec. 5.7) This provides confidence in the PD theories for the structure they propose is quite capable of producing the problematic behaviour.

Fig. 1.2 (Reproduced): A Self-Drawn Reference Mode Showing Panic Attacks over Time Using the *Average Heart Rate* Symptom

One of the negative aspects of the PD conceptualizations is that they lack fine details, for instance, how neurochemicals precisely effect one another, in how much excess NE produces in response to various low efficiency levels of alpha-2 receptor sites, how much time the amygdala takes to arouse, how much time the PFC takes to process the incoming

fear inducing information etc. Perhaps, new research in abnormal psychology and related fields would help fill these gaps.

The stock and flow model highlights a serious problem in case when SE is impaired in the brain and cannot keep a check on the NE levels. The explanation of how the brain manages to normalize the "NE boosts"[38] in such a case could not be found in the PD theories (See Sec. 5.2 for the detailed problem discussion). This information needs to be explicitly documented in the PD theories.

The psychological aspect of PD seems somewhat unclear in the literature. For example, the theories seem vague about the sequence of events in the circular process of cognitive error and kindling.

6.2 Usefulness of the Present Study:

The present study is expected to be useful in the following ways:

- It makes explicit the dynamics processes implicit in the narrative presentations of the PD theories, especially through the causal loop diagrams (CLDs), which makes it easy to visualize and understand them.

- The CLDs and stock and flow model provide a common language for the researchers of different fields to further understand and critically examine the biological, psychological and cognitive aspects of PD.

- The stock and flow model highlights some important "grey areas" (where it is not clear whether PD should take place) and incites the researchers to investigate them (for example see the discussion on the scenarios simulated in Secs. 5.7.11 and 5.7.12).

- The stock and flow model highlights lack of information in the PD theories, most notable of which is: What keeps the NE levels from rising infinitely in the absence of NE/SE feedback mechanism? (See Sec. 5.2) This provides a critical feedback to the PD theorists.

- The stock and flow model may be used for educational purposes in the abnormal psychology and related fields for it is kept as simple and as moderate in size as possible. The CLDs and sub-system diagram developed in Sec. 4 may also prove effective for educational purposes.

- Psychoeducation about how panic is generated and why the physical methods work to stop panic attacks is an important part of PD treatment (Wehrenberg and

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38 Sudden rise of NE levels due to any reason, such as, activation of stress response reaction.

Prinz 2007, 73). Therapists may use the CLDs, sub-system diagram and stock and flow model developed in this study to help their patients understand that PD is a biopsychosocial problem.

- Brain based models are uncommon in system dynamics (SD) although the structure of the brain is full of interesting feedback systems busy interacting with each other and causing a wide range of dynamics throughout the life span of an individual. The present effort helps highlighting this aspect of the brain and invites other researchers to apply SD on the brain based dynamics, e.g., to comprehensively study the serotonin dynamics which is hypothesised to be a root cause of many problems like obsessive compulsive disorder (OCD), depression, fibromyalgia, PD etc.

6.3 Research Limitations:

The present study has limitations in the stock and flow model which is kept as simple as possible and, hence, does not undertake all aspects of the contemporary Panic Disorder (PD) conceptualizations. The original causal loop diagrams (CLDs) extracted from the literature were simplified first and then translated into the stock and flow model. More so, the cognitive error and kindling process, though is fully represented through the CLDs, but is only partially translated into the stock and flow model.

6.4 Future Directions:

The opportunity to improve this research exists in the following areas:

- The stock and flow model may be extended by fully implementing the cognitive error and kindling process.

- The model may also be extended, improved and "fine-tuned" by translating the complete CLDs (presented in Sec. 4) into the model instead of the simplified ones. However, the usefulness of such an extension depends on the use of the model. Perhaps, it is a better idea to stick to the model developed in the present study or simplify it even further if the goal is to use it for educational purposes.

- The translation work may be extended to include the impact of different treatment methods in resolving PD. These methods include medication, psychotherapy, cognitive-behavioural therapy (CBT), energy therapies, eye movement desensitization and reprocessing (EMDR) etc. They help restoring the depleted Gamma Aminobutyric Acid (GABA) and serotonin (SE) levels in the brain and help the patient get rid of the cognitive error and fear of another panic attack.

- The translation work may also be extended to include the "agoraphobia" (See Sec.

1.4) aspect of PD.

Appendix A: Causal Links and Causal Loop Diagrams (CLDs)

Causal Links: Causal links are used to show cause and effect relationship between two variables. A line followed by an arrow head is drawn from one variable towards another, for example, C -----> E. In this case, the variable *C* represents the cause whereas *E*, towards which the arrow head is pointing to, represents the effect. The arrows heads in these links are either labelled as '+' (positive) or '–' (negative). Positive sign is used to represent such a cause and effect relationship between two variables in which they move in the same direction. For example, consider: A ----->+ B. This represents that, keeping all other variables of the system constant, an increase in *A* (cause) causes an increase in *B* (effect) *as compared to what the latter would otherwise have been.* It also represents that, keeping all other variables constant, a decrease in *A* causes a decrease in *B as compared to what the latter would otherwise have been*. Negative sign, on the other hand, is used to represent the cause and effect relationship in which the two variables move in the opposite direction. For example, consider: C ----->- D. This represents that, keeping all other variables constant, an increase in *C* causes a decrease in *D as compared to what the latter would otherwise have been.* It also represents that, keeping all other variables constant, a decrease in *C* causes an increase in *D as compared to what the latter would otherwise have been* (Ford 1999, 71; Sterman 2000, 139).

Causal Loop Diagrams (CLDs): CLDs are one of the diagramming tools in SD which represent the feedback structure(s) within a system (Sterman 2000, 137). The word causal refers to the cause and effect relationship between different variables of a system and loop refers to a closed chain of cause and effect (Ford 1999, 69).

See Fig. A.1, for example. The variables, Serotonin (*SE*) and Norepinephrine (*NE*), are connected by the causal links represented by two arrows; one with a positive (+) and the other with a negative (-) sign. It makes a *negative feedback loop* which is represented by a prominent 'B'[39] in the middle of Fig. A.1. A negative loop acts in opposition to a change and, hence, is self correcting. An increase (change) to the *NE* levels will cause an increase in the *SE* levels. Rising levels of *SE* will slow down the stimulation of *NE* and, hence, cause a decrease in the *NE* levels. The decreased *NE* levels will bring the *SE* levels back down. In the whole process, the *SE* levels first increased (due to an increase in the *NE* levels) but then this change was opposed and the *SE* levels were brought back down. (See Sterman 2000, 13.)

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39 Stands for "balancing" as the negative feedback loops tend to balance out or oppose the change.
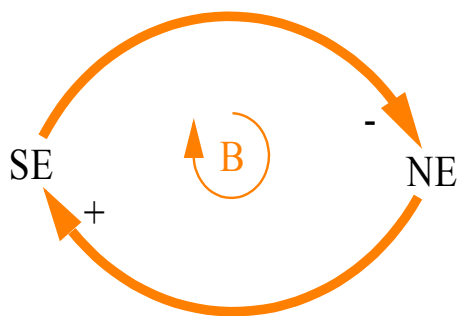
Fig. A.1: A Negative Feedback Structure in the Physiology of Panic Disorder (PD)

There is another kind of loop which is known as *positive feedback loop*. Such a loop tends to make a system grow bigger and bigger with time (Ford 1999, 72). For example, see Fig. A.2. The loop in this figure is represented by a prominent 'R'[40] in its centre which shows that the very loop is a positive one. What it implies is that the increase in the *Hypervigilance to Panicky Sensations* will cause an increase in the *Panicky Sensations* and vice versa. In this case, the *Panicky Sensations* increase (due to an increase in the *Hypervigilance to Panicky Sensations*) and then this change (the increase in the *Panicky Sensations*) is amplified or reinforced. The increase in the *Hypervigilance to Panicky Sensations* will make the *Panicky Sensations* grow higher and higher which, in return, will make the *Hypervigilance to Panicky Sensations* grow higher and higher and, consequently, the system will grow bigger and bigger with time (Sterman 2000, 13; Ford 1999, 72).
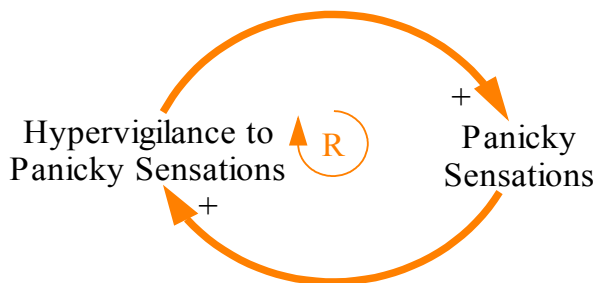
Fig. A.2: A Positive Feedback Structure in the Physiology of Panic Disorder (PD)

Another noteworthy thing regarding CLDs' notations is the delay mark. If, for example, the *hypervigilance to panicky sensations* would influence the *panicky sensations* (See Fig. A.2) with a delay, this delay would be represented by two parallel lines striking through the line connecting the two variables respectively (See Fig. A.2a).

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40 Stands for "reinforcing" as the positive feedback loops tend to reinforce a change.
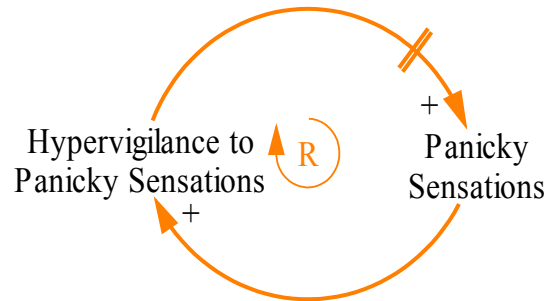
Fig. A.2a: A Positive Feedback Structure with a Delay Notation

All systems consist of the networks of positive and negative feedback loops and all dynamics – change, activity or progress – within the systems arise from either the interaction of these loops with one another (endogenously) (Sterman 2000, 13) or the external events effecting the systems from the outside world (exogenously). It is the former behaviour, i.e., endogenous, which we seek to understand through SD modelling by making explicit the feedback loops and their interactions within the systems. For further reading on causal loop diagrams, see Andrew Ford, *Modeling the Environment: An Introduction to System Dynamics Modeling of Environmental Systems* (Washington DC: Island Press, 1999), 69-87.

Appendix B: A Quick Introduction to Stocks and Flows

Stock and flow, along with feedback, is the key concept in dynamic systems. Causal loop diagrams (CLDs) well represent the feedback processes within systems, however, they lack in the ability to represent stocks and flows within systems (Sterman 2000, 191). To overcome this shortcoming, stock and flow diagrams are developed.

Perhaps, the famous "bathtub analogy" is the best to quickly grasp the concept of a stock and its flows. Water flows into a bathtub through a tap; it usually accumulates in there and flows out of it through a small drain. If it is desired to represent the water inflow, accumulation and outflow in terms of system dynamics (SD), the bathtub will be represented by a stock, the water flowing in (through the tap) by an inflow and the water flowing out (through the drain) by an outflow. The whole structure will look as shown in Fig. B.1.
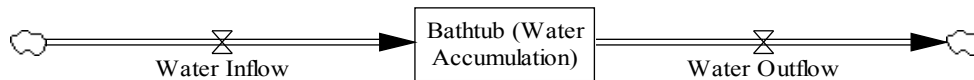
Fig. B.1: Bathtub Stock and Flow Structure

The bathtub is represented by a rectangle which, from its very appearance, highlights the concept of a stock, i.e., a container holding some information or material (water in the presented case). The *water inflow* is represented by a pipe pointing towards the *bathtub stock* which from its visual outlook gives an idea of something "adding to" the stock. The *water outflow* is represented by a pipe pointing out of the stock. This from its visual outlook highlights the notion of something "subtracting from" the stock. All stocks, inflows and outflows are normally represented in SD as shown in Fig B.1.

The quantity of water in the bathtub, at any time, is the water flowing in through the tap minus the water flowing out through the drain. Similarly, the quantity of material or information in any stock at any time is whatever is left in it after subtracting its outflow by its inflow. An important thing to note here is that a stock can only be "added to" and "subtracted from" by means of its inflow and outflow, respectively.

The reason why stock and flow is a key concept in dynamic systems is that all dynamic systems are basically made up of stocks and flows; however, it is not always as straightforward to recognize them as in the bathtub analogy. Some more examples of stocks, their inflows and outflows may respectively be:

- Bank Balance (Stock) , Deposits (Inflow), Withdrawals (Outflow)
- Inventory, Production, Shipments

- Workforce (Stock), Hiring (Inflow), Quitting (Outflow), Layoffs (Outflow), Retirements (Outflow) – like in this case, there may be more than one inflows or outflows into or out of a single stock.
- Population, Births, Deaths
- Bodily Needs, Arising, Satisfying
- Tension, Producing, Discharging
- Painkiller in Body (Stock), Drinking (Inflow), Eating (Inflow), Injecting (Inflow), Absorption in Body (Outflow), Discharging through Urine (Outflow), Discharging through Defecation (Outflow)

To simulate a stock and flow structure in any SD tool like Stella, Powersim or Vensim, simple algebraic equations are required which would represent the functioning of stocks and flows. In addition, some *auxiliary variables* are also required for clarity and ease of communication. These auxiliaries consist of functions of stocks and constants or exogenous inputs and are represented separately from the stock and flows (Sterman 2000, 202). To further illustrate it all with an example, the bathtub structure discussed above will be simulated here using Vensim.

Fig. B.1 shows a basic structure of a simple bathtub system without any algebra and auxiliary variables. First the auxiliary variables need to be added to this model. These include: *inflow time* and *tap strength* (to determine *water inflow*) and *drain strength* and *outflow time* (to determine *water outflow*). Fig. B.2 shows the modified structure with the auxiliary variables added. The algebraic equations for the *water inflow* and *water outflow* will further elaborate the function of these auxiliaries.
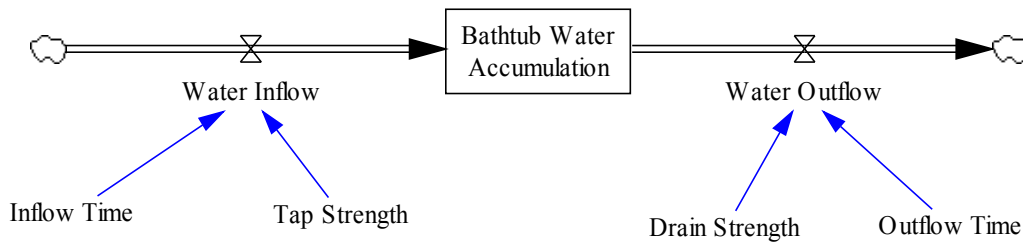
Fig. B.2 : Bathtub Stock and Flow Structure with Auxiliary Variables

Fig. B.3 shows the relevant equations (above all the variables) which are necessary to simulate the model. It also shows the unit of measures of each variable in a bracket following its name. The inflow(s) and outflow(s) of a stock are always measured in the same units as the stock's divided by time (Ford 1999, 14).

Inflow time has the equation: 1 second and *tap strength* has the equation: 1 dl. The arrow heads from these auxiliary variables to the *water inflow* show that they are being used to determine the *water inflow*. *Water inflow* has the equation: *tap strength / inflow time* or,

in other words, 1 dl / 1 second as *tap strength* is 1 dl and *inflow time* 1 second, respectively. According to this equation, the water flowing into the tub is 1 dl per second. Similarly, the auxiliaries *drain strength* and *outflow time* determine the *water outflow* (water flowing out of the tub) which has the equation: *drain strength / outflow time*. The stock *bathtub water accumulation* has the equation: *water inflow – water outflow* which shows that it accumulates the difference of inflow and outflow. The initial value of this stock is set to zero which means that it has no water in it to start with.
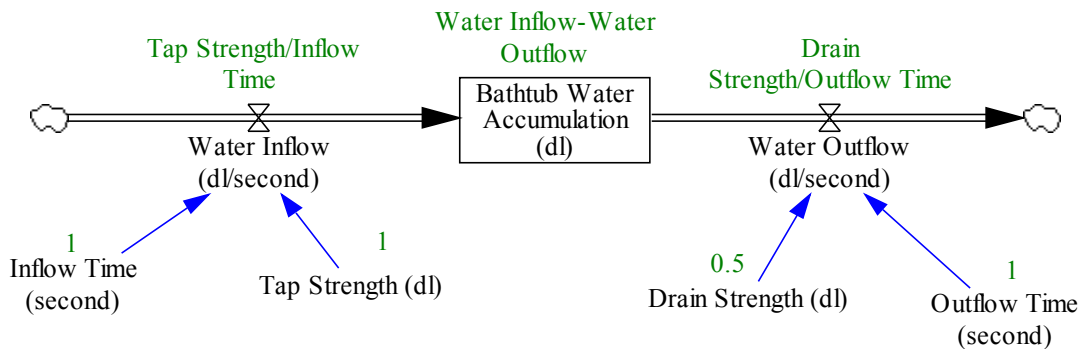
Fig. B.3: Bathtub Stock and Flow "Ready-to-Simulate" Structure

When the model shown in Fig. B.3 is simulated over a period of 5 minutes (300 seconds), it shows the following graph for the *bathtub water accumulation* stock:
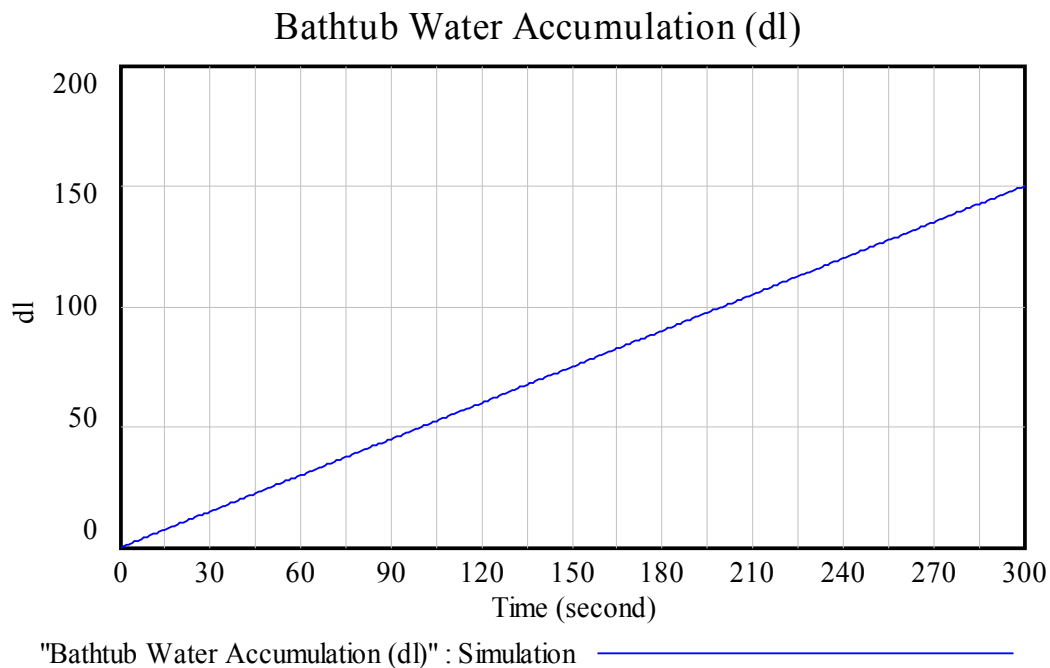
Fig. B.4: Graph showing the Behaviour of *Bathtub* Stock Over a Period of 5 Minutes

The above simulation graph (Fig. B.4) shows that the bathtub stock will linearly grow from 0 to 150 dls. of water over a period of 5 minutes if the inflow remains constant at 1dl/second and the outflow at 0.5 dl/second. For a detailed reading on stocks and flows, see John D. Sterman, *Business Dynamics: System Thinking and Modeling for a Complex World* (Irwin McGraw-Hill 2000), 191-230.

Appendix C: Stock and Flow Model Equations

C.1 Sec. 5.1's Model Equations:

(01)   "ACG's (Correct) Stress Report"= INTEG (ACG's Arousal Rate,1)
        Units: Neurons/Second

(02)   "ACG's Adj. Time"= 1
        Units: Second

(03)   ACG's Arousal Rate= ((Effect of PFC on ACG * Normal ACG Activity) -"ACG's
        (Correct) Stress Report") /"ACG's Adj. Time"
        Units: Neurons/(Second*Second)

(04)   "Amyg-ACG Adj. Time"= 6
        Units: Second

(05)   Amygdala's Crude Stress Perception= INTEG (Net Change in Amygdala's
        Perception, 1)
        Units: Neurons/Second

(06)   "Amygdala-ACG Gap"= IF THEN ELSE(Amygdala's Crude Stress Perception <
        "ACG's (Correct) Stress Report", 0 , "ACG's (Correct) Stress Report" -
        Amygdala's Crude Stress Perception)
        Units: Neurons/Second

(07)   Effect of FII on PFC= Table for FII Effect on PFC (Relaying of FII by Thalamus
        to PFC/Normal FII)
        Units: Dmnl

(08)   Effect of PFC on ACG= Table for PFC Effect on ACG(PFC's Correct Perception
        of Stress/Normal Perception of PFC)
        Units: Dmnl

(09)   End Time= 100000
        Units: Second

(10)   FII Duration= 0.05
        Units: Second

(11)   FINAL TIME = 100
        Units: Second
        The final time for the simulation.

(12)   INITIAL TIME = 0
        Units: Second
        The initial time for the simulation.

(13)   Net Change in Amygdala's Perception= (Relaying of FII by Thalamus to
        Amygdala) + ("Amygdala-ACG Gap" / "Amyg-ACG Adj. Time")
        Units: Neurons/(Second*Second)

(14)   Normal ACG Activity= 1
        Units: Neurons/Second

(15)   Normal FII= 1
        Units: Neurons/(Second*Second)

(16) Normal FII Frequency= 1e+006
Units: Second

(17) Normal Perception of PFC= 1
Units: Neurons/Second

(18) PFC's Correct Perception of Stress= INTEG (PFC's Perception Rate, 1)
Units: Neurons/Second

(19) "PFC's Perception Adj. Time"= 1
Units: Second

(20) PFC's Perception Rate= IF THEN ELSE(Effect of FII on PFC <= 0, 0 , ((Effect of FII on PFC * Normal Perception of PFC) - PFC's Correct Perception of Stress) / "PFC's Perception Adj. Time")
Units: Neurons/Second/Second

(21) Relaying of FII by Thalamus to Amygdala= (Severity of FII * PULSE TRAIN(Thalamus to Amygdala FII Start Time, FII Duration, Normal FII Frequency, End Time))
Units: Neurons/Second/Second

(22) Relaying of FII by Thalamus to PFC= (Severity of FII * PULSE TRAIN(Thalamus to PFC FII Start Time, FII Duration, Normal FII Frequency, End Time)) + 1
Units: Neurons/Second/Second

(23) SAVEPER = TIME STEP
Units: Second [0,?]
The frequency with which output is stored.

(24) Severity of FII= 500
Units: Neurons/Second/Second

(25) Table for FII Effect on PFC([(0,0)-(1000,1000)],(0,0),(10,10),(1000,1000))
Units: Dmnl

(26) Table for PFC Effect on ACG([(0,0)-(45,45)],(0,0),(10,10),(50,50),(100,50), (1000,50))
Units: Dmnl

(27) Thalamus to Amygdala FII Start Time= 4
Units: Second

(28) Thalamus to PFC FII Start Time= 6
Units: Second

(29) TIME STEP = 0.03
Units: Second [0,?]
The time step for the simulation.

C.2 Sec. 5.2's Model Equations:

(01) "Active Norepinephrine (NE)"= INTEG (NE Stimulation Rate - NE Degrading Rate, 1)
Units: molecules

(02)   "Active Serotonin (SE)"= INTEG (SE Stimulation Rate-SE Degrading Rate,1)
        Units: molecules
(03)   "Deasired NE/SE Ratio"= 1
        Units: Dmnl
(04)   FINAL TIME = 100
        Units: Second
        The final time for the simulation.
(05)   INITIAL TIME = 0
        Units: Second
        The initial time for the simulation.
(06)   NE Degrading Rate= IF THEN ELSE("Active Norepinephrine (NE)" <= 1 , 0 ,
        "Active Norepinephrine (NE)" / NE Degrading Time)
        Units: molecules/Second
(07)   NE Degrading Time= 5
        Units: Second
(08)   NE Stimulation Rate= ("NE/SE Ratio Gap"*Normal Active NE - "Active
        Norepinephrine (NE)")/NE Stimulation Time
        Units: molecules/Second
(09)   NE Stimulation Time= 1
        Units: Second
(10)   "NE/SE Ratio Gap"= "NE/SE" / "Deasired NE/SE Ratio"
        Units: Dmnl
(11)   "NE/SE"= "Active Norepinephrine (NE)"/"Active Serotonin (SE)"
        Units: Dmnl
(12)   Normal Active NE= 1
        Units: molecules
(13)   Normal Active SE= 1
        Units: molecules
(14)   SAVEPER = TIME STEP
        Units: Second [0,?]
        The frequency with which output is stored.
(15)   SE Degrading Rate= IF THEN ELSE("Active Serotonin (SE)" <= 100 :AND: SE
        Impairment Switch = 1 , 0 , "Active Serotonin (SE)"/SE Degrading Time)
        Units: molecules/Second
(16)   SE Degrading Time= 5
        Units: Second
(17)   SE Impairment Switch= 1
        Units: Dmnl
(18)   SE Stimulation Rate= (("NE/SE Ratio Gap" * Normal Active SE - "Active
        Serotonin (SE)")/SE Stimulation Time) * SE Impairment Switch
        Units: molecules/Second
(19)   SE Stimulation Time= 1
        Units: Second

(20)   TIME STEP = 0.03
        Units: Second [0,?]
        The time step for the simulation.

C.3 Sec. 5.3's Model Equations:

(01)   "ACG's (Correct) Stress Report"= INTEG (ACG's Arousal Rate,1)
        Units: Neurons/Second
(02)   "ACG's Adj. Time"= 1
        Units: Second
(03)   ACG's Arousal Rate= ((Effect of PFC on ACG * Normal Report of ACG) -
        "ACG's (Correct) Stress Report") /"ACG's Adj. Time"
        Units: Neurons/(Second*Second)
(04)   Active Cortisol= INTEG (Cortisol Stimulation Rate-Cortisol Degrading Rate,1)
        Units: Molecules
(05)   "Active Norepinephrine (NE)"= INTEG (NE Stimulation Rate-NE Degrading
        Rate, 1)
        Units: Molecules
(06)   "Active Serotonin (SE)"= 1
        Units: Molecules
(07)   "Active Stress Response Hormone (CRH)"= INTEG (CRH Stimulation Rate-CRH
        Degrading Rate, 1)
        Units: Molecules
(08)   "Amyg-ACG Adj. Time"= 6
        Units: Second
(09)   Amygdala's Crude Stress Perception= INTEG (Net Change in Amygdala's
        Perception, 1)
        Units: Neurons/Second
(10)   "Amygdala-ACG Gap"= IF THEN ELSE(Amygdala's Crude Stress Perception <
        "ACG's (Correct) Stress Report", 0 , "ACG's (Correct) Stress Report" -
        Amygdala's Crude Stress Perception)
        Units: Neurons/Second
(11)   Average Heart Rate= INTEG (Heart Rate, 1.2)
        Units: Beats/Second
(12)   Cortisol Degrading Rate= IF THEN ELSE(Active Cortisol <= 1, 0 , Active
        Cortisol/Cortisol Degrading Time)
        Units: Molecules/Second
(13)   Cortisol Degrading Time= 5
        Units: Second
(14)   Cortisol Stimulation Rate= (Effect of CRH on Cortisol*Normal Active Cortisol)/
        Cortisol Stimulation Time
        Units: Molecules/Second
(15)   Cortisol Stimulation Time= 1

Units: Second

(16)　CRH Degrading Rate= IF THEN ELSE ("Active Stress Response Hormone (CRH)" <= 1, 0, Active Cortisol / CRH Degrading Time)
Units: Molecules/Second

(17)　CRH Degrading Time= 5
Units: Second

(18)　CRH Stimulation Rate= (Effect of Amygdala on CRH*Normal Active CRH)/CRH Stimulation Time
Units: Molecules/Second

(19)　CRH Stimulation Time= 1
Units: Second

(20)　Effect of Amygdala on CRH= Table for Amygdala's Effect(Amygdala's Crude Stress Perception/Normal Amygdala's Effect)
Units: Dmnl

(21)　Effect of CRH on Cortisol= Table for CRH Effect on Cartisol ("Active Stress Response Hormone (CRH)" / Normal CRH)
Units: Dmnl

(22)　Effect of CRH on NE= IF THEN ELSE ("Active Stress Response Hormone (CRH)" <= 1 , 0 , Table for CRH Effect on NE ("Active Stress Response Hormone (CRH)"/Normal CRH))
Units: Dmnl

(23)　"Effect of Efficiency of Alpha-2 Receptor on NE"= "Table for Alpha-2 Receptor Effect on NE"("Efficiency of Alpha-2 Receptor")
Units: Dmnl

(24)　Effect of FII on PFC= Table for FII Effect on PFC ("Relaying of Fear Inducing Information (FII) by Thalamus to PFC" / Normal FII)
Units: Dmnl

(25)　Effect of NE on Heart Rate= Table for NE Effect on Heart Rate ("Active Norepinephrine (NE)" / Normal NE)
Units: Dmnl

(26)　Effect of PFC on ACG= Table for PFC Effect on ACG(PFC's Correct Perception of Stress/Normal Perception of PFC)
Units: Dmnl

(27)　Effect of SE= Table for SE Effect ("Active Serotonin (SE)" /Normal SE)
Units: Dmnl

(28)　"Efficiency of Alpha-2 Receptor"= 100
Units: Dmnl

(29)　End Time= 100000
Units: Second

(30)　FII Duration= 0.05
Units: Second

(31)　FINAL TIME = 1000
Units: Second

The final time for the simulation.

(32) Heart Rate= ((Effect of NE on Heart Rate * Normal Heart Rate) - Average Heart Rate) / "Heartbeat Adj. Time"
Units: Beats/Second/Second

(33) "Heartbeat Adj. Time"= 150
Units: Second

(34) INITIAL TIME = 0
Units: Second
The initial time for the simulation.

(35) NE Degrading Rate= IF THEN ELSE("Active Norepinephrine (NE)" <= 1 , 0 , "Active Norepinephrine (NE)" / NE Degrading Time)
Units: Molecules/Second

(36) NE Degrading Time= 5
Units: Second

(37) NE Stimulation Rate= (Effect of CRH on NE * "Effect of Efficiency of Alpha-2 Receptor on NE" * Normal Active NE) / NE Stimulation Time
Units: Molecules/Second

(38) NE Stimulation Time= 1
Units: Second

(39) Net Change in Amygdala's Perception= (Relaying of FII by Thalamus to Amygdala / Effect of SE) + (("Amygdala-ACG Gap" * Effect of SE) / "Amyg-ACG Adj. Time")
Units: Neurons/(Second*Second)

(40) Normal Active Cortisol= 1
Units: Molecules

(41) Normal Active CRH= 1
Units: Molecules

(42) Normal Active NE= 1
Units: Molecules

(43) Normal Amygdala's Effect= 1
Units: Neurons/Second

(44) Normal CRH= 1
Units: Molecules

(45) Normal FII= 1
Units: Neurons/(Second*Second)

(46) Normal FII Frequency= 1e+006
Units: Second

(47) Normal Heart Rate= 1.2
Units: Beats/Second

(48) Normal NE= 1
Units: Molecules

(49) Normal Perception of PFC= 1
Units: Neurons/Second

(50)   Normal Report of ACG= 1
        Units: Neurons/Second
(51)   Normal SE= 1
        Units: Molecules
(52)   PFC's Correct Perception of Stress= INTEG (PFC's Perception Rate, 1)
        Units: Neurons/Second
(53)   "PFC's Perception Adj. Time"= 1
        Units: Second
(54)   PFC's Perception Rate= IF THEN ELSE(Effect of FII on PFC <= 0, 0 , (((Effect
        of FII on PFC * Normal Perception of PFC) - PFC's Correct Perception of
        Stress) / Effect of SE) / "PFC's Perception Adj. Time")
        Units: Neurons/Second/Second
(55)   "Relaying of Fear Inducing Information (FII) by Thalamus to PFC"= (Severity of
        FII * PULSE TRAIN(Thalamus to PFC FII Start Time, FII Duration, Normal FII
        Frequency, End Time)) + 1
        Units: Neurons/Second/Second
(56)   Relaying of FII by Thalamus to Amygdala= (Severity of FII * PULSE
        TRAIN(Thalamus to Amygdala FII Start Time, FII Duration, Normal FII
        Frequency, End Time))
        Units: Neurons/Second/Second
(57)   SAVEPER = TIME STEP
        Units: Second [0,?]
        The frequency with which output is stored.
(58)   Severity of FII= 500
        Units: Neurons/Second/Second
(59)   "Table for Alpha-2 Receptor Effect on NE" ([(0,0)-(100,10)],(0,10),(50,5),
        (100,1))
        Units: Dmnl
(60)   Table for Amygdala's Effect([(0,0)-(200,201)],(0,0),(3,0),(4,30),(5,40),
        (13.4557,79.3421),(27.5229,130.474),(100,200),(200,200))
        Units: Dmnl
(61)   Table for CRH Effect on Cartisol ([(-1,0)-(1000,1000)],(-1,0),(0,0),(1,0),(10,10),
        (1000,1000))
        Units: Dmnl
(62)   Table for CRH Effect on NE ([(0,0)-(100,120)],(0,0),(5,25),(32.1101,71.2281),
        (68.0734,97.0175),(993.884,100.114),(1000,100))
        Units: Dmnl
(63)   Table for FII Effect on PFC ([(0,0)-(1000,1000)],(0,0),(10,10),(1000,1000))
        Units: Dmnl
(64)   Table for NE Effect on Heart Rate ([(-1,0)-(120,10)],(0,0),(1,1),(38.7951,5),
        (50,6),(80,8),(100,9),(110,9),(10000,9))
        Units: Dmnl
(65)   Table for PFC Effect on ACG ([(0,0)-(45,45)],(0,0),(10,10),(50,50),(100,50),

(1000,50))
Units: Dmnl
(66)   Table for SE Effect ([(-1,0)-(1000,4)],(-1,0),(0,1),(50,1.5),(90,1.8),
(124.508,2.03509),(200,2.49123),(381.645,3),(1000,3))
Units: Dmnl
(67)   Thalamus to Amygdala FII Start Time= 4
Units: Second
(68)   Thalamus to PFC FII Start Time= 6
Units: Second
(69)   TIME STEP = 0.03
Units: Second [0,?]
The time step for the simulation.

C.4 Sec. 5.4's Model Equations:

Same as in C.3, except the following:
Table   for   Amygdala's   Effect   [(0,0)-(200,600)],(1,0),(3,40),(4,100),(5,120),
(13.4557,200),(27.5229,300),(100,500),(200,500)
Units: Dmnl

C.5 Sec. 5.5's Model Equations:

Same as in C.3, except the following:
(01)   Effect of GABA on Amygdala's Perception= Table for GABA Effect
(GABA/Normal GABA)
Units: Dmnl
(02)   GABA= 500
Units: Molecules
(03)   Net Change in Amygdala's Perception= (Relaying of FII by Thalamus to
Amygdala / (Effect of SE * Effect of GABA on Amygdala's Perception)) +
("Amygdala-ACG Gap" * Effect of SE * Effect of GABA on Amygdala's
Perception / "Amyg-ACG Adj. Time")
Units: Neurons/(Second*Second)
(04)   Normal GABA= 1
Units: Molecules
(05)   Table   for   GABA   Effect   ([(0,0)-(1000,6)],(0,1),(50,1.5),(85.6269,1.88596),
(140.673,2.54386),(177.37,3.64035),(214.067,4.47368),(293.578,4.89474),
(379.205,4.97368),(446.483,5),(489.297,5),(581.04,5.02632))
Units: Dmnl

C.6 Sec. 5.6's Model Equations:

Same as in C.5, except the following:

(01)   Effect of Heart Rate on Stressful Events= Table for Effect of Heart Rate on Stressful Events (Average Heart Rate/Normal HR)
        Units: Dmnl

(02)   Effect of Stimuli on FII= Stimuli/Normal Stimuli
        Units: Dmnl

(03)   Effect of Stressful Events on Stimuli= Table for Effect of Stressful Events on Stimuli(Stressful Events/Normal Stressful Events)
        Units: Dmnl

(04)   Normal Stressful Events= 1
        Units: Events

(05)   Normal Stressful Events Rate= 1
        Units: Events

(06)   Normal Stimuli= 1
        Units: Stimuli

(07)   Stimuli= INTEG (Stimuli Building Rate,1)
        Units: Stimuli

(08)   "Relaying of Fear Inducing Information (FII) by Thalamus to PFC"= (Severity of FII * PULSE TRAIN(Thalamus to PFC FII Start Time, FII Duration, (Normal FII Frequency/Effect of Stimuli on FII), End Time)) + 1
        Units: Neurons/Second/Second

(09)   Relaying of FII by Thalamus to Amygdala= (Severity of FII * PULSE TRAIN (Thalamus to Amygdala FII Start Time, FII Duration, (Normal FII Frequency / Effect of Stimuli on FII), End Time))
        Units: Neurons/Second/Second

(10)   Stimuli Building Rate= ((Effect of Stressful Events on Stimuli) *Normal Stimuli) /Stimuli Development Time
        Units: Stimuli/Second

(11)   Stimuli Development Time= 60
        Units: Second

(12)   Stressful Events= INTEG (Stressful Events Rate, 100)
        Units: Events

(13)   Stressful Events Building Time= 100
        Units: Second

(14)   Stressful Events Rate= (Effect of Heart Rate on Stressful Events * Normal Stressful Events Rate) / Stressful Events Building Time
        Units: Events/Second

(15)   Table for Effect of Heart Rate on Stressful Events ([(0,0)-(6,1)],(0,0),(1.2,0), (1.66972,0.52193),(2.69725,0.802632),(3.41284,0.872807),(6.09174,0.877193))
        Units: Dmnl

(16)   Table for Effect of Stressful Events on Stimuli ([(0,0)-(100,3)],(0,0),(50,1), (100,2),(150,3),(1000,3))
        Units: Dmnl

C.7 Sec. 5.7's Model Equations:

Same as in C.6 except the following:

(01)   Average Fear of Another Panic Attack= INTEG (Fear Development Rate, 0)
        Units: Sensations/Second
(02)   Average Panicky Sensations= INTEG (Panicky Sensations Development Rate, 1)
        Units: Sensations/Second
(03)   Effect of Fear on Panicky Sensations= Table for Effect of Fear on Panicky Sensations (Average Fear of Another Panic Attack / Normal Fear)
        Units: Dmnl
(04)   Effect of Heart Rate on Panicky Sensations= Table for Effect of Heart Rate on Fear (Average Heart Rate/Normal HR)
        Units: Dmnl
(05)   Effect of NE on Panicky Sensations= Table for NE Effect on Sensations("Active Norepinephrine (NE)"/Normal NE)
        Units: Dmnl
(06)   Effect of Panicky Sensations on Fear= Table for Effect of Panicky Sensations on Fear (Average Panicky Sensations / Normal Panicky Sensations)
        Units: Dmnl
(07)   Effect of Panicky Sensations on Stimuli= Table for Effect of Panicky Sensations on Stimuli (Average Panicky Sensations / Normal Panicky Sensations)
        Units: Dmnl
(08)   Fear Development Rate= (Effect of Panicky Sensations on Fear * Normal Fear) / Fear Development Time
        Units: Sensations/Second/Second
(09)   Fear Development Time= 1
        Units: Second
(10)   Normal Fear= 1
        Units: Sensations/Second
(11)   Normal Panicky Sensations= 1
        Units: Sensations/Second

(12)   Panicky Sensations Development Rate= (((Effect of Fear on Panicky Sensations + Effect of Heart Rate on Panicky Sensations + Effect of NE on Panicky Sensations) * Normal Panicky Sensations) - Average Panicky Sensations) / Panicky Sensations Development Time
        Units: Sensations/Second/Second
(13)   Panicky Sensations Development Time= 1
        Units: Second

(14)   Table for Effect of Fear on Panicky Sensations ([[(0,0)-(1000,105)],(0,0),(100,10),
       (200,20),(300,30),(400,40),(500,50),(600,60),(700,70),(800,80),(900,90),
       (1000,100),(2000,100),(1e+009,100))
       Units: Dmnl

(15)   Table for Effect of Heart Rate on Fear ([[(0,0)-(10,101)],(0,0),(1.2,0),(1.3,40),
       (1.4,50),(1.5,65),(1.6,100),(1.7,100),(1.8,100),(1.9,100),(2,100),(5,100))
       Units: Dmnl

(16)   Table for Effect of Panicky Sensations on Fear ([[(0,0)-(20000,1200)],(0,0),
       (428.135,121.053),(5321.1,689.474),(13516.8,1000),(20000,1000))
       Units: Dmnl

(17)   Table for Effect of Panicky Sensations on Stimuli ([[(0,0)-(1000,1.5)],(0,0),
       (100,1),(10000,1))
       Units: Dmnl

(18)   Table for NE Effect on Sensations ([[(0,0)-(100,10)],(0,0),(100,10),(200,20),
       (300,30),(400,40),(500,50),(600,60),(700,70),(800,80),(900,90),(1000,100),
       (2000,100),(1e+009,100))
       Units: Dmnl

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