CHAPTER 1. INTRODUCTION

Depression has been alternately described as (i) a *disorder* of the central nervous system with a neurological basis (Purves, Augustine et al. 2008), (ii) a mental health *disease* (APA 2000; WHO 2007), and (iii) an *adaptive behavioural process* that may hold some benefits for the person experiencing it (Kanter, Busch et al. 2008). These different views indicate the lack of a comprehensive model of depression. That is, despite a great deal of research from within the separate disciplines of psychiatry, genetics, neuroscience, endocrinology, immunology, pharmacology, psychology, behaviour analysis and evolutionary theory, few attempts have been made to describe the cross-linkages between these disciplines in ways that produce an inclusive model of depression. Such a model of depression should encompass the wider literature from the disciplines referred to above and aim to present depression within its organismic and environmental contexts as well as from a consideration of its biological and behavioural bases.

This thesis addresses this issue by reviewing the extant literatures from the areas mentioned above, culminating in a comprehensive model of depression that represents the literature at the time of writing. Because research on depression arises from a variety of theoretical perspectives and covers a wide range of aspects of depression, it may be more appropriate to refer to depression as a "disorder" or "behaviour pattern" rather than a "disease", and that convention will be adopted herein.

Chapter 2 describes the incidence and effects of depression, some historical views of depression, the currently accepted definitions of depression, and then discusses the various methods of identifying and assessing depression and the subtypes of this disorder, producing a working definition for the remainder of the thesis. Chapter 3 describes the

methodology used to focus the literature review undertaken for this thesis, plus the procedures used to identify research studies for inclusion in the review. Chapter 4 examines the biological pathways to depression, including genetics, neurotransmitters, endocrine factors, immunology and neurobiological concomitants. Building upon the neurobiological processes that underlie depression, Chapter 5 describes the effects of environmental factors such as early psychological maltreatment and also the effects of physical illness, both of which have been reported to instigate depression via epigenetic mechanisms. From these bases, Chapter 6 concludes the thesis by discussing the notion that depression may function in an adaptive way to help preserve the organism, and presents a model of depression that includes biological, psychological and behavioural perspectives, with a brief discussion of the implications this model has for treatment options.

CHAPTER 2. WHAT IS DEPRESSION?

2.1 Effects and incidence

Clinical and subsyndromal depression adversely affect physical health, relationships and cognitive performance (Druss and Rosenheck 1999). The symptoms of this disorder themselves are sufficiently unpleasant as to prevent most sufferers from completing their normal work and social responsibilities, even driving about 15% of patients to suicide (APA 2000), with the male:female ratio for suicide in depressed persons possibly being as high as 10:1 (Blair-West, Cantor et al. 1999), although a greater proportion of depressive patients are women than are men (APA 2000). When compared to chronic physical diseases such as angina, arthritis, asthma and diabetes, depression produces the greatest decrement in personal health (Moussavi, Chatterji et al. 2007), and the highest cost of care (Langa, Valenstein et al. 2004). As a result, depression has been described as the major contributor to the total disease burden (Ustun, Ayuso-Mateos et al. 2004) and predicted to become the second leading cause of mental illness by 2020 (Murray and Lopez 1997; WHO 2001). In fact, some recent data suggest that depression poses a similar risk as does smoking for mortality from all causes, even when related health factors such as blood pressure, alcohol intake, cholesterol and social status isol (and all account (Mykletun, Bjerkeset et al. 2009).

Although there are some differences in the clinical presentation of depression across cultures (Kirmayer 2001; Bhugra and Mastrogianni 2004), between 13% (Europe) and 17% (USA) of people have a major depressive episode at some time in their lives (Alonso, Angermeyer et al. 2004; Kessler, Berglund et al. 2005), and these rates are increasing (Bland 1997). In Australia, the National Survey of Mental Health and

Wellbeing (ABS 2007) reported that 8.8% of men and 14.5% of women met the criteria for a lifetime depressive disorder, although up to five times as many men than women committed suicide. The age range 35 to 44 years had the highest incidence of all mood disorders for both males and females. ABS data also indicated that the incidence of depression appears to decrease with age (Henderson, Jorm et al. 1998), a position denied by others (O'Connor 2006). Although the ABS report indicated that a number of demographic factors also influenced the incidence of depression and suicide (eg, substance abuse, family and marital status, employment status, urban *vs* rural residence, presence of a disability), these are outside the ambit of this thesis. Some reports have argued that levels of major depression in Australia have remained fairly static between 1998 and 2004 at 7.4% and 8% respectively (Hawthorne, Goldney et al. 2008), but these incidences are higher than desirable, and justify the exploration of possible causal factors of depression.

When combined with the finding that only about one-third of persons diagnosed with depression receive treatment (Kocsis, Gelenberg et al. 2008), the serious effects upon daily functioning, cost of care and personal distress mentioned above, plus the fact that many people with depression find themselves in a chronic state rather than experiencing a passing condition (as evidenced by the finding that depression has a longitudinal stability over a 15-year period (Merikangas, Zhang et al. 2003), depression clearly ranks very highly in terms of worthwhile targets for investigation.

2.2 Depression in History

Depression is not new to humans, and was originally referred to as “melancholia”, a term derived from the Ancient Greek *melas* (meaning black) and *khole* (bile). Melancholia described an imbalance in the four basic humours, and was characterized by Hippocrates (*Aphorisms,* section 6.23) as “If a fright or despondency lasts for a long time, it is a melancholic affliction.” (Hippocrates 400 BC/2007AD). Others of that period described melancholics as being dejected and torpid without reasonable cause. For example, Aretaeus of Cappadocia commented of melancholia that “It is a lowness of spirit from a single phantasy, without fever” (Adams 1856, p. 29). Thus, these ancient definitions described melancholia as anger, grief, and sad dejection of mind, but differentiated from the kinds of ‘normal’ sadness that people experienced due to bereavement or loss. That is, the experience of sadness, dejection, despondency and fear occurred without a major event or condition as the primary cause (Radden 2003). This distinction between ‘reactive’ (to an event) and ‘endogenous’ (no external stimulus) depression remains in modern nomenclatures (APA 2000; WHO 2007).

During the Middle Ages, Avicenna, in his *Canon of Medicine*, described melancholia as a depressive mood disorder which was also called “acedia”, meaning an absence of caring (Daly 2007), much like anhedonia in modern definitions of depression (APA, 2000). In his comprehensive account, Robert Burton (Burton 1621, p. 32) reported melancholy, its causes, symptoms and remedies in great detail, describing a typical sufferer as “we call him melancholy, that is dull, sad, sour, lumpish, ill-disposed, solitary, any way moved, or displeased”. Samuel Johnson, in his description of *Rasselas, Prince of Abisinnia* (Johnson 1759/1968), referred to “melancholy” as containing a strong dose

of unwarranted guilt, thereby linking the disorder with those who were prone to superstition. During the 18th century, this focus upon the personality characteristics of those who suffered from melancholy was replaced by an emphasis upon more physiological bases, principally low energy and slowed circulation (Jackson 1983).

While melancholia remained a label for a mental illness, the term "depression" (from the Latin *deprimere*, to press down) began to be used to describe someone who was low in spirits, and medical dictionaries of the 19th century referred to depression as a physiological lowering of emotional functioning (Berrios 1988). This term replaced melancholia in psychiatric circles by the end of that period (Davison 2006), and remains in use today.

2.3 The International Classification of Diseases model (ICD-10)

The *International List of Causes of Death* was adopted by the International Statistical Institute at a meeting in Chicago in 1893. Following several decades of development of lists of the causes of death and disease, the World Health Organisation (WHO) released its 6th edition in 1949, the first to include mental illnesses. Several editions followed, and the current version is *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*, published by WHO in 1992 and updated in 2007 (WHO, 2007).

The ICD-10 lists depression under its categories F.32: *Depressive Episode* and F 33: *Recurrent Depressive Disorder* (which is repeated occurrences of a *Depressive Episode*). The ICD-10 definition of *Depressive Episode* is presented in Table 1 (p. 7).

Table 1: ICD-10 Diagnostic criteria for Depressive Episode.

In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe.

Thus, the ICD-10 allows for graduated severity of depression, and includes cognitive, emotional and physiological symptoms.

2.4 The Diagnostic and Statistical Manual of Mental Disorders model (DSM-IV-TR)

The development of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I), produced by the American Psychiatric Association in 1952, included *depressive reaction* to major loss and showing symptoms in excess of those for mourning. The 'reactive' nature of depression was reinforced in the DSM-II in 1968, which introduced the classification of *depressive neurosis* as a reaction to loss, and distinguished between this type of depression and that which had a more biological cause, diagnosed as *endogenous depression*. However, that distinction gave way to a definition in the DSM-III that was reliant upon the severity of symptoms rather than their cause. At about this time, the theoretical model of depression as an illness caused by a chemical imbalance of

brain neurotransmitters (the ‘Monoamine’ hypothesis) became established, and the diagnoses of *Major Depressive Episode* and *Major Depressive Disorder* were accepted from the mid-1970s and remain in place in the most recent version, the DSM-IV-TR (Text Revision). This diagnosis is based upon a set of symptoms or criteria that are shown in Table 2 (p. 9).

Table 2: DSM-IV-TR Diagnostic criteria for *Major Depressive Episode* (*Depressive Disorder* is defined by the presence of these symptoms for at least two weeks).

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: *Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.*

- *depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).* ***Note:*** *In children and adolescents, can be irritable mood.*
- *markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)*
- *significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.* ***Note:*** *In children, consider failure to make expected weight gains.*
- *insomnia or hypersomnia nearly every day*
- *psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)*
- *fatigue or loss of energy nearly every day*
- *feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)*
- *diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)*
- *recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide*

The symptoms do not meet criteria for a Mixed Episode

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

As for the ICD-10, cognitive, emotional and physiological aspects are included in the DSM-IV-TR definition. Both the ICD-10 and the DSM-IV-TR are widely used, with some data from a survey of 205 psychiatrists in 66 nations and all continents (Mezzich 2001) indicating that the former is more relied upon for clinical diagnosis and the latter for research purposes. It is also of note that only the DSM-IV-TR includes criteria related to functional impairment in social and occupational areas.

There are some criticisms of the approach taken to depression by both of these models, particularly addressed to the DSM-IV-TR. For example, some authors have criticized the acceptance of intense sadness following adverse life events as constituting depression if the severity, duration and impairment criteria are fulfilled, except for when this occurs following bereavement (Maj 2008). The rationale given by the DSM-IV-TR for excluding intense sadness following bereavement from a diagnosis of depression is that bereavement is "an expectable and culturally sanctioned response to a particular event" (APA, 2000, p. xxi). However, as Maj (2008) and others (Wakefield, Schmidt et al. 2007; Kendler, Myers et al. 2008) have noted, most people will experience several major stressful life events, some of which will engender intense sadness (e.g., losing a job, ending a longterm relationship, being diagnosed with a major illness), and the distinction between these events and bereavement may be difficult to maintain. This argument has led some to advise deletion of the bereavement exclusion from DSM-IV-TR (Pies 2009), or to extend the exclusion to other major losses (Wakefield, Schmidt et al. 2007).

A second criticism of the system used in DSM-IV-TR is based upon the instability of symptoms across episodes of recurrent Major Depressive Disorder (MDD)

(Angst, Sellar et al. 2000; Oquendo, Barrera et al. 2004), a comment that is supported by the finding that, when seen in primary medical care settings, there are more false positive diagnoses of depression than either missed or identified cases (Mitchell, Vaze et al. 2009). Finally, although the absence of previously-present symptoms is accepted as evidence of remission under the ICD-10 or DSM-IV-TR systems, there are some data which challenge this on the basis that some patients who show remission of depressive symptoms remain functionally impaired, producing discordance between the presence of symptoms and the patient's functional adequacy as defined by the DSM-IV-TR (Kendler and Gardner 1998; Zimmerman, McGlinchey et al. 2006; Zimmerman, McGlinchey et al. 2008). Together, these findings challenge the validity of the symptom- and impairment-based categorization systems underlying the DSM-IV-TR in particular and also the ICD-10, thus also challenging the validity of research studies of depression that are based upon these criteria.

2.5 Definitions from morphology: Self-report scales

Perhaps because of the general acceptance of the comprehensiveness and clarity of the ICD and DSM diagnostic systems (which largely agree on their definitions of depressive symptomatology), a great deal of research and some clinical practice is done via assessments of depression that rely on self-report scales that are completed by research participants or patients themselves and which are drawn to a greater or lesser degree from the ICD-10 and/or DSM-IV-TR criteria listed above.

This is for two reasons. First, because the ICD-10 and DSM-IV-TR criteria are applied via clinical interview by appropriately-qualified interviewers (medical or psychological personnel), the diagnostic process is resource-intensive, particularly for

research where ‘screening’ of participants’ depressive status is required but clinical examination is not. Second, each of those interviews takes about 20 to 30 minutes, creating a major logistic problem for research projects that may (for example) seek to assess several hundred people for their depression status. Thus, the use of self-report depression scales is widespread in research, indicated by the fact that, using the search terms ‘depression scales *vs* DSM ICD’ in Google Scholar produced 20,200 hits in April, 2010.

It is relevant to enquire as to the degree of correlation between self-report scales and ICD-10 and DSM-IV-TR diagnostic criteria, and even to the degree of agreement between the various self-report scales themselves. While exhaustive examination of those issues is beyond this thesis (and not centrally relevant to it), it is worthwhile noting that several papers have found most of the more common self-report scales such as the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961), Hamilton Depression Rating Scale (Hamilton 1960), Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), and the SCL-90 (Derogatis, Lipman et al. 1973) have sound *specificity* (i.e., the test can identify people who are not depressed) and *sensitivity* (i.e., the test will identify people who are depressed) (Aben, Verhey et al. 2002), indicating that all these tests can, in fact, measure depression and so are sufficiently “valid” as to be used in research and clinical settings. Similar findings have been reported for correlations between: the Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff 1977) and the BDI (Geisser, Roth et al. 1997); the CES-D, BDI and Zung Self-Rating Depression Scale (Zung 1971; Zung 1980) (Fountoulakis, Bech et al. 2007); HADS, Patient Health

Questionnaire (Spitzer, Kroenke et al. 1999), WHO Well Being Index (WHO 1998), and the Major Depression Inventory (Bech 1997; Bech, Rasmussen et al. 2001; Aben, Verhey et al. 2002; Olsen, Jensen et al. 2003; Löwe, Spitzer et al. 2004). Those studies have concluded that all of these scales significantly correlate with each other in their overall classification of whether a participant is suffering from depression. Further, most of them have also reported that each of the scales significantly agrees with DSM-IV diagnoses derived from clinical interviews.

Therefore, these results suggest that many self-report scales of depression may be used interchangeably and with a good degree of confidence that their diagnostic results will agree with the 'yardstick' of the DSM–IV and DSM-IV-TR, and the ICD-10 diagnostic criteria for depression. This justifies the inclusion of research studies that use such self-report scales within the remainder of this thesis, as well as acceptance that the findings of various factors which relate to depression measured by self-report scales will also apply to ICD-10 and DSM-IV-TR diagnoses of depression. However, 'Quality of Life' (QoL) inventories which do not necessarily ask respondents to address the specific symptoms mentioned in Tables 1 and 2, are fraught by a "lack of standardization in definitions, conceptualizations and psychometric testing", leaving QoL "to mean very different things" (Chen 2007, p. 2695). This thesis will therefore avoid studies which use QoL inventories to assess the presence of depression.

2.6 Subtypes of depression

Depression is a ‘Mood Disorder’, and may appear in various forms. Both the ICD-10 and DSM-IV-TR cover the following types of depression:

- Unipolar depression (the sufferer is fairly continuously depressed);
- Bipolar I and Bipolar II disorder (in which the sufferer’s mood varies from extreme depression to extreme elation, with varying ratios of each);
- Dysthymic disorder (the depressed mood has lasted for at least two years);
- Cyclothymic disorder (the mood swings characteristic of Bipolar disorder are frequent, dramatic and have lasted for at least two years);
- Depression due to a substance (e.g., drug of abuse, medication, toxin, or other somatic treatment);
- Depression due to a medical condition;
- Depression with catatonic features (marked by immobility, excessive stereotypic motor activity, extreme resistance to all instructions, plus other symptoms such as echolalia, stupor or cataplexy);
- Depression with melancholic features (loss of interest in all, or almost all, activities, a lack of responsiveness to otherwise pleasant stimuli so that the sufferer’s mood does not improve, even temporarily whenever something good happens, plus early morning awakening, feeling more depressed in the morning, and other symptoms listed in Table 2);
- Depression with atypical features (characterized by loss of pleasure and lack of reactivity to pleasant stimuli, plus increased appetite or weight gain, hypersomnia, leaden paralysis and extreme sensitivity to

interpersonal rejection), although this subcategory of depression has been challenged as a valid diagnosis (Stewart, McGrath et al. 2009; Thase 2009);

- Depression with postpartum onset (after birth, with symptoms including mood fluctuations and preoccupation with the newborn's well-being).

Although assumed to represent different forms of depression, these different diagnoses all contain the basic features of sadness, loss of interest and pleasure in activities, plus a number of cognitive, emotional and physiological symptoms which remain common across these varieties of depressive disorder. These features may therefore be accepted as representing the 'core' symptoms of depression.

Depression is often observed with symptoms of anxiety (McLaughlin, Khandker et al. 2006). For example, one paper which reported on the comorbidity of anxiety and depression found that 10.2% of a patient sample met the diagnostic criteria for both disorders (Wilson, Chochinov et al. 2007). A more recent study (Brintzenhofe-Szoc, Levin et al. 2009) identified the incidence of anxiety-depression comorbidity among 374 prostate cancer patients as also being 10.2%, with 6.2% fulfilling the criteria for depression alone, and 8.5% for anxiety alone. The concept of a 'mixed anxiety-depression' disorder has been developed and subjected to field trials, with results arguing for the inclusion of this diagnosis in the next revision of the DSM series (Zinbarg, Barlow et al. 1994). As an indication of the force of that argument, the current DSM-IV-TR includes the Mixed Anxiety Depression Disorder (MADD) as a disorder for further study. Field studies have shown that up to 19.2% of patients in a community setting fulfilled the

criteria for this diagnosis (Stein, Kirk et al. 1995), supporting the argument for its existence as a unique disorder (Barlow and Campbell 2000).

2.7 Degrees of feeling bad: Subsyndromal Depression to Major Depressive Disorder

As may be noted in the final sentence of Table 1, the ICD-10 provides procedures for counting the number of symptoms and defining depression as mild, moderate or severe. DSM-IV-TR (Table 2) defines Major Depressive Disorder (MDD) but does not allow for less severe degrees of this subtype of depression, a system that is not without criticism. For example, large-scale studies have identified nonclinical classes of depression (Solomon, Haaga et al. 2001), arguing that depressive symptoms ought to be considered on a continuum rather than a categorical basis. Perhaps for that reason, the concepts of 'subsyndromal depression' (Sadek and Bona 2000), 'Minor Depression' (Rapaport, Judd et al. 2002) or 'Major Depressive Disorder with fewer symptoms' (than required in Table 2) have been developed (Judd, Rapaport et al. 1994). The most commonly-used term is 'Subsyndromal depression' (SSD), and has been defined as "any any 2 or more simultaneous symptoms of depression, present for most or all of the time, at least 2 weeks in duration, associated with evidence of social dysfunction, occurring in individuals who do not meet criteria for diagnoses of minor depression, major depression, and/or dysthymia" (Judd, et al, 1994, p.18). However, despite the lack of a requirement for the symptoms of sadness and lack of interest or pleasure in usual activities, SSD patients suffer from increased medical burden and poor subjective health status and social support compared to people without SSD (Lyness, Heo et al. 2006). In fact, SSD patients have been shown to suffer the same levels of household strain, social irritability, financial

pressure, limitations in physical or job functioning, restricted activity days, and bed days as patients with MDD, and only differ on the single criterion of overall health status (Judd, Paulus et al. 1996), thus making SSD almost as costly as MDD for society and for those who suffer from it.

This finding appears to confirm that the presence of even relatively few of the symptoms of MDD, and the concomitant deleterious effects upon daily functioning, is sufficient to render the sufferer depressed for the purposes of being 'ill' and unable to function effectively. This position has been supported by several studies, some of which have shown that the DSM-IV-TR requirement of number of symptoms, impairment of social and occupational functioning and duration of symptoms for at least two weeks, were not adequate for defining depression, and that there is a continuity in depressive symptoms that is not reflected in the definition represented by diagnostic criteria displayed in Table 2 (Kendler and Gardner 1998; Angst, Sellar et al. 2000; Solomon, Haaga et al. 2001; Rapaport, Judd et al. 2002; Kendell and Jablensky 2003).

2.8 A working definition

As indicated above, the World Health Organisation defined unipolar depression in its ICD-10 in 1990, updated in 2007 (WHO, 2007). In much of the English-speaking world the American Psychiatric Association's DSM-IV-TR (APA, 2000) is used more commonly than the ICD-10. Tables 1 and 2 show the relevant definitions from each of these sources for Depressive Episode and indicate that they are almost congruent.

However, as noted above in section 2.5, there is satisfactory agreement between the scores obtained on a range of self-report scales (which do not apply the duration and interference in function components of the DSM-IV-TR definition) and the DSM-IV-TR

diagnostic criteria themselves. In addition, the necessity for the strict number of symptoms set out in Table 2 has been effectively challenged by data presented in section 2.7 regarding the effects of SSD upon patients. Therefore, depression may be defined from a range of perspectives, all of which appear to be valid in terms of suffering, cost to society and requiring treatment. As such, and for the purpose of this thesis, a working definition of depression has been derived and is presented below in Table 3 (next page).

This definition is congruent with the key symptoms from ICD-10 and DSM-IV-TR, as well as the items that constitute the various self-report scales described above in section 2.5. This working definition highlights the importance of negative emotions, reduced ability to think clearly and somatic symptoms, but does not require interference with the individual's ability to function (as stated by DSM-IV-TR). For the remainder of this thesis, depression will be accepted as present in research studies that are reviewed herein if a sufficient number of these symptoms of depression occur in a research sample so as to allow the researchers who are conducting the study to determine that some form of depression is present, whether clinical interviews based upon the ICD-10 or DSM-IV-TR criteria or scores from self-report scales are used to make that determination.

Table 3: Major criteria for depression, after ICD-10 (WHO, 2007), DSM-IV-TR (APA, 2000) and a range of self-report scales.

Symptoms must be present most of the time and not due to bereavement or a medical condition or treatment.

- *Feeling depressed most of the time*
- *Lost interest or pleasure in activities.*
- *Diminished concentration.*
- *Fatigue.*
- *Sleep disturbances.*
- *Loss of appetite, weight loss or gain.*
- *Lowered self-esteem and confidence.*
- *Feelings of worthlessness or guilt.*
- *Psychomotor agitation or retardation.*
- *Thoughts of death or suicide.*
- *Symptoms cause significant impairment in the individual's functioning.*

CHAPTER 3: METHODOLOGY

3.1 Research areas for investigation

As indicated above, depression constitutes a major health issue for much of the Western world, if not humanity. The lack of a comprehensive (at least at the commencement of this thesis) model of the contributing factors which underpin its symptomatology may limit the identification of those individual potential 'causal' factors in patients' everyday lives and thus the development of preventative measures to reduce the incidence of depression. In addition, modeling of the *interaction* between those factors might assist in understanding *how* depression occurs and also *why* it happens at all. Therefore, as mentioned above, the aim of this thesis was to develop a comprehensive model of depression, including the findings from several related areas of research that had been shown to contribute to the current understanding of depression.

3.2 Identification of research reports for inclusion

Following this aim, the first major task in this thesis was the identification of the potential 'causal' factors which have been shown to link with depression (the second task was to synthesise those factors into a unifying model). That first task involved three strategies: (1) reference to several recently published major commentary and descriptive texts such as the American Psychiatric Association's *Textbook of Mood Disorders* (Stein, Kupfer et al. 2006*)*, *Risk Factors in Depression* (Dobson and Dozois 2008), *Depression and Physical Illness* (Steptoe 2007), and *Manufacturing Depres*sion (Greenberg 2010) to gain an understanding of the current *zeitgeist*. The discipline areas identified from those texts as having made significant contributions to an understanding of the causes of depression were: general psychiatry, genetics, neuroscience,

endocrinology, immunology, pharmacology, psychology, behaviour analysis and evolutionary theory; (2) an initial search of the previous 10 years' published research using PubMed, Science Direct, PsychInfo, and Google Scholar, with the terms 'depression' 'MDD', 'depressive disorder', which also indicated the predominant journals that published research relevant to this thesis; (3) an ongoing weekly search of those journals. Although it is by no means a comprehensive list (the Reference list at the end of this thesis will show more titles), some of the major journals that were surveyed for the previous 10 years and also every new issue that emerged during the period of candidature were:

Molecular Psychiatry
Archives of General Psychiatry
Neuropsychopharmacology
Biological Psychiatry
Nature Neuroscience Reviews
Journal of Clinical Psychiatry
Science
Neuropharmacology
Science Translational Medicine
Journal of Consulting & Clinical Psychology
Psychoneuroendocrinology
Journal of Neuroscience
American Journal of Psychiatry
Depression & Anxiety
Psychosomatic Medicine
Journal of Affective Disorders
JAMA
Journal of Neurophysiology
British Journal of Psychiatry
European Journal of Psychiatry

From these three steps, over 100 book chapters and 3,500 journal articles were identified as relevant to depression, from which a subsection of 768 sources was selected for inclusion here for reasons of (i) their relevance to the thesis, and (ii) the word-limit restriction of the MSc thesis at UNE.

3.3 Presentation of findings

Several methods of reviewing the results of research studies are used in the wider literature, such as meta-analysis, tabulation of results, synthesis of common and uncommon data, and simple descriptions of findings. In order to present the information found from the search procedures described above in a fashion that would most likely lead to an overall synthesis of the data from the various discipline areas described under section 3.2 (above), and thence assist in building of a hypothetical model of the development and function of depression, all of these methods were incorporated in this thesis, although new meta-analyses were not conducted but several major meta-analyses of genetic factors were included as representing the application of that review procedure in this area of research into depression.

Therefore, sections of the Chapters 4 and 5 use different methodologies to review and present the findings of research studies identified in those discipline areas. Although this introduces some element of inconsistency of review methodology across these areas of research into depression, the findings that were identified within each area require different methodologies to present them in the most informative manner possible. For example, although there are very many studies of genetic factors in depression, thus arguing for the use of meta-analysis here, that procedure has already been done by several authors, and the findings from those meta-analyses will be presented instead of conducting a new meta-analysis on genetic factors in depression. In addition, such a new meta-analysis of genetic factors in depression would encompass the entirety of this MSc thesis in itself (at least), and therefore defeat the aim of producing a synthesis of several areas of research.

By comparison, there are fewer studies of endocrinal, immunological or behavioural factors in depression than for genetic factors, and therefore description and discussion are used to uncover the major findings from research found in those areas. As suggested above, the second major task for this thesis was to use the literature identified by the steps described in sections 3.2 to form a synthesis of findings that encompasses each area and the findings from each area. The first stage in that process is presented in Chapter 4: Biological pathways to depression.

CHAPTER 4: BIOLOGICAL PATHWAYS TO DEPRESSION

4.1 'Causes' of depression

Multiple biological 'causes' of depression have been suggested. These range from a neurologically-based inability to: enjoy life and its challenges (Pizzagalli, Iosifescu et al. 2008), resolve ambiguity with a negative bias (Lawson, MacLeod et al. 2002; Enkel, Gholizadeh et al. 2010) or accurately appraise events (Beck 2008; Chan, Harmer et al. 2008); to the physiological effects of: a lack of physical exercise (Salmon 2000), dietary inadequacy (Jacka, Pasco et al. 2010), obesity (Luppino, de Wit et al. 2010) and alcohol abuse (Fergusson, Boden et al. 2009); and even the effects of high levels of daily television use upon brain activity (Primack, Swanier et al. 2009). However, these factors may not be the primary or direct 'causes' of depression, but rather behavioural responses that occur in people with depression. Because this distinction between 'cause' and 'correlate' is potentially confusing, the following discussion will take place within the ambit of the latter term at this stage.

Apart from the brief list of possible factors that are linked with depression that was given in the preceding paragraph, the principal biological correlates of this disorder that have received most attention in the research literature are: genetic factors, neurotransmitters, stress as indicated by exaggerated Hypothalamic-Pituitary-Adrenal (HPA) activation to environmental demands, changes to the structure and function of specific brain regions, immune system factors, and the comorbidity of other diseases. Each of these biological factors will be discussed below.

4.2 Genetic bases for depression

4.2.1 Family studies

It is has been convincingly established for some time that having relatives with depression is a risk factor for development of the disorder (Downey and Coyne 1990). For example, family studies of depression reliably produce a figure of 80% heritability (McGuffin, Rijsdijk et al. 2003; Berrettini 2006), with some data identifying specific alleles that are responsible for parent-child transmission of bipolar disorder (Lin and Bale 1997). Similar data have been reported in parent-child links for Major Depressive Disorder (MDD), with children whose both parents had MDD also experiencing a 74% chance of developing the same disorder, and children of one parent with MDD having a 27% chance of becoming severely depressed, compared to 7% for children with neither parent meeting the criteria for MDD (Gershon, Hamovit et al. 1982). Other studies (Wickramratne and Weissman 1998; Wickramaratne, Warner et al. 2000; Weissman, Wickramratne et al. 2005) reported similar results, suggesting that having parents who suffered from depression is a strong indicator of elevated risk for offspring also developing depression. Weissman, Wickramratne et al. (2005) emphasized the familial nature of depression by extending data to an extra generation, showing that the increased likelihood of developing MDD was related to the presence of that disorder in a sufferer's grandparents. In addition, Lieb, Isensee, Hofler, Pfister and Wittchen (2002) reported that, as well as increased risk of MDD, children of depressed parents also had significantly elevated risk of developing other disorders such as anxiety and substance abuse. Perhaps hinting at one method of transmission of MDD between generations, Poliwsky, Wickramratne et al. (2006) found that family discord not only significantly

predicted parental depression, but was also associated with increased risk of MDD among children of those depressed parents 20 years after the initial assessment of family discord. Other transmission vectors include parental alcoholism (Cadoret, Winokur et al. 1996) and maternal depression (Goodman and Gotlib 1999).

One recent and intriguing report regarding the way in which genetically-transmitted predisposition to depression affects the mood state of offspring was from Gotlib, Hamilton et al. (2010). In that study, non-depressed girls with depressed mothers showed less brain activity when presented with a 'rewarding' stimulus than non-depressed girls whose mothers were not depressed. Conversely, when presented with a 'loss' stimulus, the girls whose mothers were depressed showed more brain activity than girls whose mothers were not depressed. It appears from these data that there may be a genetic basis for the comparative neuronal predisposition to focus more on stimuli that are potentially unpleasant than on stimuli that are potentially pleasant, perhaps enhancing the relative valence of sources of displeasure in the environment over sources of pleasure to the individual, and thereby contributing to the symptom of anhedonia, one of the two major indicators of depression (APA, 2000).

4.2.2 Genetic association studies

Investigation of the genes that are linked with mental disorders has been relatively fruitful for some disorders such as schizophrenia and bipolar disorder (Ross and Margolis 2009), identifying abnormalities in neuronal development and signalling pathways, (e.g., the gene *DISC1*) that are associated with behavioural deficits in adulthood (Niwa, Kamiya et al. 2010). By contrast, genetic association studies in unipolar depression have been less successful, possibly because there is a large discrepancy between the

heritability of clinical samples (over 70%) and community samples (about 30%) (McGuffin, Cohen et al. 2007), and also because of the variability in MDD symptomatology patterns among patients (Lesch 2004).

Despite this limited success, genetic association studies of MDD have represented a method for investigating the underlying biological pathway(s) to MDD that is/are indicated by the familial studies referred to above. There are some recent findings regarding the genetic basis of depression that have suggested specific genes which may, when combined with perceived uncontrollable environmental challenges and exaggerated physiological responses to those challenges, have statistically significant relationships with MDD. For example, some genetic links with depression have been reported through polymorphisms and allele dominance on the serotonin transporter gene *5-HTT* (Uher and McGuffin 2008), the piccolo gene *PCLO,* which influences monoaminergic neurotransmitters in the brain (Sullivan, de Geus et al. 2009), and gene-linked malfunctions of the glutamate and GABA systems (Sanacora, Mason et al. 2000). These genes may contribute to the development of MDD by reducing the functionality of the neurotransmitters serotonin (Muller and Schwartz 2007) and dopamine (Choudary, Molnar et al. 2005), thus inducing cognitive confusion, one of the symptoms of depression (APA 2000). Clearly, this is a large field of research and presents a challenge as to how to review its major findings effectively. One method to commence that process is to examine previous major reviews of this literature.

In a landmark study of this issue, Lopez-Leon et al. (2008) identified 183 genetic association studies on MDD performed prior to June 2007. Those papers had investigated 393 polymorphisms in 102 genes, but only 22 polymorphisms across 18 genes had been

investigated in more than three studies. Lopez-Leon and colleagues performed a meta-analysis upon those 22 polymorphisms and found five which had statistically significant relations with MDD, mostly as direct predictors of MDD. These were apolipoprotein E (APOE ε2) (but in a protective direction), guanine nucleotide-binding protein (GNB3), MTHFR 677T, dopamine transporter (SLC6A3), and the serotonin transporter SLC6A4. In a previous meta-analysis, the same authors also identified the dopamine gene DRD4 as a significant risk allele for unipolar depression (López León, Croes et al. 2005). Table 4 (next page) presents a summary of these five polymorphisms and the overall findings reported by Lopez-Leon (2008), plus findings from their previous meta-analysis of DRD4 (López León, Croes et al. 2005).

Table 4: Summary findings for links between five polymorphisms and MDD (from Lopez-Leon et al., 2005, 2008).

Polymorphism	**Studies conducted**	**Participants**	**Outcome: Odds Ratio for Depression (Confidence Interval)**
DRD4	5	318 Depressed, 814 Control	1.73 (1.29-2.32)
APOE ε2	7	827 Depressed, 1,616 Control	0.72 (0.51-1.0)
GNB3	3	375 Depressed, 492 Control	1.38 (1.13-1.69)
MTHFR	6	875 Depressed, 3,859 Control	1.20 (1.07-1.34)
SCL6A3	3	151 Depressed, 272 Control	2.06 (1.25-3.40)
SLC6A4	24	3,752 Depressed, 5,707 Control	1.11 (1.04-1.19)

Each of the polymorphisms shown in Table 4 has an association with MDD, although none are large (only *SCL6A3* has an odds ratio > 2.0), and one (*APOE ε2*) has a protective effect for MDD. *DRD4* is a gene for the receptors of dopamine, a neurotransmitter which is implicated in MDD (Drevets, Gautier et al. 2001). *APOE* is recognized as a major determinant of lipoprotein disease, cardiovascular disease, Alzheimer's Disease, cognitive functioning and immunoregulation (Mahley and Rall 2000), all of which may be implicated in MDD. *GNB3* encodes G proteins, which are a target for some antidepressant medications; the *MTHFR* enzyme metabolises folate, and depression has been associated with low folate levels (Crellin, Bottiglieri et al. 1993); *SCL6A3* is a dopamine transporter which mediates the reuptake of dopamine from the synapse; and *SLC6A4* regulates serotonin reuptake there also. Both *SCL6A3* and *SLC6A4* are targets for antidepressants.

Although none of the Odds Ratios for each of these polymorphisms with MDD are dramatic (Tabachnick and Fidell 2001), Lopez-Leon et al. (2008) concluded that their two meta-analyses found significant evidence for "six MDD susceptibility genes" (p. 779). Each of these six polymorphisms represents a potential avenue for further reviewing the links between genes and depression, and text and tabular presentations of the recent findings on each of those six polymorphisms are presented in the next 14 pages. To gather these studies, each polymorphism was entered into PubMed, Science Direct and Google Scholar in April, 2010 with the term "depression", and only studies published after June 2007 were included in these tables so as to avoid duplicating Lopez-Leon et al.'s (2008) findings. Updating of this database was performed in April, 2011 for

the major genetic polymorphism that has been associated with depression (ie, the 5-HTTLPR polymorphism of the *SLC6A4* gene).

4.2.2.1 DRD4

As mentioned above, DRD4 has been associated with MDD via its role in coding for dopamine receptors, which are involved in neural transmission in many areas of the brain. In addition, DRD4 has been associated with a range of behavioural and psychological disorders including Alzheimer's Disease (Pritchard, Ratcliffe et al. 2009), ADHD (Brookes, Xu et al. 2006) and Obsessive-Compulsive Disorder (Millet, Chabane et al. 2003). In their 2005 meta-analysis of DRD4 and depression, Lopez-Leon and colleagues identified five studies which included a total of 319 MDD patients and 814 non-MDD Control participants. The association they found between MDD and the DRD4.2 was statistically significant ($p < .0003$), and also that between MDD and DRD4.7 ($p < .02$), but not that for DRD4.4 ($p = .24$). From the PubMed, Science Direct and Google-Scholar (plus hand searches) performed on the descriptors 'DRD4' and 'depression' in April, 2010, two recent (post 2007) papers were found that focused specifically on MDD, and these are summarised below.

Guo and Tillman (2009) found "robust" (p. 14) associations between DRD4 and depressive symptoms in a sample of 2500 individuals drawn from the National Longitudinal Study of Adolescent Health in the USA, after adjustment for socioeconomic status, family income, parental education, and child-parent ties and social support. There were no significant gender effects. In a study using post-mortem brain samples from 11 persons (3 male) with MDD who died at an average age of 49 years, plus two females and nine males who had no indications of MDD, Xiang, Szebeni et al. (2008) determined

MDD status via Structured Clinical Interviews (DSM-IV-TR) with the next of kin of all subjects and measured the concentration of dopamine receptor DRD4 mRNA r in these participants' amygdalae. Amounts of DRD4 mRNA were significantly higher in subjects with MDD compared to subjects without MDD, suggesting that elevated gene expression of DRD4 had occurred, perhaps due to lower dopamine presence (although this is not the only explanation possible). Additionally, while it is a relatively common procedure with living patients and their families, clinical interviews of the relatives of deceased persons may be subject to some degree of bias.

4.2.2.2 Apolipoprotein E isoforms 4 (APOE ε4)

Apolipoprotein E (APOE) is essential for the catabolism of triglyceride-rich lipoproteins and APOE ε4 has been implicated in the development of coronary heart disease and Alzheimer's Disease, as well as having been shown to have deleterious effects upon cognition (Corder, Saunders et al. 1993). APOE is mapped to chromosome 19, and there are four major isoforms of APOE (Singh, Singh et al. 2006), with the fourth form (ε4) being particularly linked to Alzheimer's Disease and impaired cognitive function (Corder, Saunders et al. 1993). Although Lopez-Leon et al. (2008) focused upon the protective effects of APOE ε2 and MDD, they also reported data on APOE ε4. When entered into the PubMed, Science Direct and Google Scholar search in April, 2010, APOE ε2 was not linked to any recent studies of MDD but APOE ε4 was (but not in a protective direction), and therefore the latter allele of this gene was reviewed and those data are presented in Table 5 (p. 33).

Table 5: Studies of depression and APOE ε4 identified post-June 2007 (as at April, 2010).

Author	Year	Sample, place	Measure of depression	Finding
Yung-Chieh et al.	2007	283 (166M) community sample aged 65-75 years, Taiwan	Taiwanese Depression Questionnaire (S-R)[1]	APOE ε4 significantly associated with severe depression, confounded with heart disease.
Irie, et al.	2008	1932 men aged 71 to 90 years, Hawaii	Centre for Epidemiological Studies Depression Scale[1]	Sig. relationship between depression and APOE ε4, with 7.1-fold risk of Dementia in men with both APOE ε4 and depression.
Delano-Wood et al.	2008	323 Alzheimer's Disease Pts, Mean age = 72 years, California	DSM-IV-TR CISD[2]	Sig. higher presence of APOE ε4 in depressed group (n = 61), mostly in women.
Qui et al.	2009	38 depressed "elder" pts without APOE ε4, 14 depressed "elder" pts with APOE ε4, 31 healthy "elder" controls without APOE ε4, North Carolina	NIMH Diagnostic Interview Schedule[1], plus DSM-IV-TR CISD[2]	Depressed Pts with APOE ε4 showed more reduction in hippocampal volume than depressed Pts without APOE ε4 or healthy controls.
Julian et al.	2009	101 Multiple Sclerosis Pts, M age = 46.9 years, NY	Patient Health Questionnaire[1]	APOE ε4 did not significantly predict depression status.
Surtees et al.	2009	17,507 M and F, aged 41-80 years, UK	Mental Health Inventory[1]	No significant relationship between APOE ε4 and depression status.
Slifer et al.	2009	528 Alzheimer's Disease Pts, 524 non-AD controls, 60-89 years, North Carolina	Geriatric Depression Scale[1]	No sig. relationship between depression and APOE ε4 in AD Pts or non-AD controls.
Yuan et al.	2010	37 Pts with geriatric depression, China	DSM-IV-TR CISD[2]	Depressed Pts with APOE ε4 had significantly smaller frontal gyri than depressed Pts without APOE ε4
Elovainio et al	2008	660 young adults 24-29 years, Finland	Beck Depression Inventory[1]	No significant relationship between APOE ε4 and depression.

[1] Self-Report method; [2] Clinical Interview method.

As shown in Table 5, Yen and colleagues (2007) found a significant association between APOE ε4 and depression in their community sample of Taiwanese aged between 65 and 75 years, although the significantly elevated presence of heart disease among the severely depressed participants represents a confound (Steptoe 2007). Irie et al. (2008) examined Hawaiian men aged 71 to 90 and found a significant relationship between presence of the APOE ε4 and depression. In their sample of 323 Alzheimer's Disease patients from California, Delano-Wood and colleagues (2008) also noted a significantly higher prevalence rate of the APOE ε4 genotype among the 61 depressed patients, although this was skewed by gender---women with the APOE ε4 allele were nearly four times as likely to be depressed as women who did not carry that allele. Qiu et al. (2009) examined the links between APOE ε4, depression and reduced hippocampal volume in their sample of "elders" from North Carolina, finding that depressed patients with the APOE ε4 allele had greater reductions in hippocampal volume than depressed patients without the APOE ε4 allele or than non-depressed controls (reductions in hippocampal volume are reliably related to depression, as discussed later in this thesis). Julian et al.'s (2009) study on 101 Multiple Sclerosis patients (Mean age = 49 years, SD = 10 years) from New York failed to find a significant relationship between depression and APOE ε4, as did that conducted by Surtees and colleagues (2009) on a large-scale community sample of 17,507 males and females in the UK. Yuan et al.'s (2010) report of 37 geriatric depressed patients from China indicated that those with the APOE ε4 allele had significantly smaller frontal gyri than depressed patients without the APOE ε4 allele. In an attempt to "resolve" (p. 116) the apparent discrepancy between the results of some studies into the relationship between depression and APOE ε4, Slifer and colleagues

(2009) reviewed "at least nine studies (that) have reported an association between APOE ε4 and depressive phenomenology" (p. 116). However, all of those studies were published prior to 2001 and therefore included in the large meta-analysis conducted by Lopez-Leon et al. (2008), leaving Slifer and colleagues' own data for consideration here. They compared 528 Alzheimer's Disease patients with 524 "cognitively intact controls" (p. 116) aged between 60 and 89 years, and found no significant relationship between the presence of APOE ε4 and depression. Finally (and the only study to use a relatively young sample), Elovianio et al (2008) found no significant association between APOE ε4 and depression in a sample of 660 24- to 29-year old adults in Finland.

From Table 5 it is apparent that no consistent association exists between APOE ε4 and depression. As mentioned earlier, data from Structured Clinical Interviews and self-report scales may be equated with each other, and therefore the findings from all nine studies may be legitimately compared. Perhaps the most conspicuous aspect of these studies is the age of the participants, with (apart from the study by Elovianio and colleagues, 2008) none being less than 40 years of age, and most samples being several decades older. Second, the focus of most of these studies appeared to be upon possible links between APOE ε4, age-related disability and depression, thus providing some challenge for interpretation of the findings for the links between this allele and depression *per se.* That is not a criticism of the research, but rather a limitation of the data's ability to provide an understanding of how these genetic factors might contribute to the development of depression across the lifespan. From these studies, it might be reasonable to conclude that APOE ε4 may be associated with depression, but probably not in the sense of instigating depression at an early age, and also perhaps relying on other age-

related diseases for its link with depression. In addition, in the single study which investigated the links between APOE ε4 and depression among a younger age group, there was no significant relationship found. That conclusion fits with other data indicating that APOE ε4 is the major risk factor for Alzheimer's Disease (Kivipelto, Helkala et al. 2002), a profoundly cognitively damaging illness that may, simply by its effects upon memory and clarity of thinking, contribute to depression, but is probably not associated with the development of depression via increasing susceptibility at younger ages.

4.2.2.3 Guanine nucleotide-binding protein (GNB3)

GNB3, a member of a family of proteins that are intermediate paths for signal transmission across membranes (Rawn 1989), has been associated with other illnesses such as dyspepsia (Oshima, Nakajima et al. 2010), is particularly important in the brain reward system, and has been implicated in affective disorders (Zill, Baghai et al. 2000). The PubMed, Science Direct and Google Scholar search of GNB3 and depression produced only four reports since June 2007 and these are presented in Table 6 (p. 37)

Antilla et al. (2007) included 119 (65 women) Finnish MDD patients (M age = 58 years) who were referred for electroconvulsive therapy (ECT), plus 398 non-depressed control participants (216 males) with an average age of 45 years, and found a significant relationship between the GNB3 C825T allele and depression, but only for female MDD patients. GNB3 was not associated with the ECT treatment response. Kang et al. (2007) recruited 101 MDD patients and examined the relationship between scores on the Hamilton Depression Scale and GNB3 C825T, and also found no significant relationship between this polymorphism and MDD. Prestes et al. (2007) found no significant relationship between presence of GNB3 and depression among alcohol and nicotine

dependent patients nor among non-dependent control participants. Kato and colleagues (2008) specifically examined the links between GNB3 and remission of depression following antidepressant treatment with a sample of 146 Japanese MDD patient, but also reported a lack of significant association between GNB3 and MDD.

Table 6: Studies of depression and GNB3 identified post-2007.

Author	**Year**	**Sample, place**	**Measure of depression**	**Finding**
Antilla et al.	2007	119 MDD Pts (M age = 58 years), 398 Controls, Finland	DSM-IV-TR CISD[2]	Link between GNB3 and MDD for females only.
Kang et al.	2007	101 MDD Pts, Korea	DSM-IV-TR CISD[2] Hamilton Depression Scale (HAMD-21)[1]	No sig. relationship between HAMD-21 and GNB3
Prestes et al.	2007	109 alcohol dependent Pts, 117 nicotine dependent Pts, 108 non-dependent Controls, Brazil	DSM-IV-TR CISD[2]	No sig. relationship between GNB3 and any sample
Kato et al.	2008	146 Japanese MDD Pts.	HAMD[1]	No sig. relationship between GNB3 and treatment response to antidepressants

[1] Self-Report method; [2] Clinical Interview method

Therefore, it must be questioned as to whether GNB3 has a consistent demonstrable association with depression, despite the meta-analytic findings reported by Lopez-Leon et al. (2008) for studies conducted before June 2007. It appears unlikely that all of the four studies published since 2007 that were identified from the search

conducted in April, 2010 were methodologically flawed, even Antilla et al. (2007), where the association was found only for females. GNB3 has a sound hypothetical association with MDD and it is unlikely that there is no effect whatsoever. However, Lopez-Leon and colleagues' meta-analysis for GNB3 was conducted on only three studies, whereas there are four studies described above that were not included in the previous meta-analysis, leaving this hypothesis (at best) unproven.

4.2.2.4 MTHFR 677T

MTHFR 677T is involved in a number of biochemical reactions, some of which influence folate levels (Girelli, Martinelli et al. 2003). Folate is an essential ingredient of human metabolism, assisting with the synthesis of neurotransmitters and gene expression. Deficits in folate have been associated with coronary atherosclerosis (Girelli, Martinelli et al. 2003), schizophrenia (Roffman, Weiss et al. 2008) and depression (Bottiglieri, Laundy et al. 2000). Lopez-Leon et al. (2008) identified six studies on the relationship between MDD and MTHFR 677T and the current search in 2010 found four more. These four are summarized below and in Table 7 (p. 39).

Dempster, Kiss and others (2007) measured the comparative incidence of MTHFR 667T in samples of MDD children (n = 583) and non-MDD children (n = 134) and found no significant difference in the incidence of this genotype across the two samples of children. Slopien, Jasniewiscz et al. (2008) compared the depression status of 172 postmenopausal women with or without MTHFR 677T and found that those women with that polymorphism also had a 5.7-fold increased risk of having depression according to the Hamilton Depression Scale. In their study of 178 MDD patients and 85 non-MDD controls, Hong, Taylor et al. (2009) found no significant relationship between carriers of

the polymorphism and incidence of MDD. Finally, Pan, Quiod et al. (2009) examined the volume of the putamen (a forebrain structure that is associated with neurological disorders) and from 170 MDD patients and 83 non-MDD controls, comparing that putamen volume (which is decreased in depression) with the presence of MTHFR 667T. No significant relationship was found between presence of the polymorphism and putamen volume changes previously reported in depressive patients. These findings provide no consistent support for the presence of an association between MTHFR 677T and depression.

Table 7: Studies of depression and MTHFR 677T identified post-2007.

Author	**Year**	**Sample, place**	**Measure of depression**	**Finding**
Dempster, Kiss et al.[154]	2007	134 MDD children, 583 non-MDD children	DSM-IV-TR CISD[2]	No significant relationship between child MDD and MTHFR 677T
Slopien, Jasniewicz et al.[155]	2008	172 postmenopausal women, 42-65 years, Poland	HAMD[1]	MTHFR 667T women had 5.7-fold increased risk of depression
Hong, Taylor et al.[156]	2009	178 MDD Pts, 85 non-MDD Controls, North Carolina	DSM-IV-TR CISD[2]	No significant relationship between MTHFR 677T and depression
Pan, McQuiod et al.	2009	170 MDD Pts, 83 non-MDD Controls, 60+ years.	Putamen volumes	No significant relationship between MDD and MTHFR 677T

[1] Self-Report method; [2] Clinical Interview method

4.2.2.5 SCL6A3

Despite searching PubMEd, Science Direct and Google Scholar in April, 2010 for studies using the descriptors ‘SCL6A3’ and ‘depression’, only one study was found to be

published since 2007. Dong, Wong et al. (2009) examined a number of potential gene variations for their association with MDD in 272 (66% female) MDD patients and 264 healthy control persons (60% female) recruited in California, and noted that four polymorphisms in SCL6A3 were significantly ($p < .03$) and positively associated with presence of MDD according to patients' DSM-IV-TR diagnosis and elevated Hamilton Depression Scale score. SCL6A3 is a dopamine transporter gene which influences the re-uptake of dopamine from the synapse (Vandenberg, Persico et al. 1992) and has been shown to be implicated in susceptibility for mood disorders (Greenwood, Alexander et al. 2001) and antidepressant actions (Zhou, Zhen et al. 2007).

4.2.2.6 SCL6A4

SCL6A4 encodes the serotonin transporter protein 5-HTT, which is the target of many pharmacological treatments for depression (Routledge and Middlemiss 1996). The gene SCL6A4 encodes the serotonin transporter protein 5-HTT, which carries serotonin (also referred to as 5-HT) away from the synapse after a nerve impulse has transmitted a signal across that synapse. In humans, SCL6A4 resides on chromosome 17q11.1, but its ability to encode 5-HTT is influenced by the presence of the coding sequence 5-HTTLPR in the upstream transcriptional control region. The 5-HTTLPR polymorphism of the gene SCL6A4 may occur in 'short' (*s*) or 'long' (*l*) forms, referring to the number of base pairs (the components of DNA) in each form. The short form has 44 fewer base pairs than the long form (Heils, Teufel et al. 1996). In humans, a person may carry a single short form (*s*), a single long form (*l*), a combination of each (*sl*), or double short (*ss*) or long (*ll*) forms. The short (*s*) form polymorphism of 5-HTTLPR restricts the transcriptional activity of the promoter, producing low functional expression of SCL6A4 and hence

lowering 5-HTT and reducing serotonin reuptake; the long (*l*) form does not have this effect.

Lopez-Leon et al (2008) found 24 studies which investigated the relationships between MDD and SCL6A4, 20 of which had an Odds Ratio greater than 1.0 for the *s* allele versus the *l* allele, but only three of these studies produced statistically significant differences between these two forms. The 2010 search revealed a further six studies, which are summarized below and in Table 8 (p. 43).

Dannlowski, Ohrmann et al. (2007) used 27 MDD patients from Germany and investigated the association between the 5-HTTLPR polymorphism and MDD (assessed via DSM-IV-TR Clinical Interviews). They used increases in amygdala activity in response to emotional stimuli as an indicator of depressive-like behaviour as their Dependent Variable, and found a significant positive relationship between carriers of the short form of the 5-HTTLPR polymorphism and amygdala activity, arguing that this was an indicator of the kind of dysfunctional neural activity during emotional processing that is exhibited by MDD patients. In a similar study, Smolka, Buhler et al. (2007) presented unpleasant pictures to 48 healthy participants and measured activity in the limbic system (amygdala, hippocampus, limbic cortex). They found that there was a significantly higher level of limbic activity to unpleasant stimuli in participants who carried 5-HTTLPR. Responsivity to stress, particularly in the HPA-axis, has been associated with development of MDD in a range of studies that are discussed below (see Chapter 4, section 4.4, pp. 80-101). Segers (2007) found that participants in the East Flanders Prospective Twin Survey who carried 5-HTTLPR showed significantly higher cortisol responses to daily social stressors than non-carriers, thus perhaps contributing to the

possible relationship between genes, environmental stress and MDD. Heinz, Smolka, et al. (2007) also reported a significantly higher amygdala response to unpleasant pictures among carriers of 5-HTTLPR than non-carriers. Lazary, Lazary et al. (2008) investigated the links between MDD and 5-HTTLPR in a sample of 447 female and 120 male Hungarian volunteers without any psychiatric diagnosis. Participants who carried the *s* allele of 5-HTTLPR had significantly ($p < .01$) higher scores on the Zung Self-Rating Depression Scale. As well as investigating SCL6A3, the study described above by Dong, Wong et al. (2009) also found a significant association between SCL6A4 and MDD ($p < .05$).

Table 8: Studies of depression and SCL6A4 identified post-2007 (April, 2010).

Author	**Year**	**Sample, place**	**Measure of depression**	**Finding**
Dannlowski, Ohrmann et al. [164]	2007	27 MDD pts, Germany	Amygdala activity response to emotional stimuli	Significantly elevated amygdala activity response to emotional stimuli in carriers of 5-HTTLPR
Smolka, Buhler et al.	2007	48 healthy Ss, Germany	Limbic response to unpleasant stimuli	Carriers of 5-HTTLPR had significantly higher limbic activity to unpleasant stimuli than non-carriers
Segers	2007	Female twins, Netherlands	HPA (cortisol) reactivity to social stress	Carriers of 5-HTTLPR had significantly higher social stress response than non-carriers
Heinz, Smolka et al.	2007	29 healthy males, Germany	Amygdala activity to unpleasant pictures	Carriers of the short form of 5-HTTLPR had significantly higher amygdala activity to unpleasant stimuli than non-carriers
Lazary, Lazery et al.[168]	2008	447F, 120M community, Hungary.	Zung Self-Rating Depression Scale[1]	Carriers of 5-HTTLPR had significantly higher ZSDS scores than non-carriers
Dong, Wong et al.	2009	272 (66% F) MDD Pts, 264 (60% F) Controls, California	DSM-IV-TR CISD[2] HAMD[1]	Significant link with MDD and HAMD scores in carriers of four polymorphisms in SLC6A4

[1] Self-Report method; [2] Clinical Interview method

4.2.2.7 Other genes

As well as the genes most intensively studied and reviewed above, several other genetic factors have received attention for their role in MDD. Although not intended to be comprehensive, a search of some of these was undertaken at the same time as those above (April, 2010) in order to elucidate the *zeitgeist* in this area. Table 9 presents the results of that attenuated search and may serve as an indicator of the wide range of genes and related factors that have been studied for their relationship with MDD, especially during the last few years. Just in that small sample of 11 research studies since Lopez-Leon et al.'s (2008) major review, nearly 600 genetic factors have been investigated and shown to have an association with depression in a variety of ways, from influencing the transport of serotonin (and thence affecting SSRI efficacy), to affecting the function of the HPA axis, T-cells, the volume of gray matter in the hippocampus and the experience of emotion via the cannabinoid gene, as well as interfering with circadian rhythms. MDD-dependent variables range from scores on standardized tests of depression, psychiatric diagnosis via ICD-10 and DSM-IV-TR clinical interviews, and familial history of depression.

It is clear that this is an active and wide-ranging field of research, although restricted in its findings of how genes are correlated with depression. Three recent genome-wide papers exemplify the relatively weak outcomes of studies of depression which seek to examine the links between the entire genome and the disorder. Shi, Potash et al. (2011) and Shyn, Shi et al. (2011) examined large samples of 1020 and 1221 MDD subjects respectively, with 1636 control subjects, but found no genome-wide significant evidence of an association with depression, despite examining over two million single-nucleotide polymorphisms. Similar findings were reported by Bosker, Hartman, et al. (2011), who examined 92 single-nucleotide polymorphisms

in 1738 MDD cases and 1802 controls. Although four genes were significantly associated with MDD, those authors commented that these "may well be false positives" (p. 516) due to the "heterogeneity of the MDD phenotype as well as contextual genetic or environmental factors" (p. 516).

As suggested by the comments from Bosker and colleagues, the consideration of how genetic and environmental factors (such as stress) may interact to influence the individual's likelihood of developing MDD emerges from these findings of studies of single genes or polymorphisms. That is, although genome-wide studies fail to show clear associations between genes and depression, the examination of how particular genes interact with environmental factors (such as stress) may be more fruitful. That issue will be discussed next.

Table 9: Some recent gene association studies for MDD (April, 2010).

Author	**Year**	**Sample & place**	**Factors identified**	**Links with depression**	**Findings for carriers**
Levinson, Evgrafov et al.	2007	631 European-ancestor families with MDD (*n* = 2161), USA	Single nucleotide polymorphisms on *15q25-q26* chromosome	Previous epidemiological linkage with MDD	Sig. ($p < .000$) link with elevated risk of MDD
Holmans, Weissman et al.	2007	656 families with MDD, USA	*15q25-q26, 17p12*, and *8p22-p21.3* chromosomes	Previous epidemiological linkage with MDD	All 3 chromosomes linked with MDD, but no single chromosome with large risk
Wang, Kamphuis et al.	2008	7 deceased MDD, 7 deceased non-MDD Pts, Netherlands	11 genes that upregulate CRF in hypothalamus; 4 genes that downregulate CRF	Elevated CRH associated with MDD	*CRFR1*, *ESR1*, *MR*, *AVPR1A* increase and *AR* decrease associated with MDD
Wong, Dong et al.	2008	284 MDD Pts, 331 non-MDD, USA	Genes responsible for T-cell function	Inflammation associated with MDD	Two T-cell genes (*PSMB4*, *TBX21*) significantly associated with MDD
Ising, Lucae et al.	2009	339 MDD, 361 Depression, 832 MDD Pts, Germany	328 single-nucleotide polymorphisms (SNP)	Previously linked with MDD	Interaction between multiple gene factors and clinical features
Inkster, Nichols et al.	2009	134 MDD Pts, 143 non-MDD, Germany	*GSK3β* polymorphisms	May determine regional gray matter volumes in MDD Pts	*Rs6438552, rs112630592* linked with reduced hippocampus gray matter volumes in MDD pts
Unschuld, Ising et al.	2009	541MDD Pts, 541 non-MDD, Germany	*GAD-2* gene	Rate limiting enzyme for conversion of glutamic acid to GABA	GAD-2 polymorphisms linked to MDD pts
Polanczk, Caspi et al.	2009	1116F, 1037F, community, NZ	Haplotype of *rs7209436*,	CRH-releasing gene	Haplotype protected women with childhood

			rs110402, rs242924 on CRHR1 gene		maltreatment against depression.
Juhasz, Chase et al.	2009	1520 community, UK	Haplotype of *CB1* cannabinoid receptor gene	CB1 influences emotional behaviour	*CBI* haplotype sig. predicted depression scores on BSI[1]
Segman, Golster-Dubner et al.	2010	9 mothers with post-partum depression, 10 without, Israel	Peripheral blood mononuclear cell gene expression profiles	May be indicator of DNA replication, immune activation, and cell repair processes	425 transcripts sig. correlated with EPDS[2] scores
Soria, Martinez-Amoros et al.	2010	335 MDD Pts, 440 community, Spain	209 single-nucleotide polymorphisms (SNP) of 19 circadian genes	Disruptions in circadian rhythms found in Mood Disorders	CRY1 and NPAS2 SNPs significantly associated with MDD

[1] Brief Symptom Inventory (Derogatis, Lipman et al. 1973); [2] Edinburgh Postnatal Depression Scale (Cox, Holden et al. 1987)

4.2.2.8 Gene-Environment Interactions

While the studies reviewed above in Tables 5 to 9 focussed upon identifying the *specific* genetic factors that are associated with depression, another perspective has attended to the *interaction* of genes and environment that may lead to depression. For example, Lesch (2004) noted the difficulty in identifying specific gene-MDD connections, perhaps due to the fact that depressed persons "differ remarkably regarding the profile of clinical features, severity and course of illness as well as their response to treatment" (p. 174). That is, as noted in the preceding section, the predisposing genetic factors for depression have not been found to function simply in a unilateral fashion, but may interact with environmental events which depressed persons have undergone and which may trigger some symptoms rather than others. Other more recent reviews have drawn similar conclusions.

A paper by Caspi, Sugden, et al. (2003) was the first to postulate the relationship between genetic factors, environmental stress and depression, reporting that the presence of one or two copies of the *s* form of the 5-HTTLPR polymorphism was significantly associated with the likelihood of developing depression when the carrier was experiencing stressful life events. That paper has been cited over 2,000 times and is a landmark in this field. Similar findings were reported by Grabe, Lange et al. (2005) and others, so that (at the time of writing this thesis) 54 unique reports of that association had been published (Karg, Burmeister et al. 2011), including an update by Grabe and colleagues (2011) which confirmed the relationship between 5-HTTLPR, stress and depression in a further 4000 subjects.

In a clear conceptualization of the association between stress, 5-HTTLPR and depression, Uher (2008) argued that it was the *interaction* of genetic and environmental factors over the life course that accounted for the heterogeneous aetiology of depression, thus adopting a bi-directional causality model for the disorder. Uher also made the important point that, although stressful environmental events have been associated with depression, that association does not occur in the absence of pre-existing (genetic) vulnerability, commenting that "no single genetic polymorphism causes depression" (p. 1071). Uher went on to suggest that the variability in efficacy of psychological and pharmacological treatments might be attributable to the different genetic predispositions of individuals. That is, depressed patients who possess genetic vulnerability to depression following adverse life experiences (Uher identified *s* 5-HTTLPR and/or *66met* BDNF as those genetic factors which predispose a person in this way) might benefit more from psychological therapies that provide them with an opportunity to develop a sense of mastery over their environment, plus behavioural strategies to enact that mastery. By contrast, people who are depressed and who carry a genotype that is relatively insensitive to aversive environments (*l* 5-HTTLPR and /or *66val* BDNF) or who have not experienced aversive environmental events, might require pharmacological treatment to modify their symptomatology. Evidence for this hypothesis comes from a later meta-analysis of 34 studies of the interaction between 5-HTTLPR and environmental adversity (Uher and McGuffin 2010) which confirmed the relationship between the length of the 5-HTTLPR polymorphism of this serotonin transporter gene and environmental adversity, leading to depression. An important aspect of Uher and McGuffin's latest review was the comparison of self-reported aversive events and those which can be objectively verified.

While the association between the length of 5-HTTLPR and depression was consistent for the latter measures of adversity, it was inconsistent when self-reports alone were used.

Support for Uher's hypothesis of an association between depression and the short (*vs* long) form of the 5-HTTLPR polymorphism is evident in studies that showed correlations between the occurrence of stressful life events, presence of the *s* 5-HTTLPR allele and depression (Li, Wichems et al. 1999; Barr, Newman et al. 2004; Kendler, Kuhn et al. 2005). Additional support comes from a study of the interaction of very early stressful life events (in the form of childhood neglect), presence of the *s* form of 5-HTTLPR, reduction in hippocampal and prefrontal cortex volumes (also associated with depression) and presence of major depression.

As well as the objective recording of previous 'naturally-occurring' aversive environmental events, the use of laboratory stressors acting as 'contrived' aversive events is another method of controlling the veracity of participants' reports of the occurrence of such events. Gotlib, Joorman, Minor and Hallmayer (2008) genotyped girls with high (n = 25) *vs* low (n = 42) risk of depression (based upon the presence or absence of family history of depression determined via the DSM-IV-TR Structured Clinical Interview for Depression) and subjected them to a standardised stress task consisting of serial subtraction. In that study, girls who were homozygous for the short form of the 5-HTTLPR polymorphism had significantly higher and more prolonged salivary cortisol responses (an index of Hypothalamic-Pituitary-Adrenal Axis activity) to the stressor task than their peers with the long form, although there were no significant effects associated with family history of depression. That study was conducted on females, but Alexander, Kuepper, Schmitz, Osinsky, Koyra and Hennig (2009) used 100 adult males who

underwent a similar laboratory stressor test (public speaking). When grouped according to having had a history of stressful life events (assessed via self-report) and the presence of the *s* or *l* form of 5-HTTLPR, those subjects with a high frequency of stressful life events plus the *s* allele had significantly higher cortisol responses to the stressor than all other groups. Related to this response to environmental stress and the *s* allele of the 5-HTTLPR, Kalbitzer, Erritzoe and colleagues (2010) reported significantly higher incidence of Seasonal Affective Disorder (a form of depression brought about by lack of sunlight in high latitudes during winter) among carriers of the short versus the long form of the polymorphism.

Frodl, Reinhold et al. (2010) noted that children who had *both* the *s* form of 5-HTTLPR *plus* childhood neglect also had smaller hippocampal and left PFC volumes than children who had *either* the *s* form of 5-HTTLPR *or* childhood neglect. Of particular interest, children with the *l* form of 5-HTTLPR and who had experienced neglect had larger PFC volumes, suggesting that this form of 5-HTTLPR may have conferred a preventative effect upon those children who carried it (via greater PFC volumes and consequently increased problem-solving ability for environmentally-presented stressors).

One other gene deserves comment for its relationship with depression. The BDNF *Val66Met* has been mentioned above briefly in conjunction with 5-HTTLPR (Uher 2008). BDNF has been extensively studied for its effects on a variety of functions, including aging and memory (Licinio and Wong 2010). For example, when they used BDNF knockdown by RNA interference and lentiviral injections into the hippocampi of Sprague-Dawley male rats, Taliaz, Stall, Dar and Zangen (2010) noted reduced hippocampal neurogenesis and increased anhedonic-like behaviour (defined as significant

reductions in preference for sucrose, swimming activity in a swim test, and locomotion in the home cage) and concluded that these were indications of depressive behaviour in those rats. However, Kohli, Salyakina et al. (2010) reported that they found no associations between any BDNF polymorphisms and suicide in 178 male and 227 female patients with MDD, but a significant association between the incidence of suicide and combinations of several alleles within the *NTRK2* locus among the same sample (the *NTRK2* locus codes for BDNF receptors). In their summary meta-analysis of the relationships between MDD and BDNF *Val66Met*, Verhagen and colleagues (2010) reviewed 14 studies with 2,812 MDD cases and 10,843 non-depressed control subjects and specifically examined the effects of gender and ethnicity. While the BDNF *Val66Met* was not significantly related to MDD in the total population, it was for men (but not women), perhaps explaining the nonsignificant association between BDNF and MDD that was reported by Kohli and colleagues (2010) in their mixed gender sample. No significant associations were noted for ethnic origin. Verhagen and colleagues argued that their data suggested the presence of different interplay processes between environmental and genetic factors for men and women, particularly in the way that each gender experiences aversive life events and the fact that women generally have larger hippocampi than men. Verhagen and colleagues also noted that depression is characterized by symptoms of (a) behavioural despair (negative mood, hopelessness, agitation, suicidal ideation) and (b) anhedonia, and that these different sets of symptoms are related to different brain regions, with the former linked to the hippocampus-HPA axis (‘stress’ system) and the latter with the ventral tegmental area-nucleus accumbens (VTA-NAc) and ventral tegmental area-prefrontal cortex areas connections (Goldstein,

Seidman et al. 2001). Interestingly, BDNF elicits opposite effects on these two systems: when injected into the hippocampus, its effects are antidepressant, but prodepressive when infused into the VTA-NACv reward system (Martinowich, Manji et al. 2007). BDNF has also been shown to exert epistatic effects upon 5-HTTLPR and another serotonin transport factor gene SLC6A4 (Martinowich, Manji et al. 2007), suggesting that loss of BDNF exacerbates brain monoamine deficiencies and increases stress abnormalities, perhaps contributing to the conditions for development of depression.

4.2.3 5-HTTLPR: Not just a 'vulnerability to depression' gene

As a final observation upon the nature of gene polymorphisms such as 5-HTTLPR, there are considerable data which show that this polymorphism may act to protect as well as expose its carriers to stress, further elaborating the relationship between genes, environmental stress and depression. For example, Pezawas, Meyer-Lindenberg et al. (2008) reported that individuals with two short form alleles were most adversely affected by stressful life events, but individuals with two long form alleles were least affected, thus confirming the 'vulnerability to depression' role of the double short form allele of 5-HTTLPR. However, these double short form carriers were also found to be least depressed when they were not exposed to stressful life events, indicating that the *ss* 5-HTTLPR polymorphism might be more accurately described as a '*sensitive to environment*' genetic factor rather than a 'vulnerability to depression' factor. These findings about the plasticity role of *ss* 5-HTTLPR have been reported elsewhere (Caspi, Sugden et al. 2003), and support the classification of the double short form of the 5-HTTLPR polymorphism as more strongly associated with sensitivity to environment rather than predisposition to depression *per se*. A recent commentary paper suggested

that the *s* allele of 5-HTTLPR may enhance the reactivity of the corticolimbic neural circuitry, thus leading to enhanced responding to both positive and negative stimuli (Murrough and Charney 2011). Further, Homberg and Lesch (2011) argued that this hyperactivity of the corticolimbic regions contributed to hypervigilance, and has been preserved by natural selection because of the advantages that this brings to the individual within a threatening environment. However, when threat is absent, such hypervigilance (and the consequent behavioural manifestations of anxiety) may be self-defeating, perhaps contributing to depressive symptomatology. This issue of the 'evolutionary usefulness' of the *s* form of the 5-HTLPR polymorphism will be revisited later in this thesis.

Finally, as a graphical indicator of the association between the *s* and *l* forms of the 5-HTTLPR polymorphism, environment and depression, Figure 1 (p. 55) is derived from data presented by Eley, Sugden et al. (2004) to demonstrate the interaction between allelle form, environmental risk and proportion of participants who were depressed.

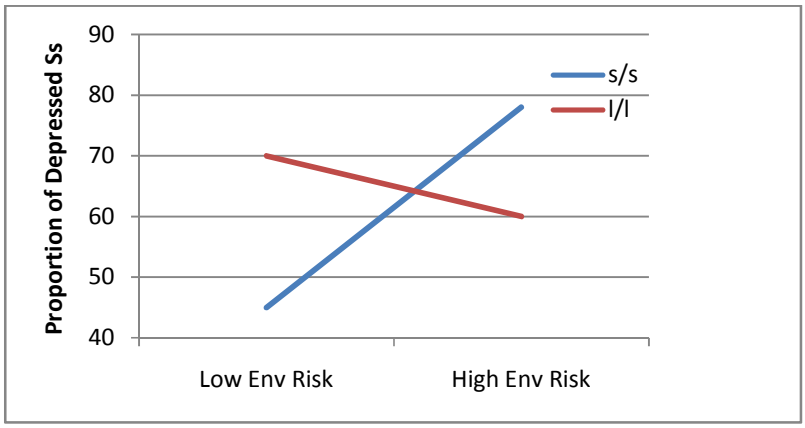

Figure 1: Proportion of female participants with a high level of depression by environmental risk group and 5-HTTLPR genotype (after Eley et al. 2004).

Of interest, the literature suggests that the frequency of the occurrence of the *ss* 5-HTTLPR polymorphism in the normal population ranges between 17.9% (Lazary, Lazary et al. 2008), 17.9% (Vinberg, Mellerup et al. 2010), 19% (Coventry, James et al. 2009), 21.6% (Zalsman, Huang et al. 2006), 23.7% (Brummett, Boyle et al. 2008), 26% (Alexander, Kuepper et al. 2009), 27% (Taylor, Way et al. 2006), 33.1% (Eley, Sugden et al. 2004), and 33.3% (Heinz, Smolka et al. 2007). Although several of these studies also included depressed patients and those who had experienced significant stress, the data presented above and in Table 10 (p. 56) refer to the findings for non-depressed individuals, as extracted from the publication details.

Table 10: Incidence of 5-HTTLPR polymorphism in non-depressed samples.

Author	**Year**	**Population (all non-depressed)**	**Sample size**	**Percent *ss* 5-HTTLPR**
Lazary, Lazary et al.[168, 212]	2008	Caucasian healthy volunteers, Hungary	120M, 447F	17.9
Vinberg, Mellerup et al.	2010	Healthy twins, Denmark	84	17.9
Coventry, James et al.	2009	Australian Twin Registry	1,232	19
Zalsman, Huang et al.	2006	Caucasians, source not stated	125	21.6
Brummett, Boyle et al.	2008	Community volunteers, USA	Caucasian = 203; African American = 85	C = 23.7 A-A = 16.5
Alexander, Kuepper et al.	2009	Healthy male adult volunteers, Germany	100	26
Taylor, Way et al.	2006	Healthy male and female volunteers, USA	51M, 67F	27
Eley, Sugden et al.	2004	Low depression, low risk volunteers, UK	110 (49 F)	33.1
Heinz, Smolka et al.	2007	Healthy male adult volunteers	29	33

The mean sample size of these studies was 265, and the average incidence of the 5-HTTLPR polymorphism was 22.57% (SD = 6.11%). There was a nonsignificant correlation of -.400 between sample size and incidence of 5-HTTLPR. However, due to there being only nine ‘cases’ (i.e., published reports), the fact that the correlation accounted for 16% of the variance might justify further investigation of the variability in 5-HTTLPR incidence shown by the data in Table 10. Where reported, the incidence of 5-HTTLPR among depressed samples ranged from 17.8% (Zalsman, Huang et al. 2006) and 22.5% (Vinberg, Mellerup et al. 2010) to 26.2% (Eley, Sugden et al. 2004).

There are also indications that the 5-HTTLPR polymorphism is associated with other psychiatric disorders (Rutter, Thapar et al. 2009). Recent data suggest that the role of 5-HTTLPR in making individuals who experience aversive events more likely to develop depression may be more accurately related to the presence of methylation of that polymorphism (van Ijzendoorn, Caspers et al. 2010). This issue will be more fully discussed in a later section of this thesis that deals with the ways in which adverse events during childhood influence later vulnerability to depression.

Finally, it should be stated that, although these data are strongly supportive of a role for 5-HTTLPR in depression, the status of that role was challenged by Risch, Herrell et al. (2009), who performed a meta-analysis of 14 studies of the interaction between 5-HTTLPR and depression, and concluded that there was "no evidence" (p. 2,462) for the hypothesis put forward by Uher and others. A similar finding was noted in a meta-analysis of five studies of the interaction between 5-HTTLPR, significant aversive life events and depression, by Munafo, Durrant et al. (2009), who concluded that the "5-HTTLPR and SLE interaction effect is negligible" (p. 217).

4.2.3.1 May, 2011 update

However, in an update of this field in May, 2011, some criticisms were found of the statistical and methodological procedures used by Risch, Herrell et al. (2009) and Munafo, Durant et al. (2009) in their meta-analyses, such as over-selectivity of studies for inclusion, and reliance upon only standardised clinical interviews to assess depression. These criticisms have urged the reinstatement of the original 5-HTTLPR-depression 'interaction' hypothesis (Rutter, Thapar et al. 2009; Rutter 2010). A later comment on this disagreement, plus an examination of 34 observational studies (of the kind used in

the meta-analyses by Risch, Herrell et al., 2009, and Munafo, Durant et al., 2009) by Uher and McGuffin (2010) indicated that the attenuation of the interaction between 5-HTTLPR and depression due to aversive life events (that was reported by Risch et al., 2009, and Munafo et al., 2009) was a function of the kind of assessment devices used to assess the experience of adversity rather than the lack of an association between the polymorphism and depression *per se*.

In a very recent meta-analysis of the association between the 5-HTTLPR polymorphism and depression, Karg, Burmeister et al. (2011) noted that, although there were 54 unique studies of the association between 5-HTTLPR and depression, Risch, Herrell et al. (2009) and Munafo, Durant et al. (2009) had included only 14 and 5 of these studies, respectively. When Karg and colleagues (2011) replicated the meta-analysis with those samples, they also found no significant association between 5-HTTLPR and depression. However, when they included all 54 of the studies that had investigated this association, there was a significant ($p < .00002$) association between the presence of the *ss* allele and depression.

One challenging comment regarding the veracity of data gleaned from large-scale meta-analytic studies such as these was put forward by Caspi, Harari et al. (2010) that "the purely statistical approach is not sufficient, or necessary…" (p. 521) for this task. On that basis, the summation of findings via alternative methods such as tabulation and discussion, may be justified.

In addition to these refutations of the two papers which challenged the link between stress, 5-HTTLPR and depression, data continue to accumulate regarding the association between 5-HTTLPR and reactivity to stress. For example, the previously-

reported association between allele type and responsivity to negative emotional information when under stress (Gotlib, Hamilton et al. 2010) was confirmed to act via increased cognitive attentional bias for negative information when subjects were under stress, at least in females who carried the *ss* allele of the 5-HTTLPR polymorphism (Markus and De Raedt 2011). Allied to the kinds of neuroanatomic changes that accompany depression and which are discussed later in this thesis, Selvaraj, Godlewska et al. (2011) studied 113 non-depressed volunteers (43 females) with a mean age of 37.6 years, and noted that carriers of the *s* allele of the 5-HTTLPR polymorphism had significantly less regional gray matter volume in the anterior cingulate (responsible for integration of emotional and cognitive information) than carriers of the *l* allele, perhaps predisposing the *s* carriers to less effective interpretation and emotional management of aversive information. Mueller and colleagues (2011) found a significant interaction between the 5-HTTLPR genotype and the response to stressful life events, but only for young adults who had experienced the stressful life events during the first five years of their lives, suggesting a role for specific ages and type of stressors in the association between the *ss* allele and depression.

4.2.4 Summary of the role of genes in depression

The strong familial effect for depression is most probably a function of both genetic and environmental factors such as family discord and parental behaviour patterns. Although there are several genes that have been shown to make their carriers more vulnerable to depression regardless of environmental pressures, the presence of environmental stress is also a necessary factor in the equation between other genetic factors and depression. At least one of the principal genes associated with depression

(i.e., 5-HTTLPR) may be more accurately described as a ‘plasticity’ gene rather than a ‘vulnerability’ gene (Eley, Sugden et al. 2004; Taylor, Way et al. 2006; Zalsman, Huang et al. 2006; Wilhelm, Siegel et al. 2007; Brummett, Boyle et al. 2008; Lazary, Lazary et al. 2008; Coventry, James et al. 2009; Vinberg, Mellerup et al. 2010), and may confer protective effects as well as vulnerability effects upon its carriers depending upon the kinds of environmental events experienced. The identification of these genetic factors and the roles they play in the development of depression helps to clarify this aspect of the biological underpinnings of depression.

From this first step in determining how depression occurs, it may be concluded that genetic factors may influence the likelihood of depression in two ways. First, some genes or genetic factors appear to predispose individuals who carry them to become depressed. For example, Tables 5 to 9 show about 600 genetic factors that have been associated with depression to at least some extent, and it may be that at least some of these are responsible for the presence of melancholic depression, with its strong physiological aspects and resistance to verbal therapies. Second, other genetic factors may encompass certain inherited characteristics that play a ‘set up’ role for the later development of depression by making some individuals more/less vulnerable and responsive to environmental events. If those events are predominantly negative, then the likelihood of depression developing is increased.

From the data reviewed in this section, it is apparent that the pathway by which genes influence an individual’s predisposition to develop depression in response to stress is principally via alterations to neurotransmitters such as serotonin and their receptors. It is therefore relevant to comment on how neurotransmitters impact upon brain function

and how these functions (and their impairment) are related to depression. Therefore, the next section of this chapter on biological pathways to depression will consider the role of neurotransmitters, and how alterations in their concentration are related to mood, or at least to some of the symptoms of depression.

4.3 Neurotransmitters and depression

4.3.1 The brain as the seat of emotion, mood and depression

As indicated above, depression is primarily a disorder of mood or emotion. Emotion has been described as having three major components (Heilman 1997). These are: emotional *behaviour* (changes in physiology induced by the autonomic nervous system), emotional *communication* (words, facial expressions, gestures), and emotional *experience* or feelings (Thompson 2000; Bear, Connors et al. 2007; Purves, Augustine et al. 2008). Of these three components, it is the neurological *experience* of emotion (i.e., how the individual 'feels') that is most relevant to a discussion of depression.

Emotional *experience* may be represented by synaptic phenomena in the brain which are associated with particular feeling states (Bear, et al, 2007), and may consist of any of the three primary emotions anger, fear and joy (Epstein 1984), plus those secondary emotions which may include guilt, sadness, melancholy and embarrassment (Ekman 1992). Many of these emotions are incorporated in the ICD and DSM definitions of depression; therefore, the communication between various brain regions that occurs during the experience of emotion becomes relevant to this discussion of the biological bases of depression.

4.3.2 Major brain regions involved in depression

The accepted symptomatologies of depression (i.e., DSM, ICD) highlight the central presence of apathy and anhedonia. These have been localized to the 'reward system' in the limbic region, specifically the loop between the nucleus accumbens, the ventral globus pallidus and the anterior cingulate gyrus. These loops are heavily involved with dopaminergic communication systems (Lieberman 2006) and have been called the "neural circuitry of depression" (Nestler, Barrot et al. 2002, p. 16). In addition to these specific regions that are linked with depression, other regions have also been associated with the disorder. For example, Siegle, Thompson, Carter, Steinhauer and Thase (2007) found that blood flow increased in the amygdala and decreased in the dorsolateral PFC in depressed patients compared to non-depressed subjects. Quirk and Gehlert (2006) noted that there were four potential pathways between amygdala malfunction and psychopathological states. Nitschke and Mackiewicz (2005) described the lack of volition (i.e., apathy) in depression as involving the dorsolateral PFC and the anterior cingulate cortex.

Because apathy prevents depressed persons from taking action to reduce their depressive behaviour and increase action plans for finding more productive strategies (APA, 2000), these key areas may be the neurobiological sites which, when they malfunction, restrict depressive patients from undertaking successful self-activated behaviour change aimed at relieving depressive symptoms (Nitschke & Mackiewicz, 2005). This hypothesis has been supported by a study of the dysregulation of the influence of the dorsolateral PFC on the anterior cingulate cortex (Schlosser, Wagner et al. 2008). Additionally, deep brain stimulation of the cingulate gyrus of depressed

patients produced increases in metabolic activity and remission of depression in 35% of that sample within one month of treatment (Lozano, Mayberg et al. 2008). Similar reductions in depressive symptoms were reported by Friedman, Frankel Flaumenhaft and colleagues (2009) following electrical stimulation of the ventral tegmental area in rats.

A major review of the neurobiology of depression (Maletic, Robinson et al. 2007) proposed a model of MDD in which a circuit including the prefrontal cortex, amygdala and hippocampus influenced not only mood regulation, but also learning and contextual memory processes. Specifically, during MDD, the ventromedial prefrontal cortex (VMPFC) and lateral orbital prefrontal cortex (LOPFC) are hyperactivated and the dorsolateral prefrontal cortex (DPFC) is hypoactivated (Drevets 1998). These changes are consistent with the symptoms of MDD because hyperactivation of the VMPFC is associated with sensitivity to pain, anxiety, depressive ruminations and tension; and hypoactivity of the DPFC is associated with psychomotor retardation, apathy, and deficits in working memory and attention (Maletic, et al, 2007).

Studies of the connectivity between these areas have also suggested that decreased communication between the amygdala and anterior cingulate complex (ACC) is present in MDD (Anand, Li et al. 2005). Because the ACC assists in emotional regulation (Whittle, et al., 2006), decreases in communication efficacy between it and the amygdala could be involved in the disruption of mood that is a symptom of MDD (Malatic, et al, 2007). Maletic and colleagues offered a diagrammatic model of this process (see Figure 2, p. 64), in which connectivity is disrupted between the integrative and executive functions of the lateral orbital PFC, rostral PFC, medial PFC, dorsolateral PFC and dorsal ACC on one hand, and the emotional/visceral functions of the ventral

ACC and ventral medial PFC plus the hippocampus, amygdala and nucleus accumbens on the other hand. This disruption produces a lack of regulatory feedback from the former 'rational' regions to the latter 'emotional' regions, which in turn allows the latter to dominate control of the hypothalamus and consequent neuroendocrine activity, leading to sympathetic nervous system (SNS) responses. This hypothesis will be further examined later in this chapter, but the point of most relevance here is the linking of impaired communication between certain brain regions and the presence of depression. That impairment in communication is a direct outcome of reductions in available neurotransmitters, thereby focusing this discussion on the nature, function and causes of impairment of those neurotransmitters.

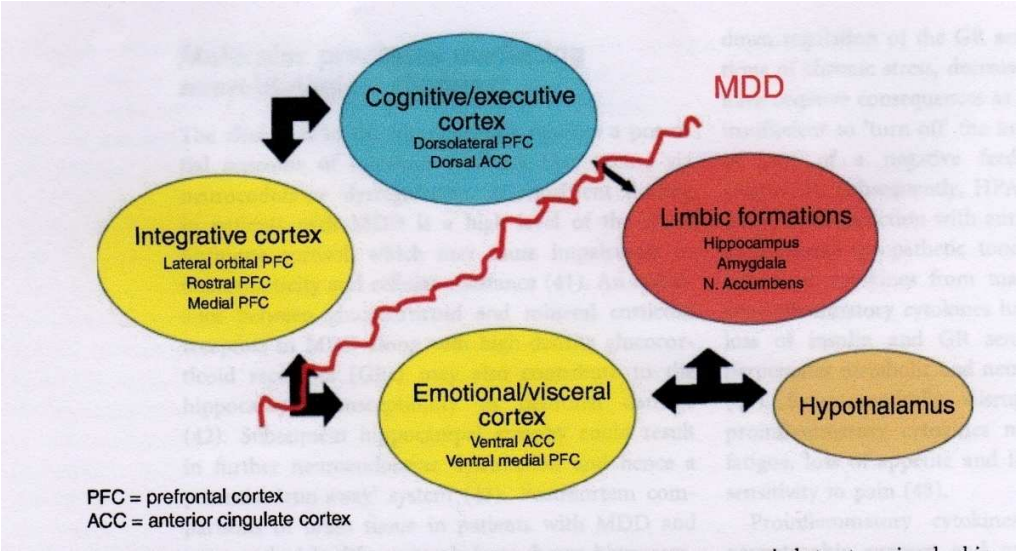

Figure 2: Interconnectivity dysregulation in MDD (Maletic, et al., 2007, p. 2033)

4.3.3 Neurotransmitters

Although some emotions and aspects of mood may be influenced by the actions of hormones that are synthesized outside the brain (e.g., adrenalin from the adrenal glands), those hormones result from downstream activation by trophic hormones that are secreted by the brain itself. The agents that are primarily responsible for communication between brain regions (and most synapses elsewhere in the body) are the neurotransmitters, of which there are over 100 (Purves, Augustine et al. 2008). However, the major neurotransmitters that have been associated with depression are serotonin, dopamine, noradrenalin, and (although less widespread and established in research) GABA and glutamate. All of these except GABA are excitatory in their effects upon the postsynapse; GABA is inhibitory. Following a brief explanation of the ways in which neurotransmitters are synthesised, deployed and reclaimed, each of these five major neurotransmitters will be briefly described before a consideration of the role of decrements in these neurotransmitters in instigating or exacerbating depression.

In general, neurotransmitters are synthesized in presynaptic nerve endings and neuronal cell bodies and stored in vesicles in the axon for release at the synapse. Neurotransmitters fall into three categories: amines (including serotonin, noradrenalin and dopamine), amino acids (GABA, glutamate) and neuropeptides (Nolte 2009), and are synthesized in several different ways and released into the synapse. After being released into the synapse, neurotransmitters contact receptors on the postsynaptic side of the synaptic cleft and cause the transmission of the potential across the synapse and thus transmission of nerve impulses. Once this has occurred, neurotransmitters need to be quickly removed so that they will not block the receptor sites for future bursts of

neurotransmitters. This removal occurs via multiple processes, including diffusion, reabsorption into the presynaptic ending or being taken up by neighbouring glial cells, or in the postsynaptic process; sometimes, enzymes degrade the neurotransmitter.

4.3.3.1 Serotonin, also called 5-Hydroxytriptamine (5-HT), is the predominant cohesive neurotransmitter system in the brain and innervates all brain areas (Delgardo and Morena 2006), with projections from the raphe nuclei to most other regions (Hornung 2003). Figure 3 shows the distribution of the serotonin transmitter system in the brain.

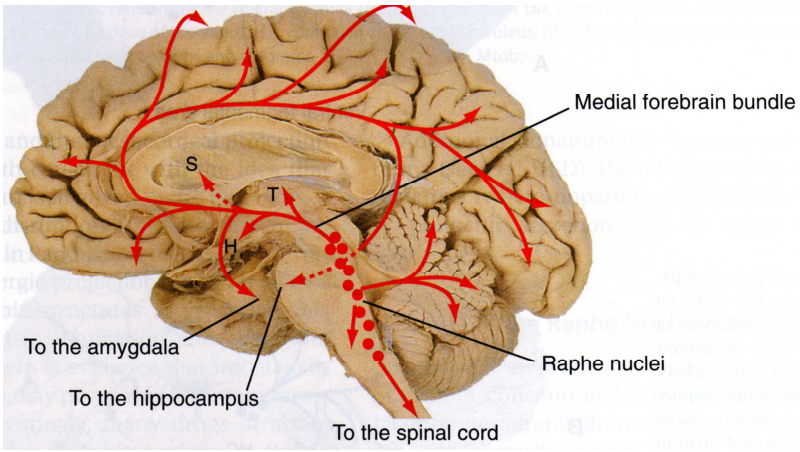

Figure 3: Serotonin transmitter system in the human brain (Nolte 2009).

5-HT is synthesized in platelets from dietary tryptophan and occurs in the greatest concentrations in the wall of the intestine, blood and in the CNS (Twarog and Page 1953), but it is the latter that is relevant here. Despite only about 1% of the total body supply of 5-HT being in the brain, it is widely distributed there (Steinbusch 1981) and is an important CNS neurotransmitter (Cooper, Bloom et al. 2003).

Changes to serotonin have been shown to influence the core behavioural and somatic functions that underlie depression in laboratory animal studies, including appetite, sleep, sex, pain response, body temperature and circadian rhythm (Maes and Meltzer 1995). Human postmortem studies have shown lowered levels of serotonin in depressed patients (Stockmeier 2003; Reimold, Batra et al. 2008), and even in studies of reduced emotional processing (Cowen 2008), although serotonin depletion studies indicate that reduced serotonin function may be a necessary, but not a sufficient, condition for depression (Delgardo 2004). Indicative of the complex relationship between levels of serotonin and depression, some data have demonstrated that depressed patients who are not receiving medication have serotonin levels twice as high as non-depressed control subjects (Barton, Esler et al. 2008) and that, while high serotonin in some brain regions may lead to improved mood, it may also be associated with depression when present in other brain regions (Forster, Feng et al. 2006).

4.3.3.2 Noradrenalin (NA) is also a major neurotransmitter, with NA neurons spreading from the brain stem to almost all brain areas (Figure 4, p. 68) and modulating the functioning of the prefrontal cortex (which uses working memory to regulate behaviour and attention), as well as having an important role in the acquisition of emotionally-arousing memories (Delgardo & Marena, 2006). NA is also produced in synaptic vesicles in noradrenergic neurons in sympathetic ganglia.

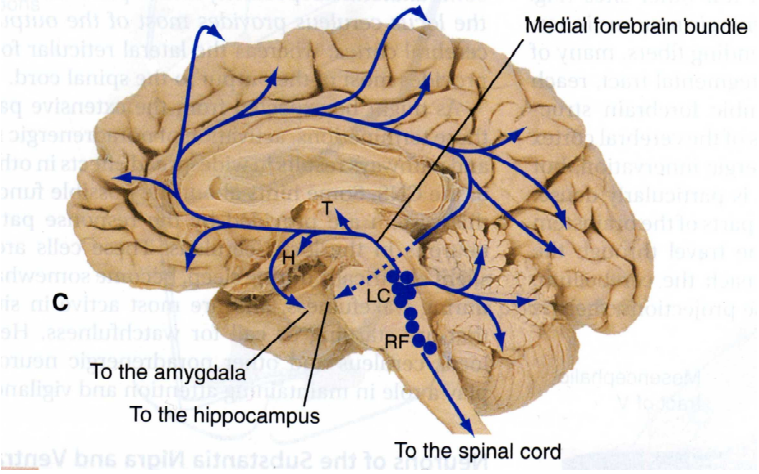

Figure 4: Noradrenergic transmitter system in the human brain (Nolte, 2009).

4.3.3.3 Dopamine (DA) is synthesized by dopaminergic neurons, stored in vesicles and released in the same way as 5-HT and NA. DA is less well-distributed than 5-HT and is mostly found in the corpus striatum, limbic system and hypothalamus. DA modulates activity primarily in brain areas involved with reward and motivation, working memory and attention (Chen and Zhuang 2003), and has been implicated in the development of depression (Willner 1983), although postmortem and depletion studies have been equivocal (Delgardo & Mareno, 2006). Figure 5 (p. 69) shows the dopaminergic transmitter system in the human brain.

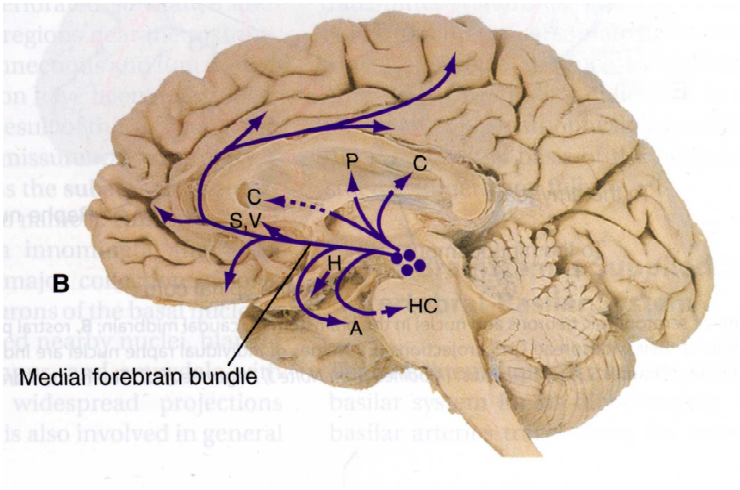

Figure 5: Dopaminergic pathways in the human brain (Nolte, 2009).

4.3.3.4 Glutamate is one of the small molecule neurotransmitters which act very quickly as exciters, allowing rapid nervous system responses, including transmission of signals from the senses to the brain and motor signals back to muscles (Guyton and Hall, 2006). Neuronal glutamate is derived from glutamine (Bear, Connors et al. 2007). Glutamate (which later produces GABA) is secreted by the cytosol of the presynaptic terminals in sensory pathways and the cerebral cortex and is stored in transmitter vesicles in the presynaptic terminal. As for 5-HT, NA and DO, storage vesicles release glutamate into the synaptic gap when an action potential reaches the presynaptic terminal. Glutamate is taken up post-synaptically by amino acid transporters in neurons and glial cells.

4.3.3.5 GABA (gamma-aminobutyric acid) is also a small, fast-acting amino-acid neurotransmitter that is derived from glutamate via the enzyme glutamic acid decarboxylase in GABA-ergic neurons (Jaume 2007), stored in synaptic vesicles and then

secreted in their axon terminals in the spinal cord, cerebellum, basal ganglia and cortex upon depolarisation. With glycine, GABA is one of the two major inhibitory neurotransmitters of the CNS (Bear, Connors et al. 2007), although GABA is more concentrated in the telencephalon (cerebral cortex, basal telencephalon) and diencephalon (thalamus and hypothalamus), whereas glycine is present mainly in the spinal cord (Burt 1993). GABA has been described as "the major source of synaptic inhibition in the nervous system" (Bear, Connors et al. 2007). After GABA has interacted with receptors at the postsynapse, it is taken up amino acid transporters, both in neurons and glial cells.

4.3.4 How decreased concentration of certain neurotransmitters may cause depression: The 'Monoamine Hypothesis'.

The 'Monoamine' model of depression suggests that general deficits of the monoamine neurotransmitters 5-HT, NA and DA in the brain lead to depression (Schildkraut 1965; Coppen 1967). Glutamate and GABA may also be added to this list of relevant neurotransmitters. The reduction in these monoamine neurotransmitters is often brought about by Monoamine Oxidase (MAO), an enzyme that degrades monoamines for resynthesis of their components. MAOs are of two types: AO-A and AO-B, both of which act upon NA and DA, but AO-A also acts upon 5-HT (Rang, Dale et al. 2007). Other agents may also contribute to this removal of neurotransmitter process. For example, serotonin is transported back into the presynaptic terminal by specific serotonin transporters as well as Monoamine Oxidase (MAO); noradrenaline and dopamine are quickly transported back into the presynaptic ending for repackaging into the storage vesicles; GABA and glutamate are removed from the synaptic cleft into glial cells by amino acid transporters.

The principal evidence base for the Monoamine Hypothesis lies in the effects of monoamine oxidase inhibitors (MAOs) and other substances designed to disrupt MAO efficacy, leaving higher levels of neurotransmitters available to the synapse and theoretically lowering the likelihood of depression. There are several categories of these substances that interfere with the actions of MAOs, all of which have been developed as antidepressant medications, and some of these will be described below to elaborate the links between reduced levels of 5HT, NA and DA with depression. The logic describing the link between reductions in available neurotransmitters and depression is via research which aims to demonstrate that re-establishment of neurotransmitter concentrations by interferences with the degradation functions of MAOs and other agents also results in reduced depressive symptomatology.

4.3.4.1 MAOI efficacy and side effects

First reported by Bloch, Doonief, Buchberg and Spellman (1954) and Zeller (1963) from serendipitous observations, the MAOI *iproniazid* reversed the effects of *reserpine* (used to treat high BP) which had been shown to cause psychotic depression in some cases (Potter, Padich et al. 2006). However, *iproniazid* has major hepatotoxic side effects and was replaced by *phenelzine* and *tranylcypromine*, although some of these also produced hypertension (Rang, et al. 2007). Other MAOIs include *moclobemide, mianserin, trazodone, mirtazapine* and *hyperforin* (the active ingredient in the herb St John's Wort).

MAOIs act quickly to increase 5-HT (strongest effect), NA, and DA (least effect) in the cytoplasm throughout the body, causing increases in motor activity and elevated mood in non-depressed persons (Rang, et al., 2007), although reduction of depression

takes several weeks in patients. Side effects include hypotension, tremors, insomnia, increased appetite (weight gain), dry mouth, blurred vision, urinary retention, plus headaches when taken with some food substances that include tyramine (e.g., cheese, Vegemite).

4.3.4.2 Tricyclic and Tetracyclic antidepressants (TCAs)

Also discovered by accident, *imipramine* was found to reduce depressive symptoms (Kuhn 1958), as did other similarly constructed drugs which had three contiguous rings (*tri*-cyclic). This class of drugs includes *desipramine, amitriptyline, nortriptyline, clomipramine, doxepin, protriptyline, amoxapine, maprotiline*, and has dominated pharmacological treatments for depression for about 30 years (Potter, et al. 2006). TCAs act to inhibit the transporter proteins that uptake NA and 5-HT from the synaptic cleft, leaving more of these neurotransmitters to facilitate mood (mostly attributed to 5-HT) and reduce somatic symptoms of depression (NA).

Although generally successful in treating depression, TCAs also produce unwanted side effects including sedation, confusion and problems with motor coordination, which pass after a few weeks at about the same time as the antidepressant effect begins to take place (Rang, et al. 2007). Other lasting side effects are dry mouth, blurred vision, constipation and urinary retention, drowsiness and difficulty concentrating. Some patients experience ventricular dysrhythmias, and TCAs also exacerbate the effects of alcohol, anesthetics and antihypertensive drugs (Rang, et al. 2007).

4.3.4.3 SSRIs, NRIs, SNRIs

Selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), or combinations of both (SNRIs) such as *fluoxetine, duloxetine, fluvoxamine, paroxetine, nefazodone, citalopram, paroxetine, venlafaxine* and *sertraline* are the most commonly prescribed antidepressants (Shelton and Lester 2006), mainly due to their intensive use in primary care settings since 1998 (Olfson and Marcus 2009). As indicated by their name, these drugs act upon 5-HT and NA rather than DA (although NRIs also have an affinity for DA) (Shelton and Lester, 2006), and have fewer side effects than MAOIs or TCAs (Rang, et al. 2007) while being just as effective in treating moderate depression (hence their high rate of use in primary care) but not so effective for severe depression (Rang, et al. 2007). They also have a delay of about two to four weeks in treatment effects.

Side effects of SSRIs, NRIs and SNRIs include nausea, anorexia, insomnia, loss of libido and failure to reach orgasm and may, when combined with MAOIs, cause tremor, cardiovascular collapse and hyperthermia (Rang, et al. 2007). While these side effects are rarer than for MAOIs or TCAs, and therefore these newer antidepressants are better tolerated by patients (Olfson and Marcus, 2009), SSRIs have been associated with an increased risk of suicide (Gunnell, Saperia et al. 2005).

Finally, to further emphasize the side effects of each of these classes of antidepressant medication, it is worthwhile noting that the levels of side effects reported in the literature and derived from patients' records probably represent only 5% of the actual side effects experienced and reported by patients themselves (Zimmerman, Galione et al. 2010). These data suggest that the efficacy of antidepressants needs to be

high so as to justify their application for depression, and that issue is discussed in detail later in this section.

4.3.4.4 Glutamate and GABA.

Malfunction of these two neurotransmitters upsets their balancing excitatory (glutamate) and inhibitory (GABA) effects upon brain synaptic activity, supporting potential links to depression via loss of cognitive ability (Cryan and Kaupmann 2005), neuron and glial apoptosis (Rajkowska, Miguel-Hidalgo et al. 1999; aan het Rot, Mathew et al. 2009), dysregulation of growth factors in the brain (Evans, Choudary et al. 2004), interference in neuronal firing (Choudary, Molnar et al. 2005) and decreased serotonin and noradrenaline expression (Nishikawa and Scatton 1983; Muller and Schwartz 2007).

Several studies have demonstrated that depressed patients experience malfunction of GABA and glutamate systems (Sanacora, Mason et al. 1999; Auer, Putz et al. 2000; Sanacora, Mason et al. 2000; Mason, Anand et al. 2001; Sanacora, Gueorguieva et al. 2004; Choudary, Molnar et al. 2005; Bhagwagar, Wylezinaka et al. 2007; Hasler, Willem van der Veen et al. 2007). A major recent review of the role of GABA in depression (Luscher, Shen et al. 2011) concluded that, as well as being implicated in depression, GABA "has a prominent role in the brain control of stress, the most important vulnerability factor in mood disorders" (p. 383).

Glutamatergic drugs which target glutamate receptors (AMPA, NMDA and KA) may enhance synaptic signalling within the glutamate system. Price, Shunga et al. (2009) found decreased levels of GABA in treatment-resistant depressed patients, arguing for consideration of antidepressants which focussed upon re-establishment of GABA. However, no trials of the effects of medications based upon these data that support

GABA's role in depression have yet been reported (Sen and Sanacora 2008), although preclinical data suggest that common antidepressants may counter deficits in GABA (Luscher, Shen et al. 2011).

4.3.5 The test of the Monoamine Hypothesis

4.3.5.1: Do pharmacological antidepressants work?

Hollon, Thase and Markowitz (2002) claimed that antidepressants represent the current standard of treatment for major depressive disorder, and Thase and Denko (2008) argued that the application of antidepressant medication during the initial or acute phase of MDD represented the only justifiable course of treatment. These firm positions on the role and efficacy of antidepressants reflect one side of the argument regarding the validity of the monoamine hypothesis of depression, and are based upon a great deal of data supporting the use of antidepressants to re-establish neurotransmitter levels in the brain and thereby improve mood. As recently noted by Fournier, de Rubeis, et al. (2010) there are "thousands of controlled clinical trials" (p. 47) that show antidepressants to be superior to placebo. It is beyond the scope of this thesis to review all of those studies, but an overview of some major findings that are most relevant to this thesis will help in this examination of the monoamine hypothesis.

For example, in terms of the preceding section of this thesis, it has been shown that the efficacy of antidepressants increases with the presence of specific genes (Horstmann and Binder 2009). In regard to the following discussion of the role of stress in depression, Wichers, Barge-Schaapveld et al. (2008) noted that antidepressants reduced patients' sensitivity to stress and increased their sensitivity to rewards, thus contributing to an increased hedonic capacity (anhedonia is a major symptom of MDD).

Further, in terms of MDD symptomatology, Bruhl, Kaffenberger and Herwig (2010) found that a single dose of either a 5-HT or NA reuptake inhibitor caused significant increases in patients' speed of emotional processing, thus potentially assisting patients to respond appropriately to environmental stressors that might otherwise cause distress and depression.

However, data also exist that challenge the efficacy of antidepressants. For example, Kirsch, Scoboria et al. (2002), noted that 57% of the "thousands of controlled clinical trials" supporting the efficacy of ant idepressants over placebos failed to show a significant difference between the effects of drugs and placebos, and only 10% to 20% of patients in that 57% of trials showed a true drug effect, leaving between 80% and 90% of patients who failed to respond to the antidepressant. A review of the effectiveness of antidepressants on adults revealed that, while they had a statistically significant superiority over placebo, the difference (1.7 points on the 52-point Hamilton Depression Scale) was "clinically negligible" (Kirsch, Scoboria et al. 2002, p. 1; Moncrieff and Kirsch 2005). Kirsch's findings have been supported more recently by Moncrieff, Wessely and Hardy's (2010) Cochrane review of the relative effectiveness of active placebos and antidepressants.

Further challenging the role of neurotransmitters in depression, several commentaries have noted that, while the evidence supporting use of antidepressants is based upon clinical trials, this methodology is flawed because it does not represent everyday clinical practice (Parker 2004; Hatcher 2005). In addition, antidepressants elevate the levels of monoamine neurotransmitters within a few days but do not alter mood for several weeks (Bear, et al. 2007), leading Rang, et al. (2007, p. 558) to

conclude that monoamines may be “regulators of longer-term trophic effects” rather than having a direct and immediate influence upon mood.

Perhaps the most indepth discussion of this issue has been in a detailed meta-analysis by Kirsch (2009) who, as well as arguing that the effects of antidepressants were only minimally greater than placebo, also suggested that the original data on which the monoamine hypothesis was based consisted of a few clinical impressions of serendipitous patient responses to various drugs that were not (at the time) intended to function as antidepressants. Kirsch’s comments are not without their critics however, and Moller (2008) has argued that Kirsch’s use of meta-analyses as a basis for concluding that antidepressants may be ineffective is flawed, and that systematic reviews of the data and reliance on the use of ‘clinical judgment’ in everyday practice are more relevant to the evaluation of the role of MAOIs in depression (p. 454). Further, Oken (2008) reviewed placebo research and reported that several neurotransmitter systems were altered by administration of placebos, suggesting that the comparative efficacy of placebos *vis-à-vis* antidepressants may be a result of the effectiveness of placebos rather than a reflection of the ineffectiveness of antidepressants.

One recent review of the effectiveness of antidepressants may hold the key to reconciling the apparent differences in the literature regarding their efficacy for depression. Fournier, de Rubeis, et al. (2010) screened the literature from 1980 to 2009 for randomized control studies that compared the effects of placebos and antidepressants on patients who were classified as having mild, moderate and severe depression as indicated by their scores on the Hamilton Depression Rating Scale (HDRS). From 2,164 studies identified, Fournier and colleagues excluded 2,158, leaving only 6 that met their

criteria of: randomization, use of placebos, use of an FDA-approved antidepressant, having a full range of patient depression severity, including only adult outpatients, using a treatment that lasted for at least 6 weeks, applying the HDRS at intake and end of treatment, and reporting patient-level data so that individual responses could be used in the overall review analysis. These 6 studies had a total of 434 patients who received antidepressants and 284 who received placebos, with HDRS scores ranging from 10 to 39 (HDRS scores of 8 to 13 = mild depression, 14 to 18 = moderate depression, 19 to 22 = severe depression, 23+ = very severe depression). Regression analysis indicated that there were no significant drug effects for patients with mild, moderate or severe depression, but large effects for patients with very severe depression. That is, although these data suggest that, in order for antidepressants to demonstrate greater efficacy than placebos, patients must have extremely severe depression, Fournier, et al. (2010) commented that "the majority" of patients receiving antidepressants in everyday clinical practice do not meet this criterion (p. 52). However, despite the attractiveness of this finding by Fournier et al., several criticisms have been made of the methodology used (e.g., the elimination of 99.7% of identified studies) (Elkin 2010; Finkelstein 2010; Gotzsche 2010; Suzuki, Uchida et al. 2010), thereby challenging Fournier et al.'s conclusions and leaving the comparative efficacy of antidepressants over placebos open to further argument and investigation.

A more recent review of four meta-analyses of the efficacy of drug treatments for depression (Pigott, Leventhal et al. 2010) supported Kirsch and others' findings that antidepressants were only marginally better than placebos as treatments for depression (Kirsch, Moore et al. 2002). Piggott and colleagues also found that there was a clear

publication bias in favour of drug treatment trials with positive outcomes, a finding also reported previously by Rising et al. (2008), who noted that studies which showed positive outcomes from medication for depression were nearly five times more likely to be published than studies which had negative outcomes. This overview of previous meta-analyses seriously challenges the efficacy of drug treatments for depression and suggests a closer examination of the hypothesised causal links between reinstatement of neurotransmitters and alleviation of depression.

4.3.5.2 Are neurotransmitters really associated with depression?

A further challenge to the monoamine model of depression comes from studies in which various neurotransmitters that are hypothesized to be linked with depression are artificially reduced in non-depressed research participants, and comparisons are made between pre- and post-change in mood. This kind of research is called a 'depletion' study because it aims to reduce the levels of a targeted neurotransmitter in participants by administering an agent that blocks the source of that neurotransmitter. For example, administration of a tryptophan-free amino acid mixture will reduce tryptophan and thence 5-HT. Similar effects are found for NA and DA following administration of blocking agents (such as reserpine).

To determine if data from this kind of research provided support for the monoamine hypothesis, Ruhe, Mason et al. (2007) conducted a meta-analysis of 90 depletion studies performed between 1966 and 2006. They found that the depletion of the monoamine systems 5-HT, NA and DA did not decrease mood in healthy controls, but that MDD patients who were in remission showed moderate decreases in mood following depletion, especially during the first five months after remission. Those authors

concluded that “Although previously the monoamine systems were considered to be responsible for the development of MDD, the available evidence to date does not support a direct causal relationship with MDD.” (p. 354).

4.3.6 Summary of the role of neurotransmitters in depression

The essence of the information reviewed above is that, although there are data showing that antidepressants do increase levels of 5-HT, NA and DA in some depressed persons, that some patients appear to show minor improvements in mood from these medications, and that there is a basis for assuming that antidepressants may be advisable for patients with very severe depression, it has yet to be proven that antidepressants have clinically significant effects on a reasonably large section of the depressed patient population as to justify their prescription for many cases.

In addition, although decreased levels of 5-HT, NA and DA (and perhaps glutamate and GABA) have been observed in depressed patients, deprivation of those neurotransmitters does not decrease mood in healthy persons. Further, the fact that antidepressants increase neurotransmitter concentrations within a few days but do not reduce depressive symptoms until several weeks after commencement of administration, argues that it may not be the antidepressant *per se* that is ‘treating’ the depression, but that the treatment path between antidepressants and alleviation of symptoms may be more complex than suggested by the Monoamine hypothesis.

From these considerations, it is appropriate to conclude that the precise role and efficacy of neurotransmitters in general depression is yet to be demonstrated. It may be that, like some of the genes described earlier in this thesis, neurotransmitters make a

contribution to the causal chain that is responsible for depression, or they may be affected by depression, but they are not the sole (or even primary) cause of that disorder.

These findings regarding the equivocal role of neurotransmitters in depression lead back to a further consideration of the links between genetic factors and environmental stress in the development of depression that were described earlier. As noted by Shyn and Hamilton (2010), the possible interaction between genes, environmental stress and depression (perhaps *accompanied* by reduced levels of neurotransmitters but not *caused* by them) is a plausible model. A link between these factors and neurotransmitters has been suggested by Keers, Uher et al. (2010), who showed that the presence of the 5-HTTLPR polymorphism and stressful life events led to depression, and that the intensity of those stressful life events predicted response to antidepressant treatment. These finding were replicated by Kato and Serretti (2010). It is appropriate therefore to examine more closely how stress might be involved in the development of depression. The primary stress-reactivity pathway in the human that is relevant to this discussion is the Hypothalamus-Pituitary-Adrenal (HPA) axis, and this will be described below.

4.4 Stress, HPA-axis activity and depression

4.4.1 Stress

Stress has been defined as the "nonspecific response of the body to any demand made upon it" (Selye 1974, p. 14). That is, 'stress' is a physiological mechanism or process by which the organism prepares itself for, and reacts to, demands (called 'stressors') that it meets. Those demands/stressors may be external or internal and may originate in the home, at work, or within the wider environment (Kalia 2002) to engender

the ‘fight or flight’ stress response (Toates 1995). Internal demands usually take the form of pain or associated systemic malfunction, and may be subsumed within the same nomenclature as external demands that threaten survival, although they may act via different neurological and endocrine pathways (Guyton and Hall 2006).

Selye’s notion of ‘stress’ represents the high arousal state; the low-arousal state is characterized in the construct of ‘physiological homeostasis’, which an organism will naturally seek in order to conserve resources. The movement of an organism along a continuum from low to moderate to high arousal is accompanied by a change in performance from low to high to low, as depicted in the inverted-U relationship between stress arousal and performance (Yerkes and Dodson 1908) shown in Figure 6 (below) and confirmed across a range of physiological and psychological indices (eg., integration of visual information: Colzato, Kool et al. 2008; memory acquisition and retention: Mateo 2008; job role conflict and sales performance: Onyemah 2008; sporting performance: VaezMousavi, Barry et al. 2009; working memory:Yuena, Liua et al. 2009; animal learning: Salehi, Cordero et al. 2010).

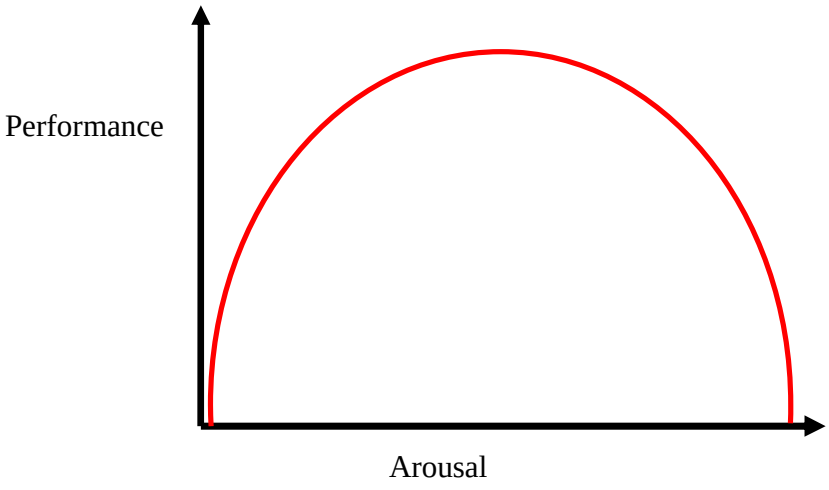

Figure 6: The ‘Inverted-U’ Curve (after Yerkes and Dodson, 1908).

4.4.2 Why we react to environmental stressors: An evolutionary advantage.

For the overwhelming portion of animal history, life has been tenuous. Multiple threats from predators, competition for resources, infection from microbial agents, scarcity of shelter, food and water, and an environment which has been almost completely non-controllable, placed powerful selective pressures upon our non-human and human ancestors (Freeman and Herron 2007). Being able to react quickly, strongly and purposefully to threat from any of these sources has provided a clear reproductive advantage (Kirkwood, Kapahi et al. 2000; Dufty, Colbert et al. 2002; Flynn 2006; Keller and Nesse 2006). The ability to meet a threat with an appropriate (ie, survival-enhancing) response but also to conserve resources when no threat is apparent requires a balance of arousal and non-arousal states, and an ability to move between those states when necessary.

The stress response to threats is mediated by hormones and other neurotransmitters, cytokines and growth factors so that, after the appropriate stress response has occurred, these mediators return to a non-aroused state of “dynamic equilibrium” or homeostasis (Chrousos 2009, p. 374). However, many of the primeval threats which drove the evolutionary selection process that shaped our stress responses are now gone, leaving the human stress response somewhat superfluous but nontheless active. Thus, many stress responses which modern humans emit are unnecessary or out of proportion to the challenge posed by a particular stressor and may, in fact, damage the organism itself, especially if the return-to-normal-homeostasis mechanisms are impaired.

4.4.3 Neurological and Endocrine stress responses

When external stressors occur, the individual becomes aware of them via sensory data which may proceed to the brain or instigate simple spinal reflexes. Sensory inputs delivered from pain or temperature receptors in the skin, retinal images, stretch receptors in muscle, auditory signals, etc, project to different levels of the central nervous system (CNS) (Guyton and Hall 2006). These sensory signals may cause immediate reflexes (e.g., spinal cord responses to limb pain), reach into lower brain regions for more complex responses (e.g., brainstem reactions to blood loss) or travel to specific projection areas within the brain (e.g., visual cortex) via the thalamus for interpretation by specialised neurons (Burt 1993). Once a sensory input has been received, the stress response may take either or both of two forms (described in the next section), each of which is activated by the brain in reaction to specific stressor demands (Ulrich-Lai and Herman 2009). Although these two forms act via different systems and have traditionally been classified according to their temporal nature, with one acting quickly (within seconds) via sympathetic nervous system impulses and the monoamines adrenaline and noradrenaline, and the second acting more slowly (within minutes or hours) via corticosteroids, this separation of the two systems and their respective sets of responses has recently been challenged. Instead, Joels and Baram (2009) have proposed a model in which both of these response systems interact within specific brain sites and over time to form three domains of functioning that combine to enable the organism to respond to stressors most effectively immediately (i.e., within seconds) as well as over minutes, hours, days and months.

The distinction between acute and chronic stressors is important in understanding the form and function of the stress response. Acute stressors occur quickly and elicit fast stress responses. For example, the sight of an oncoming car will cause a surge of neurotransmitters, sympathetic neuronal activation and hormones, followed by a rapid return to resting levels. Chronic stressors are usually defined as those which last for a week or more (Joels and Baram 2009) and instigate sustained gene expression and altered neuronal restructure and firing patterns (McGaugh 2004; McEwan 2007). In addition, over-responsivity to acute and chronic stressors can lead to different stress-related diseases. For example, acute stressors lead to allergic responses such as asthma and eczema, migraines, pain and panic attacks, whereas chronic stressors are more likely to cause psychological dysfunction (anxiety, depression, cognitive problems), cardiovascular phenomena and metabolic disorders (Chrousos 2009). While the stressors themselves do not cause these illnesses, they instigate stress responsivity pathways which, when prolonged or intense enough, can do so. These stress pathways to disease will be described below.

4.4.3.1 Fast responses to stressors: The SAM axis

The first stress response pathway is called the *sympatho-adrenomedullary* (SAM*) axis* because it acts via the sympathetic nervous system (SNS) and the adrenal medulla to respond very quickly to stressors. The SNS is part of the autonomic nervous system (ANS), which controls most visceral functions of the body and acts in concert with the parasympathetic nervous system (PNS) to achieve that control rapidly and dramatically. For example, the SNS can double heart rate within three seconds, and BP within 10 seconds of a stressor being sensed (Toates 1995). *Physical stressors* produce afferent

signals from organs to the CNS and cause an immediate response via ANS reflexive processes (Bear, Connors et al. 2007). These signals are processed quickly within the autonomic ganglia, spinal cord, brain stem or hypothalamus and generate efferent reflex responses to the target organ to assist it to adapt to the stressor. There may also be some input from the cerebral cortex and limbic cortex (Ulrich-Lai and Herman 2009). By contrast, *psychogenic stressors* require less direct transmission of the nature of their threat, with the stress response to them being based upon prior experience of the stressor, memory of that experience and consequent emotional arousal, none of which are necessary for purely physical stressors which cause largely reflexive stress responses (Ulrich-Lai and Herman 2009).

As indicated above, the SAM acts via direct and very fast sympathetic nerve stimulation of many target organs (e.g., to dilate pupils, increase heart rate, constrict blood vessels, elevate arterial BP, and inhibit salivary gland activity and digestion), and also sends signals into the chromaffin cells of the adrenal medulla, causing it to secrete adrenaline into the circulation, which has major and widespread effects upon the body that enhance responsivity to stress, albeit a little slower than direct sympathetic nerve stimulation. This aspect of the SAM response is therefore endocrine and (because it is part of a fast stress response pathway), these effects are primarily aimed at increasing the body's ability to react immediately and strongly to threat. Some of the effects of elevated serum adrenaline include increased blood flow to muscles (by vasodilation of blood vessels, increased heart rate and contractile force), increased blood fatty acid levels (via stimulation of lipolysis) to provide glucose, increased basal metabolic rate and increased oxygen uptake (via dilation of the bronchioles), again to support muscle activity

(Fitzgerald 2007). Circulating noradrenaline is also elevated by its release from the adrenal medulla as well as from sympathetic paraganglia, brain and spinal cord nerve cells, but mostly from the synaptic vesicles of postganglionic neurons in various organs (Fitzgerald 2007). Noradrenaline is principally concerned with body maintenance but also helps the body focus its resources for fight or flight by inhibiting the activity of the gastro-intestinal tract so as to marshal blood flow for muscles, induce sweating on palms, forehead and armpits for cooling during activity, increase cardiac contraction and heart rate to bring oxygen and glucose to muscles, and lipolysis to provide glucose (Fitzgerald 2007). Thus, many of the functions of adrenaline and noradrenaline overlap in this stress response pathway, perhaps ensuring (via natural selection) that these fight-or-flight responses occur when they are needed for the organism's survival. While adrenaline and noradrenaline are often considered to be activating hormones which fulfill the stress response associated with the SAM axis, the actual effects of adrenaline or noradrenaline are dictated by the adrenergic receptors they meet in particular tissue (i.e., α, β_1, and β_2 adrenergic receptors) and the specific role which these receptors may have, which can be either excitatory or inhibitory. PNS responses work through postganglionic nuclei and the vagus nerve to cause organ relaxation and re-establish homeostasis as part of this fast stress response.

4.4.3.2 The hypothalamus-pituitary-adrenal (HPA) axis

The second stress response pathway takes longer but also lasts longer. It acts via the *hypothalamus-pituitary-adrenal* (HPA) axis to produce elevations in circulating glucocorticoids about 10 minutes after the stressor onset (Sapolsky, Romero et al. 2000).

Thus, this pathway is primarily endocrinal and is the major focus of this section of the thesis. Figure 7 shows the HPA axis.

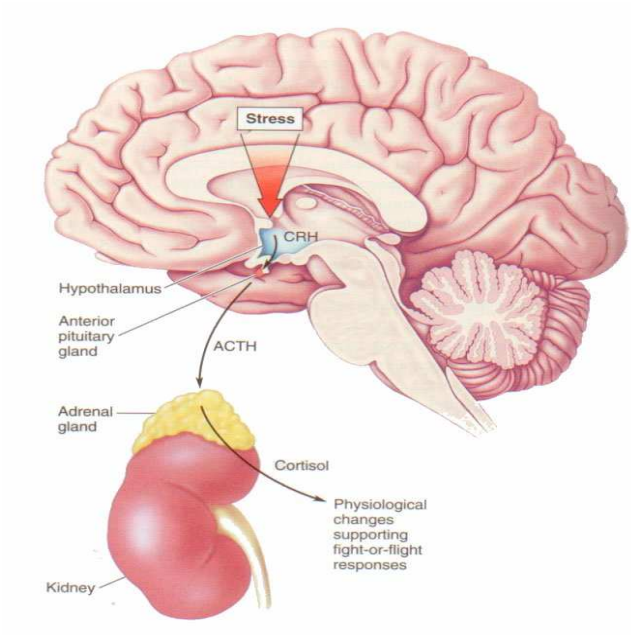

Figure 7: The Hypothalamus-Pituitary-Adrenal axis (Bear, et al. (2007, p. 668).

4.4.3.2.1 HPA hormonal responses

The hypothalamus and pituitary gland act together to control the thyroid, adrenal glands and the gonads in addition to regulation of metabolic activities, autonomic functions and emotional-behavioural responses as well as temperature, drinking, eating, sleeping and alertness. Eight major neurohormones are secreted by the hypothalamus and may be classified into two groups according to their destinations. The first group (the hypophysiotropic hormones, so named because they are secreted into the pituitary to stimulate further neurohormones) include growth hormone-releasing hormone, somatostatin, dopamine, thyrotropin-releasing hormone, Corticotropin-Releasing

Hormone (CRH) and gonadotropin-releasing hormone. The second group is released by the hypothalamus-pituitary system and sent directly into the blood circulatory system to target organs, and includes arginine, vasopressin (AVP) and oxytocin (Guyton and Hall 2006). Only CRH and AVP are part of the HPA axis stress response (Seidman 2006) and, of these, AVP is relatively less important, although regulation of water balance within the body may become relevant if the stress response continues for some time and dehydration occurs (Robinson 2007). Prolactin-releasing hormone and growth-hormone-releasing hormone are also secreted during stress but do not appear to have important stress response-related effects upon prolactin, thyrotropin or follicle-stimulating hormone (Aron, Findling et al. 2007).

4.4.3.2.2 The endocrine cascade for HPA stress responsivity: CRH, ACTH, Cortisol

CRH (and AVP): After relevant inputs have been received by the hypothalamus, CRH is released from CRH-containing neurons situated within the medial parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus, as well as oxytocin, AVP and vasoactive intestinal peptide. CRH and AVP reach the pituitary gland via the portal hypophysial vessels that originate in the hypothalamic median eminence and join with the anterior pituitary, allowing for two-way exchange of blood and neurohormones between the hypothalamus and the pituitary gland (Aron, Findling et al. 2007). Direct electrical stimulation of the PVN has been shown to increase portal levels of CRH and peripheral levels of adrenocorticotropic hormone (ACTH) (Tannahill, Sheward et al. 1991), affirming its role in CRH secretion. Additionally, chemical stimulation of the dorsomedial hypothalamus (DMH) increases ACTH secretion to the blood and elevates

heart rate and mean arterial pressure (Bailey and DiMicco 2001). It has been suggested that there is a causal link between the CRH-producing neurons in the DMH and those within the PVN, with the former stimulating the latter (Ulrich-Lai and Herman 2009). As well as coming from the PVN and DMH, CRH is also expressed by the central nucleus of the amygdala, with a degree of specificity of response that differs between physical and psychogenic stressors and that is not present in the PVN (Hand, Hewitt et al. 2002). Those authors noted that the "central CRH pathways" (i.e., those in the central nucleus of the amygdala) were particularly associated with fear-related behaviours and "are more responsive to stressors with a large cognitive component" whereas "hypothalamic CRH pathways are sensitive to stressors with either large cognitive or physical components" (p. 128). In addition, CRH activates the *locus coeruleus* noradrenergic circuit which promotes general arousal and attention to selected stimuli and also inhibits appetite, libido and other vegetative functions (Wolkowitz, Epel et al. 2001), clearly establishing optimum conditions for the organism to focus its resources upon the stressor.

ACTH (and POMC): Once released from the PVN (and perhaps the DMH and amygdala), CRH and AVP travel to the pituitary gland and both stimulate the release of pro-opiomelanocortin (POMC), although AVP has only a minor role in this process (Ma, Levy et al. 1997). POMC is a precursor to ACTH and is synthesised by a single mRNA into several smaller biologically active fragments, including the amino-terminal fragment of POMC (N-POMC), ACTH and β-Lipotropin (β-LPH) (Aron, Findling et al. 2007). ACTH is composed of 39 amino acids and contains α-melanocyte stimulating hormone (α-MSH) and corticotropin-like intermediate lobe peptide (CLIP); β-LPH contains the β-melanocyte stimulating hormone (β-MSH), γ-LPH and β-endorphin. If ACTH is

hypersecreted, it binds with the MSH receptor and causes excess skin pigmentation (as in Addison's disease), which may be linked to UV protection during intense and/or prolonged solar radiation periods. ACTH secretion follows a pulsatile flow pattern (Aron, Findling et al. 2007) that may vary diurnally, a fluctuation sometimes also reflected in cortisol secretion (Weitzman, Fukushima et al. 1971).

Cortisol (and adrenal androgens): ACTH travels via the bloodstream from the pituitary gland to the adrenal glands located on the anterosuperior aspect of the kidneys and stimulates the adrenal cortex to secrete glucocorticoids including cortisol, which acts upon target cells via intracellular glucocorticoid receptors. The adrenal cortex has three zones: the outer *zona glomerulosa* (which produces aldosterone but not cortisol), and the two areas that produce cortisol but not aldosterone, the middle *zona fasciculata* and the inner *zona reticularis*. These latter two areas also produce the androgens and both are regulated by ACTH, with excess or deficiency altering their structure so that they enlarge with chronic ACTH stimulation and atrophy with under-stimulation of ACTH (Aron, Findling et al. 2007). This may be an adaptive mechanism to assist the organism to deal with prolonged periods of stress by increasing cortisol production.

Synthesis of cortisol (and all steroids) starts with cholesterol from plasma lipoproteins, principally (80%) low density lipoproteins. Cholesterol is converted to pregnenolone in the mitochondria via two hydroxylations and one side cleavage by the enzyme CYP11A. The pregnenolone is transported to the smooth endoplasmic reticulum and acted upon by the enzyme CYP17 to form 17α-hydroxypregnenolone. Endoplasmic reticula enzymes then act on the 17α-hydroxypregnenolone to produce 17α-hydroxyprogesterone. Enzyme CYP21A2 hydroxylises the 17α-hydroxyprogesterone to

11-deoxycortisol and the 11-deoxycortisol is then transported back to the mitochondria and further hydroxylated to produce cortisol.

4.4.3.2.3 How cortisol enhances survival

Cortisol binds to cytosolic glucocorticoid receptor proteins present in most tissues, enters the cell nucleus and alters the expression of specific genes and mRNAs. From these mRNAs, resulting proteins elicit the glucocorticoid response but these proteins vary according to the specific cell type and genes expressed and thus, depending on the specific tissue and gene, the glucocorticoid response may be inhibitory or stimulatory. Cortisol affects intermediary metabolism, calcium homeostasis, the immune system, other endocrines, skin and connective tissue, breast, lung and cardiovascular systems, and mood, appetite, sleep, memory and vision (Guyton and Hall 2006).

However, although cortisol is clearly a major regulatory hormone for everyday homeostasis, its major relevance in the present discussion is its role in instigating rapid and dramatic responses by the organism to threat---the so-called stress response. Cortisol has been termed “the stress hormone” (Aron, Findling et al. 2007) and works to assist the organism to cope effectively with threat by the release of stored lipids and amino acids from fatty tissue (for synthesis of glucose and protein which enhance the organism’s ability to mobilise musculature for immediate and prolonged intense activity). Cortisol also helps the body to defend itself against infectious agents (which may occur as a result of attack) by stabilising the membranes of lysosomes (Weissmann and Thomas 1962; Weissmann and Thomas 1963; Weissmann 1967; Persellin and Ku 1974). This improves their ability to engulf foreign species that have been brought into the cell by phagocytosis. The lysosome then undergoes enzymatic responses that reduce its pH so

that it can necrose the engulfed infectious agent, contributing directly to the immune response to infection (Weissmann and Thomas 1962; Weissmann 1967). Guyton and Hall (2006) conceptualized cortisol's anti-infection protective response as having two basic anti-inflammatory effects: (1) blocking the early stage of the inflammation process before it begins, and (2) rapidly resolving inflammation and speeding healing. Four pathways to achieve this are: (a) stabilising the lysosome membranes, (b) decreasing the permeability of capilliaries, preventing loss of plasma into the tissues, (c) suppressing the immune system, decreasing lymphocyte reproduction, especially T-cells and antibodies to the infected area, and (d) inhibiting the release of interleukin-1 from the white blood cells, thus reducing fever and thence vasodilation.

Although short-term inflammation is a survival-enhancing process, prolonged inflammation can be counterproductive for the organism, contributing to atherosclerosis, bowel disease, mood disorders, neurodegenerative diseases, diabetes and cancer (Jope, Yuskaitis et al. 2007). Jantz and Sahn (1999) listed several anti-inflammatory effects of cortisteroids, including: inhibition of several cytokines that are involved in inflammation; interference with transcription factors activator protein (which is involved in the expression of genes that enhance inflammation); degradation of mRNA encoding for inflammation; inhibition of nitric oxide synthase; inhibition of bronchoconstrictors; desensitisation of β_2-adrenergic receptors; inhibition of intercellular adhesion molecules; and reduction of airway inflammation. Previous research has also suggested that cortisol reduces microvascular leakage (Boschetto, Rodgers et al. 1991). Klaitman and Almog (2003) reviewed the anti-inflammatory effects of cortisol with particular reference to sepsis and listed 17 separate anti-inflammatory effects of cortisol via lipocortins,

interleukins, neutrophils and other agents. Thus, the two-stage role of cortisol in killing infectious agents and also reducing the organism's prolonged inflammatory response is of significance in promoting the overall survival of the organism.

Viewed from an evolutionary advantage perspective, rapid muscular activity in the face of threat, destruction of infectious agents and anti-inflammatory activities are responses that are likely to enhance survival and consequent gene pool transmission. During ancestral periods, major threats would have most likely been from predators and competitors, with part of the likely outcome of such attacks being damage to the skin and consequent infection from animals' claws, competitors' weapons and the contaminated detritus that was contained on them. Thus, while the fast deployment of a suitable response to isolate and destroy infectious agents within the dermis (i.e., via lysosomal engulfment and necrosis) would have assisted the organism to resist infection, prolonged sepsis would not have carried such an evolutionary advantage and hence the control of inflammation becomes a parallel mechanism for survival.

However, when stress is chronic rather than acute, and therefore instigates an ongoing elevation of cortisol, negative outcomes emerge. These outcomes can include increased expression of CRH and AVP mRNA in the PVN (Herman, Adams et al. 1995; Makino, Smith et al. 1995), altered expression of neurotransmitter receptors (Zeigler, Cullinan et al. 2005) and increased synthesis of gamma-aminobutyric acid (GABA) in the hypothalamus (Bowers, Cullinan et al. 1998). Chronic stress may also lead to increased ACTH and cortisol responses to new stressors, as well as enhanced expression of noradrenaline and increased sensitivity of the *locus coeruleus* to CRH (Ulrich-Lai and Herman 2009). Stress-related increases in cortisol can also induce neuropsychiatric

disorders, particularly depression (Raison and Miller 2003). Therefore, it is relevant to discuss the effects of dysregulation of the cortisol response.

4.4.3.3 The consequences of dysregulation of cortisol responses

4.4.3.3.1 Hypocortisolaemia

Although most attention has been paid to the adverse consequence of over-production of cortisol (described below), hyporesponsiveness of the HPA axis is also associated with physical diseases which have concomitant psychopathological states. About one-quarter of patients with stress-related disorders such as chronic pain, fibromyalgia, irritable bowel syndrome, post-traumatic stress disorder and low back pain also suffer from hypocortisolism (Raison and Miller 2003; Fries, Hesse et al. 2005). It has been suggested that hypocortisolism develops after a prolonged period of hyperactivity of the HPA axis (Hellhammer and Wade 1993), via (a) reduced biosynthesis or release of CRH, AVP or ACTH or cortisol itself, (b) hypersecretion of one of these, followed by a consequent downregulation of target receptors, (c) increased sensitivity to negative glucorticoid feedback, (d) lowered free cortisol, and (e) decreased effects of cortisol on its receptors and the target cells/tissues (Fries, Hesse et al. 2005). Hypocortisolaemia may also have negative effects upon overall health by inhibiting the negative feedback effect of cortisol on catecholamine synthesis and secretion and by over-activating the immune system by absence of the anti-inflammatory effects of cortisol (Raison and Miller 2003; Fries, Hesse et al. 2005).

4.4.3.3.2 Hypercortisolaemia

Circulating cortisol flows back to the hypothalamus and inhibits CRH secretion there, and thus POMC and ACTH in the pituitary. However, this moderating mechanism

may be insufficient when the organism is under chronic stressful stimulation (Fries, Hesse et al. 2005), leading to the diseases of hypercortisolaemia, including fibromyalgia, early over-activation of the immune system that is followed by depressed activation, susceptibility to stress, pain and fatigue (Fries, Hesse et al. 2005), muscle wastage and hyperglycemia (Aron, Findling et al. 2007). Prolonged and elevated expression of cortisol leads to increased serum lipids, endothelial damage and resultant incidence of coronary heart disease (CHD) (Troxler, Sprague et al. 1977; Koertge, Al-Khalili et al. 2002; Smith, Ben-Shlomo et al. 2005) and acute respiratory failure (Jantz and Sahn 1999). Hypercortisolaemia has also been shown to cause atopic dermatitis (Amano, Negishi et al. 2008) and suppressed skin immunity (Dhabhar 2000). Other outcomes of excessively high levels of cortisol expression include decreased immunocompetence (Friedman and Lawrence 2002; Segerstrom and Miller 2004), increased risk of infection, osteoporosis, steroid diabetes, and destruction of hippocampal neurons leading to cell loss, chronic distress and depression (Chrousos 2009; Rao, Hammen et al. 2009). It is the latter of these outcomes of hypercortisolaemia that is of most concern here, and the next section presents a summary discussion of some of the data which support the link between hypercortisolaemia and depression.

4.4.4 Hypercortisolaemia and depression: research evidence

A great deal of data has been generated on the link between hypercortisolaemia and depression, beginning with Board et al.'s (1957) report of significantly higher mean serum cortisol values in depressed patients compared to non-depressed controls. For example, Halbreich, Asnis et al. (1985) sampled plasma cortisol levels for 24 hours in 32 depressed patients and 72 non-depressed controls, finding that the former had

significantly higher cortisol concentrations than the latter group. More than half of all patients with Cushing's disease (who have very high levels of cortisol) develop depressive mood (Seidman 2006), although this is reversible with anti-cortisol medication. Thompson and Craighead (2008) reported that up to 80% of depressed patients have elevated cortisol levels, although this may be more likely with patients suffering from psychotic depression than non-psychotic depression (Gillespie and Nemeroff 2005), the former having a larger component of anxiety (APA, 2000).

Although sampling of cortisol over a full 24-hour period appears reliable, it may cloud effects that are due to fluctuations in cortisol over that period. This is commonly referred to as the 'diurnal rhythm' of cortisol, and reflects the finding that cortisol may exhibit a diurnal fluctuation in many persons (Weitzman, Fukushima et al. 1971), typically with a peak concentration early in the morning (e.g., about 8.00am) and a minimal concentration later in the afternoon or early evening (Smyth, Ockenfels et al. 1997). This diurnal fluctuation is not present in everyone, with 17% of some samples showing a lack of variation over the day-night period (Smyth, Ockenfels et al. 1997), about 30% showing variation in their diurnal cycle from day to day (Smyth, Ockenfels et al. 1997), and up to 50% showing variation or reduction in the cycle due to a range of influences (Stone, Schwartz et al. 2001). Some of those influences include relationship functioning (Adam and Gunnar 2001), prenatal anxiety (O'Connor, Ben-Shlomo et al. 2005), smoking (Granger, Blair et al. 2007), financial strain (Grossi, Perski et al. 2001), stress and fear (Zorawski, Cook et al. 2005), relative dominance-submissive position within a social group (Cross and Rogers 2004), over-the-counter medications (Hibel, Granger et al. 2006), and even time of awakening (Edwards, Evans et al. 2001), several

of which are clearly related to depression. The precise points of maximum and minimum cortisol concentrations have also been shown to vary somewhat across individuals according to their mood state (Smyth, Ockenfels et al. 1997), although the maximum concentration is usually early in the morning and the minimum later in the afternoon. When it does occur**, t**his diurnal fluctuation has long been considered as 'adaptive' (Yates and Urquhart 1962) in the same way that other circadian-driven physiological variations influence survival behavior by maximizing the use of physiological resources (Minors and Waterhouse 1981), perhaps developed via evolutionary-based selection processes (Wever 1979).

For these reasons, cortisol is often measured upon waking to provide a maximum value that may be used in studies of the association between cortisol and depression. For example, Gibbons and McHugh (1966) assayed cortisol in serum collected from 17 depressed patients between 9.00am and 9.30am at weekly intervals for five to 12 weeks (according to the particular patient's treatment protocol). When compared with ratings given for the severity of depression (a five-point scale where 0 = no evident depression and 4 = severe and deep depression), there was a significant direct relationship between serum cortisol and this measure of depression intensity. In a recent large cohort study of the waking and evening salivary cortisol levels of 701 MDD patients, 579 remitted MDD patients and 308 non-depressed controls, Vreeburg, Hoogendijk et al. (2009) found that both the current and remitted MDD groups had significantly higher waking and evening cortisol concentrations than the non-depressed group. (Of particular interest in understanding the link between cortisol and depression, only comorbid anxiety was significantly associated with elevated cortisol, whereas other MDD symptoms were not.)

A recent meta-analytic review by Chida and Steptoe (2009) examined 17 studies of the relationship between waking cortisol and depression and/or hopelessness. Although there was no significant correlation between depression and/or hopelessness and the increase in cortisol collected immediately after waking until one hour later (r = -.026), there was a significant correlation between depression and/or hopelessness and the total volume of cortisol released during that period (r = 0.072, p < .001). Chida and Steptoe also commented that the lack of a significant relationship between depression and/or hopelessness and the increase in cortisol during the first hour after waking "was not because of an absence of effects, but rather because depression has been related to both increases and decreases" in waking cortisol (p. 274-5), possibly as a result of different studies including different severities of depression.

Other HPA-axis indicators are also associated with depression (Yuan 2008), as indicated by the finding of higher levels of CRH, ACTH and cortisol in depressed patients (Carroll, Greden et al. 1981; Plotsky, Owens et al. 1998; Holsboer 2004; Gillespie and Nemeroff 2005). The link between elevated CRH and depression (Anisman 2008) may be via its effect on raphe nuclei that, in turn, influence serotonin activity in the PFC (Price and Lucki 2001). Depressed suicide victims show elevated CRH in their PFC compared to non-depressed and non-suicide individuals (Merali, Du et al. 2004). Hyperresponsivity of the whole of the HPA axis response profile to stress is thus associated with depression (Yuan 2008).

Several reports indicate that HPA-axis hyperactivation may begin relatively early in life following major stressful events. For example, infant humans who have experienced adverse nurturing experiences and who are depressed also show dampening

of the hippocampal glucocorticoid receptor gene *Nr3c1* (Oberlander, Weinberg et al. 2008; McGowan, Sasaki et al. 2009; Weaver 2009), leading to impaired negative feedback to the hypothalamus regarding circulating cortisol (Bear, Connors et al. 2007). HPA function has been shown to deteriorate, producing increases in circulating cortisol in children whose parents have died (Tyrka, Wier et al. 2008), and early and recent aversive experiences predict elevated cortisol responsivity in adolescents (Rao, Hammen et al. 2008). Elevated cortisol has also been shown to predict the incidence of future depressive episodes (Goodyer, Herbert et al. 2000) in young people and adults (Cowen 2010).

The presence of a genetic link between stress and responsivity to stress and consequent depression has also been established (Charney 2004; DeRijk and de Kloet 2008; DeRijk, van Leeuwen et al. 2008), and may function via imbalanced responses between mineralocorticoid and glucocorticoid receptors, the former of which normally prevent stress-induced disturbances and the latter of which help in recovery if those disturbances have occurred (de Kloet, DeRijk et al. 2007; McMaster and Ray 2008; de Kloet, Fitzsimons et al. 2009). There are some gender differences in HPA axis responses to stress, with depressed women showing greater HPA responses to stress than depressed men. These differences emerge following puberty, indicating the influence of ovarian steroids upon the link between stress, HPA axis response and depression (Kudeilka and Kirschbaum 2005; Young and Korszun 2010)

This sample of the research findings establishes a plausible link between hypercortisolaemia and depression (perhaps via anxiety). There is also a suggestion that this relationship may be reciprocal. For instance, while cortisol has profound effects on

CNS function, altering mood, learning and memory (Erickson, Drevets et al. 2003), and is elevated when the organism is exposed to stress (Thomson and Craighead 2008), it is apparent that both anxiety and depression are associated with an impaired ability to adapt to stressors (Chrousos and Gold 1998) and consequent dysregulation of the upstream trophic hormones (ACTH, CRF) that originate in the hypothalamus and the pituitary gland and which elicit cortisol synthesis in the adrenal glands.

As supportive adjunct data to the hypothesis that elevated cortisol is associated with depression, antidepressant treatments based upon HPA axis function have included antiglucocorticoids to inhibit cortisol synthesis (*aminoglutethimide, ketoconazole, metyrapone*) (Seidman 2006), with further confirmatory data from animal studies (Surget, Saxe et al. 2008) and depressed patients (Thakore and Dinan 1995; Murphy 1997; Brown, Bobadilla et al. 2001; Ising, Zimmerman et al. 2007). CRH has been targeted by Gold, Licinio, Wong and Croussos (1995), Holsboer (2004) (2003) and Nemeroff (2002) in studies using the CRH-antagonist R121919, which has been shown to reduce major depressive disorder in clinical Phase I studies (Kunzel, Zobel et al. 2003; Held, Kunzel et al. 2004; Kunzel, Ising et al. 2005).

4.4.5 Summary of the HPA axis and depression

These data support the association of HPA axis hyperactivation, principally via its final product (cortisol), with depression. Although these data suggest that the primary causal route between elevated cortisol and depression may be via those depressive symptoms that overlap with anxiety rather than the central symptoms of MDD itself (i.e., anhedonia, apathy), the link appears to be significant. It is therefore logical to investigate

how elevated cortisol affects the functioning of those regions of the brain that are involved in mood, and the next section of this chapter focuses upon that issue.

4.5 Neuroanatomical variations: explaining the links between hypercortisolaemia and depression.

The preceding section has summarized the data which link hypercortisolaemia with depression but not the mechanism by which that link occurs. One potential candidate hypothesis for that link is via changes in certain regions of the brain and consequent alterations to the overall cognitive and emotional control processes which enable organisms to react effectively to stressors. Those changes will be discussed in this section.

The early effects of hypocortisolaemia upon general brain development have been reported by Fukumoto, Morita et al. (2009), who noted that excess of glucocorticoids in the brain retarded the radial migration of post-mitotic neurons during the development of the cerebral cortex. It is relevant in this discussion of the link between HPA activation and brain regions related to depression to consider how the HPA axis is stimulated and the brain regions that are involved in that process. Therefore, this section of Chapter 4 will describe (a) the neurological processes that instigate HPA axis reactivity to stressors, (b) the effects which elevated cortisol has upon specific brain regions that may influence cognition and emotion, contributing to the development of depressive symptomatology, and (c) the mechanisms that underlie the effects of cortisol upon those brain regions.

4.5.1 Initiation of the HPA stress response: How brain regions are involved in the stress response and depression.

The HPA axis stress response follows from the transmission of afferent sensory signals from various organs to the diencephalon, which includes the epithalamus, the thalamus, the hypothalamus and the subthalamus (Burt 1993). The diencephalon has been described as "a station that is interposed between cortex and lower levels of the brain stem and as such is intimately related to motor and sensory functions in both the somatic and visceral spheres" (Everett, Sundsten et al. 1972, p. 222). Thus, these thalamic structures also receive signals from the cerebral cortex, basal ganglia and cerebellum (Burt 1993). These signals may be evaluations of threat, direct sensory input or lower level homeostatic inputs (Guyton and Hall 2006). Many *limbic* structures that are intimately involved with emotional states project to the hypothalamus (Purves, Augustine et al. 2008), raising the profile of the hypothalamus as a focus for the organism's fear-based responses to threat. Reflecting this role, the hypothalamus has also been described as "a transducer between neural impulses and hormonal secretion" (Toates 1995, p. 41), the former being the input from the sensory and cortical centres of the organism and the latter being its major method of response to those inputs.

The first step in the activation of this pathway is the innervation of the parvocellular sections of the paraventricular nucleus (PVN) of the hypothalamus, which is achieved by several processes (Ulrich-Lai and Herman 2009). The primary regulators of the hypothalamus are the amygdala and the hippocampus, the first of which stimulates the PVN and the second acts to inhibit it (Bear, Connors et al. 2007), while also interacting with each other. Sensory information from the prefrontal cortex (PFC) is

received by the basolateral amygdala, processed and sent on to the amygdala central nucleus, which innervates and stimulates the PVN via the bed nucleus of the stria terminalis (Purves, Augustine et al. 2008).

Glucocorticoid receptors in the hippocampus provide negative feedback to the PVN, inhibiting or activating corticotrophin-releasing hormone (CRH) secretion from the hypothalamus, depending upon the serum concentration levels. The hippocampus also receives information from the PFC, and so both the stimulatory and inhibitory activities of the amygdala and hippocampus are influenced by (and, in turn, influence) the information they receive from the PFC, where decisions are made regarding the significance of external stimuli (Ulrich-Lai and Herman 2009). This reciprocal relationship between hypothalamic functioning (as influenced by the amygdala and hippocampus) and the PFC has recently been demonstrated by Minton, Young et al. (2009), who showed that flattening of the diurnal cortisol rhythm in rats was associated with changes in dopamine release in the PFC and abnormalities of PFC neurocognitive functions.

In this way, prior learning may influence HPA axis responsivity and the endocrine stress response itself, an hypothesis that is supported by the finding that experimental subjects who believed that they could not control the stressor which they encountered had higher and longer-lasting cortisol responses than subjects who believed that the stressor was within their control (Dickerson and Kemeny 2004). Of relevance to this cognitive evaluation of control over stressors (i.e., via the PFC), up to 35% of the variance in the magnitude of an individual's cortisol response to a stressor is a function of their pre-stressor appraisal of it (Gaab, Rohleder et al. 2005). When linked to the amygdala, which

inputs emotional responses such as fear (based on previous experiences, thus helping the individual to form memories of aversive events), the hippocampus and the PFC act together to interpret the threat significance of stressors and then adjust the hypothalamic response accordingly (Roozendaal, McEwan et al. 2009).

Relevant to this influence of higher-order cortical processes upon the responsivity of the HPA axis, the PVN also receives serotonergic input from the raphe nuclei in the midbrain, but only when the stressor is perceived as uncontrollable (Joels and Baram 2009). The midbrain receives input from the cerebral cortex (where threat is also evaluated) and sends axons to the brain stem and spinal cord, acting as a conduit for the exchange of information to and from the spinal cord to the forebrain. The midbrain also contributes to movement, sensory functions and (most relevant for fight or flight responses) aggression via axons from the hypothalamus to the ventral tegmental area of the midbrain (Bear, Connors et al. 2007). It has been suggested that this pathway acts in response to non-physical or 'psychogenic' stressors that are recognized by genetic programming or the individual's history (i.e., classical and instrumental conditioning experiences which may have formed associations between certain stimuli and their damaging consequences) (Ulrich-Lai and Herman 2009). These associations need to be processed in the forebrain (Herman, Figueiredo et al. 2003) and emphasise the role of learning in stress responsivity (Sanders, Wiltgen et al. 2003; Bishop 2007; LeDoux 2007), as well as highlighting the importance of aggression in coping with major stressors such as predators. At least one study has shown that cognitive appraisal of 'what might happen' is more powerful in predicting HPA axis responsiveness than reflections upon 'what did happen' (Gaab, Rohleder et al. 2005), although this interpretation may be

challenged by operant models of behaviour which would argue that the former is dependent upon previous experiences and learning from the latter, and thus both are causally intertwined (Bandura 1986). This latter position has been emphasized by Roozendaal, McEwan and Chattarji (2009), who examined the links between experiences of severe stress which induced amygdaloid plasticity and then dictated future behavioural and endocrine responses to those stressors by way of the amygdala's effects upon memory consolidation.

From this brief description of the processes and brain regions involved in the instigation of the HPA axis response to stressors, it is apparent that, although a range of regions are involved in the development of depressive symptomatology, including the neocortex and the nucleus accumbens (Nestler, Barrot et al. 2002), three major areas are specifically relevant—the hippocampus, PFC and amygdala. Each of these will be described below, plus a discussion of how elevated cortisol influences their structure and function and how this may contribute to depression. Figure 8 (p. 107) shows these three regions and the hypothalamus.

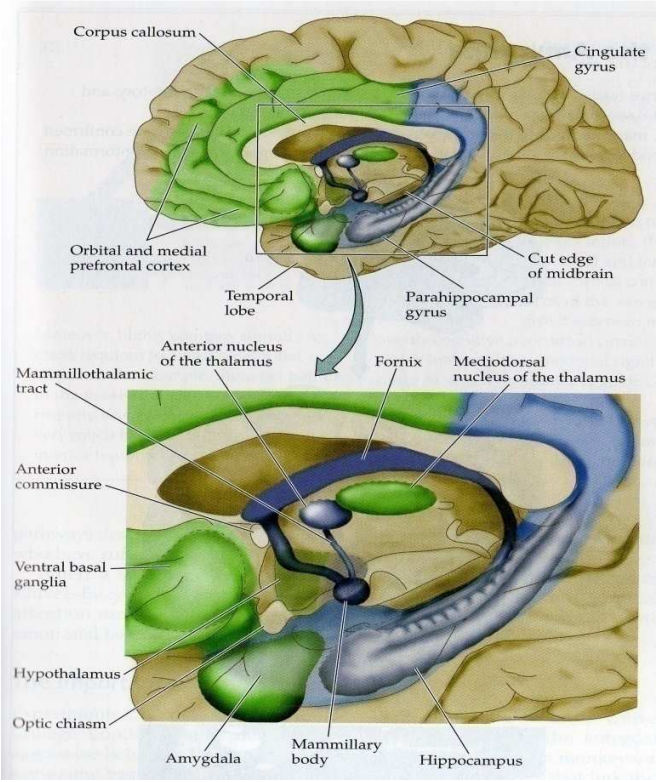

Figure 8: PFC, hippocampus, amygdala and hypothalamus (Purves, Augustine et al. 2008, p. 241).

4.5.1.1 The hippocampus: Function and effects of elevated cortisol.

The hippocampus consists of two sheets of neurons that are folded onto each other to form a curved elevation of cortical tissue that runs the full length of the temporal horn of the lateral ventricle. One of the sheets of neurons is called the dentate gyrus and the other is Ammon's horn. The hippocampus is centrally involved in memory formation and retrieval, and receives inputs from the association areas of the cerebral cortex that process information from senses. Outputs from the hippocampus are returned to the association cortex, but also go to the fornix and then the hypothalamus. Studies of lesions

to the hippocampus indicate that these may cause amnesia for specific tasks and stimuli (Burt 1993; Nolte 2009).

The link between hypercortisolaemia, depression and alterations to the hippocampus may be conceptualized as involving two processes. First, stress and consequent hypercortisolaemia impede neurogenesis in the dentate gyrus (Balu 2009) and reduce the density of pyramidal neurons in the hippocampus via cell apoptosis (Munetsuna, Hattori et al. 2009). Prolonged glucocorticoid activation due to inhibited glucocorticoid receptor responses in the hippocampus and impaired negative feedback processes (de Kloet, DeRijk et al. 2007) can cause atrophy and debranching of hippocampal apical dendrites (Magarinos and McEwan 1995; Vyas, Mitra et al. 2002; Lloyd, Ferrier et al. 2004) and resultant atrophy and volumetric reduction of the hippocampus (Sapolsky 2000). Some data suggest that glucocorticoids act within 24 hours to significantly increase the rate of apoptosis in the hippocampus (Yu, Holsboer et al. 2008). The ability of glucocorticoids to cause atrophy of dendritic processes by inhibiting glucose uptake in neurons (Sapolsky 1996; Du, Wang et al. 2009) and enhancing calcium channel expression (Joels, Karst et al. 2004) suggests how cortisol causes neural damage in the hippocampus (Mirescu and Gould 2006) and thereby decreases hippocampal volume (Lloyd, Ferrier et al. 2004). These hippocampal-damaging effects of prolonged environmental stress accompanied by elevated glucocorticoids have been conclusively demonstrated for some time (Watanabe, Gould et al. 1992; Magarinos and McEwan 1995; Magarinos, McEwen et al. 1996; Sousa, Lukoyanov et al. 2000; Fuchs, Flugge et al. 2006).

The second process is the link between reduced hippocampal volume and depressive symptoms. Several of the key symptoms of depression are apparent when the hippocampus is reduced in volume, the first of which is interference in hippocampal memory-retrieval processes, which may contribute to cognitive confusion (a symptom of depression). Depressed patients have impaired memory performance (Austin, Mitchell et al. 2001; Fossati, Coyete et al. 2002), thus again linking impaired hippocampal functioning with depression. Because the hippocampus is also involved in anxiety (Revest, Dupret et al. 2009), and there is overlap between anxiety and depression (Zinbarg, Barlow et al. 1994), exacerbation of this symptom of depression may also be linked with neurological impairment of the hippocampus.

Sapolsky (2000) reviewed the literature on the association of hypercortisolaemia, hippocampal volumetric reductions and depression in animals and humans. In rodents and non-human primates, prolonged stress and excessive glucorticoid production was associated with decreased apical dendritic branch points and shortened apical dendrites, inhibition of adult neurogenesis, and even instances of glucocorticoids acting as noxious substances in the hippocampus. Soetanto, Wilson et al. (2010) examined brain tissue from deceased depressive patients and found the same decreases in hippocampal dendrites and spines as had been reported from animal studies, concluding that the changes in humans were “analogous” to those observed in animal studies of depression (p. 448). In the human studies used by Sapolsky (2000) to buttress the link between hippocampal volume and depression, data were collected across both genders, from patients with chronic and severe depression, and those with episodic depression. Comparisons were made with age and gender-matched non-depressive control subjects,

and data were consistent in showing hippocampal volumetric reductions of between 12% and 15% in the presence of depression. Of interest, Sapolsky (2000) argued that, because hippocampal atrophy correlated with length of depression but not with its severity, it was unlikely that the hippocampal atrophy preceded the depression in some causal fashion, but rather that it was an outcome of depression. Further to this, Lloyd, Ferrier et al. (2004) found that hippocampal atrophy was associated only with late-onset depression (first depressive episode after age 60 years) but not with early onset depression (first episode before age 60 years), suggesting that factors other than hypercortisolaemia (such as vascular damage and other degenerative diseases) may play a central role in the link between stress and hippocampal reduction. These data also support Sapolsky's (2000) suggestion that hippocampal reductions follow depression rather than instigate it, and similar data were reported by Ballmaier, Narr et al. (2008). This raises the issue of what adaptive function hippocampal reduction could perform for the already-depressed patient, and will be discussed later.

Although some studies failed to show hippocampal volume reductions during depression in humans, Sapolsky (2000) argued that those data were flawed by use of fMRI procedures that were less sensitive than in studies which did show links between depression and reductions in hippocampal volume. This argument was supported by Campbell, Marriott et al. (2004), whose meta-analysis of fMRI studies of hippocampal volume and depression suggested that measurement errors may have been responsible for findings regarding the lack of a relationship between reduced hippocampal volume and depression. A recent review of the role of reduced hippocampal processes (due to apoptosis) in depression noted that the greatest degree of cognitive impairment in

depressed patients was on measures of memory, which are heavily dependent on hippocampal function (MacQueen and Frodl 2011).

Even though the reductions in hippocampal volumes of depressed patients persist during remission (aan het Rot, Mathew et al. 2009), hippocampal neural structures can be regenerated after stress-induced damage (Eriksson, Perfilieva et al. 1998; Costafreda, Chu et al. 2009), and data regarding the effects of various treatments for depression upon hippocampal volume can provide further evidence of the link between hypercortisolaemia, volumetric reductions to the hippocampus and depression. For example, Lucassen, Fuchs et al. (2004) showed that the antidepressant *tianeptine* reduced hippocampal apoptosis; Crochemore, Lu et al. (2005) reversed hippocampal apoptosis by activation of the mineralocorticoid agonist aldosterone; Oomen, Mayer et al. (2007) reversed stress-induced reductions of the hippocampus by applying *mifeprostone* for only four days; Stevenson, Schroeder et al. (2009) prevented reduction in hippocampal neurogenesis in mice by applying *desipramine* for 14 days; Marchant, Brothers et al. (2009) partially restored neurogenesis in the hippocampus of older rats by application of the cannabinoid agonist WIN-55, 212-2; Perera, Coplan et al. (2007) and Hellsten, Wennstrom, et al. (2004) re-established neurogenesis in non-human primates and adult rats respectively by repeated electroconvulsive shock (the animal analogue of ECT); Goldaple, Segal et al. (2004) increased hippocampal metabolism in unipolar, non-medicated depressed adults via 15 sessions of Cognitive-Behaviour Therapy (CBT); and Pajonk, Wobrock et al. (2010) reported increased hippocampal volumes in males with schizophrenia who participated in three months of aerobic exercise.

Several comments have been made regarding the role of hippocampal neuroplasticity and depression, some of them challenging the role of volumetric reduction *per se*. For example Fuchs, Czeh et al. (2002) found that one-month of stress in the form of social conflict in male tree shrews was related to reduced brain metabolites that were responsible for widespread neural plasticity and resilience. Data from two studies suggested that the key variable was hippocampal neuronal plasticity rather than volume alone which distinguished depressed from non-depressed persons. In the first of these, Vythilingham, Vermetten et al. (2004) examined the hippocampal volume of 38 MDD patients and 33 non-depressed participants, and found that there was no significant difference between the two groups, although the MDD patients had significantly poorer memory and retention. Successful treatment with antidepressant medication removed the memory and retention deficits in the MDD patient group, but did not change hippocampal volume, allowing those authors to argue that it was the functional aspects of the hippocampus rather than its overall size that was the distinguishing factor in MDD. These data were supported by Bessa, Ferreira et al. (2009), who reversed stress-induced depressive learned helplessness and anhedonia in rats via application of antidepressant medication, but blocked hippocampal neurogenesis, arguing that it was decreased neuronal plasticity rather than decreased volume which was the prime causal variable in the link between stress and depression. These two studies do not negate the hypothesis that hippocampal volume reductions are causally linked to depression, but rather they expand it to include consideration of the mechanism underlying that relationship, i.e., restriction of hippocampal function, whether via reduced neuronal concentration or curtailed plasticity.

Further clarification of the role of neurogenesis in alleviating depression comes from a recent report by Schloesser, Lehman et al. (2010), who examined the effects of environmental enrichment for mice that had been chronically stressed and that showed symptoms of submission and depression. (Environmental enrichment consisted of extra bedding materials, running wheels, and numerous tubes of varying sizes.) Although the environmental enrichment reversed the submissive and depressive behaviours in mice that were capable of neurogenesis, it did not have the same effect in mice that were transgenically altered to suppress neurogenesis. Schloesser and colleagues argued that these results indicated that environmental enrichment can reverse submissive and depressive behaviours instigated by chronic stress, and that these effects are dependent upon neurogenesis. While providing strong support for the role of neurogenesis in antidepressant treatments, these data also suggest that environmental factors play a key role in the mechanisms underlying those treatments. In humans, those environmental factors may include "physical exercise and positive psychosocial activities (which) can improve cognitive function, reduce depressive symptoms and increase stress resiliency" by making the "HPA axis more adaptive, resulting in decreased emotional reactivity and increased emotional stability" (Schloesser, Lehman et al., 2010, p. 10). These comments are quoted here because they are particularly relevant to the roles of HPA axis activation (mentioned above) as well as emotional reactivity (discussed in a later section of this thesis). Similarly indicating a link between the HPA axis, hippocampal neurogenesis and depression are data reported by Anacker and colleagues (2011), which demonstrated that application of the antidepressant *sertraline* increased hippocampal neurogenesis but did so via enhancement of the glucocorticoid receptor function.

Finally, the genetic origin of the link between hippocampal neuronal loss and/or decreased neurogenesis and depression is vividly illustrated in data recently reported by Chen, Hamilton et al. (2010), who found that hippocampal volumes of non-depressed girls whose mothers suffered from MDD were smaller than those in similar girls whose mothers were not depressed. Further supporting this genetic link, fMRI studies have shown that the degree of hippocampal volume reduction in depressed patients is significantly and directly related to the frequency of depressive episodes and the length of time they prevailed before treatment, and that adults who carried the double-*s* 5-HTTLPR polymorphism and who experienced childhood stress were more likely to have smaller hippocampal volumes than those who did not carry that polymorphism (Shelline, Gado et al. 2003).

4.5.1.1.1 Hypercortisolaemia, hippocampal volume reductions and depression: Summary

From a large amount of data collected in animal and human studies, it is apparent that hypercortisolaemia (whether from prolonged stress or disease such as Cushing's Syndrome) has damaging effects on the state and function of the hippocampus. Those effects may take the form of direct cell apoptosis or reduced neurogenesis, both leading to overall reductions in hippocampal function. These impairments to function are evident in memory problems, leading to cognitive confusion, which is one of the symptoms of MDD. Some data suggest that these processes may have a genetic basis. Reversal of hippocampal volumetric reduction or functional impairment via various antidepressant medication strategies further supports the role of hippocampal functional impairment in depression. However, it is not yet clear whether those changes to the hippocampus are

causes or effects of depression, and this issue will be a major focus of later discussions in this thesis regarding the possible synthesis of various neurobiological factors into a causal model of depression.

4.5.1.2 The prefrontal cortex (PFC): Anatomy and function.

The prefrontal cortex (PFC) is one of the four main lobes of the cerebral cortex, situated at the foremost part of the brain, composed of three major regions—orbital, medial and lateral, and has connections to the brainstem, thalamus, basal ganglia, limbic system and the reticular systems (Fuster 2001). While the orbital and medial regions are involved with emotional behaviour and mood disorders, the lateral region is involved in speech, reasoning and the temporal organisation of behaviour, although this localization of functions to areas has been criticized as over-simplistic and more reliant upon the connections that these regions of the PFC have to other brain regions rather than to the region alone (Fuster 2001).

Overall, the PFC assists in reasoning, judgment, motor planning, working memory, general decision-making (particularly about the self-imposition of socialized behavioural curbs, thus presenting what has been termed a 'personality') and motivation to succeed (Fuster, 2001) and, as may be expected from the development of these during the lifespan, lags behind other brain regions in terms of its maturity (Sowell, Thompson et al. 1999). The reduction in anxiety and other psychoses that followed prefrontal lobotomy in psychotic patients (Damasio, Grabowski et al. 1994) confirms the actions of the PFC in monitoring the external world and managing its demands by self-directed behaviour, a characteristic which is prominently mammalian, and which accounts for the exaggerated forehead in *H. sapiens* and other primates (Nolte 2009). In terms of the

orbital and medial cortices, both of these neocortical areas have connections with the amygdala, suggesting how they may be linked with the processing of emotion, as shown by impulsive and inappropriate behaviour in patients with lesions to these areas (Nolte 2009). Therefore, while the PFC helps to moderate behaviour appropriately for specific situations via access to working memory, judgments about the threat valence of stimuli are facilitated in the PFC by input from the amygdala and (as discussed below) its strong association with fear.

The orbital prefrontal cortex (PFCo) is situated just above the orbit and composed of the lateral, medial, anterior and posterior orbital gyri and the gyrus rectus (Fuster, 2001). The PFCo is involved in the evaluation of the consequences of behaviour, as shown in data from studies where information about changes in the value of potential positive or negative outcomes to their behaviour was unable to be used by rats and monkeys to control their behaviour if they had PFCo damage (Baxter, Parker et al. 2000; Izquierdo, Suda et al. 2004). The focus of the PFCo upon external stimuli was suggested by Ongur and Price (2000) and Ongur, Ferry et al. (2009), who reported the presence of two distinct sensory networks: the PFCo (which processes exteroceptive information), and the ventromedial PFC (which processes interoceptive information), although these two networks are densely interconnected. This two-part model of PFC processing of information for decision-making about the consequences of action was confirmed by Hurliman, Nagode and Pardo (2005) in a brain-imaging study of humans' responses to interoceptive *vs* exteroceptive information, and Rushworth, et al. (2005), who found that the PFCo made a special contribution to decision-making by selecting the most relevant environmental stimuli for evaluation. As noted by Schoenbaum, Roesch et al. (2009), the

PFCo acts to enhance flexibility in behaviour, a characteristic that is relatively absent from the repertoires of MDD patients (APA 2000).

The medial prefrontal cortex (PFCm) is that section of the frontal lobe which extends down the medial wall of the hemispheres to the base of the frontal lobe, and is composed of the medial part of the superior frontal gyrus and the most anterior portion of the cingulate gyrus (Fuster, 2001). The PFCm has a major role in the inhibition of behaviour (Quirk, Garcia et al. 2006) via extinction of conditioned fear, and is also involved in the evaluation of changes to the consequences of action (as is the PFCo) (Sotres-Bayon, Cain et al. 2006). Patients with damage to the PFCm show apathy, inability to concentrate and a lack of interest in their environment (Fuster, 2001). Because it acts to regulate and even extinguish previously-conditioned fear responses that have been established by the functions of the amygdala (see below), it is not surprising that the medial PFC also has projections to the amygdala and hypothalamus and (for access to memories) to the hippocampus (Ray and Price 1993).

Thus, each of these two sub-regions of the PFC contributes to its overall influence upon mood, perhaps via decreases in memory-based decision-making (which might elicit anxiety), inability to judge the outcomes of behaviour (perhaps leading to behavioural withdrawal from environmental stimuli) and apathy (another major symptom of MDD). Therefore, as a whole, the PFC may be hypothetically linked with mood disorders and depression, and damage or impairment in its function could induce depressive symptomatology. Apart from accidents, and disease, the most common source of damage to the PFC comes from hypercortisolaemia induced by chronic stress. This is discussed in the following section.

4.5.1.3 Links between stress, cortisol, PFC impairment and depression.

It is therefore of significance that even mild stress and consequent elevated cortisol can rapidly impair PFC function (Arnsten 2009) and structure (Fuchs, Flugge et al. 2006; Joels and Baram 2009), perhaps via down-regulation of genes which express for synaptic plasticity (Fuchs, Czeh et al. 2004; Karssen, Her et al. 2007; Belsky, Jonassaint et al. 2009; Bessa, Ferreira et al. 2009) and apical dendritic reorganization in pyramidal neurons in the PFC (Radley, Sisti et al. 2004). These alterations in PFC structure influence perceptual attention, which is impaired in stress-related psychiatric illness (Liston, Miller et al. 2006). Uncontrollable (but not controllable) stressors cause PFC impairment in animals (Minor, Jackson et al. 1984) and humans (Glass, Reim et al. 1971). In effect, non-stress conditions are marked by dominance of the PFC in decision-making, with influence over the *locus coeruleus* in the brainstem (the source of noradrenergic projections to the rest of the brain) and the *substantia nigra* and *ventral tegmental* areas (where major dopamine projections originate), giving the PFC effective command over catecholamine signals into the brain (Arnsten 2009). When the PFC is impaired (as may be indicated by reductions in its volume), cognitive appraisal of stressors is also impaired (Fuster 2001). This cognitive confusion is a major symptom of depression.

Evidence for the link between stress, elevated cortisol, reduced PFC volume and depression comes from a number of studies. Taking the link between reduced PFC volume and depression first, Kumar, Jin et al. (1998) reported that PFC volume showed a linear trend for reductions with severity of depression among 19 MDD patients, a finding replicated by Rajkowska, Miguel-Hidalgo et al. (1999). Bremner, Vythilingam et al.

(2000) reviewed 19 studies published between 1984 and 1996 that corroborated this finding, and further reported their own data for a 32% smaller PFCo in 15 MDD patients compared to 20 non-depressed controls, but no differences in volumes of other regions of the PFC, including the anterior cingulate cortex. However, in their review of the last 70 years' research, Price and Drevets (2009) noted that the "most prominent volumetric abnormality" (p. 10) in MDD was a reduction in grey matter in the left anterior cingulate cortex, and listed more than 10 studies which supported this claim. Further, Nitschke and Mackiewicz (2005) identified the dorsolateral PFC and anterior cingulate cortex as being centrally involved in the experience of volition, with damage to these areas being linked to apathy, one of the major symptoms of depression. Several recent studies offer further support for the role of the anterior cingulate cortex in depression in adults, adolescents and children (Boes, McCormick et al. 2008; Chiu, Widjaja et al. 2008; Schlosser, Wagner et al. 2008), perhaps via its influence on interpreting environmental events optimistically or pessimistically (Sharot, Riccardi et al. 2007), processing emotional responses from conditioned stimuli (Grimm, Boesiger et al. 2008), decision-making about rewarding stimuli (Bush, Vogt et al. 2002), and by its close association with the organism's processing of pain signals (Vogt 2005). The anterior cingulate cortex has also been shown to influence HPA axis responses (Diorio, Viau et al. 1993; Jahn, Fox et al. 2009), suggesting a link with stress and hypercortisolaemia. Apparently supporting the role of the cingulate cortex in depression, recent data reported by Portello and Serra (2010) indicate progressive reduction in cingulate cortex volume with the progress of MDD.

As in the hippocampus, stress and hypercortisolaemia cause reductions of the order of about 20% in the number and length of apical dendrites in the PFC (Radley, Sisti

et al. 2004), and these stress-induced alterations cause impairments in attentional processes that are present in depression (Liston, Miller et al. 2006). Even mild but acute and controlled stress has been shown to cause a rapid and dramatic decrease in PFC function via damage to neurons there (Arnsten 2009), causing a move from rational 'top-down' regulation of behaviour that is characterized by careful decision-making and a lack of impulsivity. These stress-induced reductions to the PFC have been observed in MDD patients who suffered from childhood stress and who carried the double-*s* 5-HTTLPR polymorphism (Frodl, Reinhold et al. 2010), reinforcing the links discussed above between this genetic subtype and depression. Conversely, when administered *ketamine* (which increases dendritic spine formation and synaptic transmission in the PFC) , treatment-resistant depressive patients rapidly become non-depressed (Welberg 2010)

4.5.1.4. Summary of PFC impairment and depression

Although involved in several key aspects of understanding environmental stimuli and decision-making regarding responses to those stimuli, the role of the PFC in depression is mostly concerned with how it connects to other brain regions such as the amygdala that are more intensively involved with emotional states such as fear and anxiety. Of concurrent relevance to depressive symptomatology, impairment of the PFC's ability to support flexibility in behavioural responses may also be linked with the depressive symptoms of anhedonia via inhibition of behaviour. Damage to the PFCm causes apathy, poor concentration and a lack of interest in the environment, all of which are major symptoms of MDD. Overall, stress-related hypercortisolaemia, damage to apical neurons in the PFC and consequent downgrading of memory-based decision-

making and ability to judge outcomes, apathy and behavioural withdrawal, are all aspects of depression and reinforce the causal pathway between HPA axis over-reaction and depression via alterations to the PFC and consequent deterioration in rational decision-making and involvement with environmental stimuli.

4.5.1.5. The amygdala: Anatomy and function.

The amygdala is considered by many to be the principal source of emotion within the limbic system and the entire brain (MacLean 1990; LeDoux 2007) and consequently associated with mood disorders. Therefore, description of the amygdala will be in greater detail than for the preceding regions.

4.5.1.5.1. Placement and structure

Named because of its shape (Gr: αμυγδαλή, *amygdalē*, 'almond': see Figure 8, p. 107), the amygdala is "a complex mass of gray matter buried in the anterior-medial portion of the temporal lobe, just rostral to the hippocampus" (Purves, Augustine et al. 2008, p. 742). The amygdala receives inputs from many sources, including all lobes of the neocortex, hippocampal and cingulate gyri (Bear, Connors et al. 2007), and connects cortical regions that process motor, mnemonic, autonomic and endocrinal responses to stimuli which hold emotional significance for the organism (Aggleton 1992). Thus, the amygdala connects sensory information with hypothalamic and brainstem effector systems to enable the organism to respond effectively to environmental events of major importance. In fact, one model of the amygdala suggests that, due to the intense connectivity it has with other areas of the brain, it is not a separate structural or functional unit itself but rather extensions of other areas of the brain with which it connects (LeDoux 2007). For example, the basal amygdala is seen as an extension of the cortex

rather than a set of amygdaloid nuclei with strong projections into the cortex (LeDoux and Schiller 2009). However, in order to discuss the amygdala in the same way as other components of the limbic system, it will be considered as a separate entity here, although its relationships with other brain areas will be seen as defining it.

Although commonly described as being composed of four major groups of nuclei (basal, lateral, medial, central: LeDoux, 2007), the amygdala may also be divided into *deep* nuclei (lateral nucleus, basal nucleus and accessory basal nucleus; the *superficial* nuclei (anterior cortical nucleus, bed nucleus of the olfactory tract, medial nucleus, nucleus of the lateral olfactory tract, perimygdaloid cortex, and posterior cortical nucleus); and the *remaining* nuclei (anterior amygdaloid area, central nucleus, amygdalohippocampal area and the intercalated nuclei) (Price, Russchen et al. 1987; Phillips and LeDoux 1992 ; Jolkkonen and Pitkanen 1998). However, the four-part descriptive system mentioned above (basal, lateral, central, medial) plus the intercalated cells, will be used in this discussion.

4.5.1.5.2. Connections:

(i) Inputs. The principal amygdaloid receiving site for sensory inputs is the lateral nucleus (LeDoux 2003), leading LeDoux (2007, p. R869) to describe the lateral amygdala as the “gatekeeper” of the amygdala because it is the major site for auditory, visual, somatic, olfactory and gustatory sensory inputs from the thalamus, with each sense having its own projection pattern plus interconnections which support the integration of information from different sensory modalities. In addition, the hippocampus and entorhinal cortex (part of the hippocampal formation with reciprocal connections to the hippocampus) also send signals to the lateral nuclei (Pitkanen,

Pikkarainen et al. 2006). The basal nuclei receive inputs from the orbital and medial prefrontal cortex of the PFC and also from the polymodal cortex associated with cognition; the medial nuclei get information from the olfactory bulb and cortex; the central nuclei receive inputs from the viscero-sensory cortex, the sensory brainstem and also the medial PFC; and the intercalated cells receive signals from the PFCm (LeDoux, 2007). It should be noted that this list of inputs to the various amygdaloid regions is not intended to be comprehensive. Such a list may be found in Davis (1997), although the inputs described in this paragraph are sufficient for the purposes of this discussion by demonstrating the links between the amygdala and the PFC and hippocampus.

(ii) Outputs. LeDoux (2003) described the central nucleus of the amygdala as "the interface with motor systems" (p. 729). As well as those from the central nucleus, outputs are made through the basal nuclei, which send signals to the ventral striatum (also called the nucleus accumbens, which is associated with immediate responses to threat, and which may have a role in depression (Alexander, Warner-Schmidt et al. 2010)), and also to the polymodal associative cortex (concerned with cognition), PFC and intercalated cells. The lateral nuclei send signals to the basal nuclei, the intercalated cells and the central nuclei, and the intercalated cells also send signals to the central nuclei. The central nuclei act as the major output region for emotional expression, sending signals to (i) the noradrenalin, dopamine, acetycholine and serotonin reticular modulatory systems, (ii) the periaqueductal gray matter (which instigates the freezing response in mammals when faced with inescapable threat), (iii) the hypothalamus (via the *ventral amygdalofugal* and *stria terminalis* pathways: Bear, et al., 2007) for hormonal responses and sympathetic nervous system and parasympathetic responses to threat and its cessation---the 'stress

response', and (iv) the dorsal motor nucleus of the vagus nerve, which instigates parasympathetic activity (Neidringhaus, Jackson et al. 2008). Although this description of the outputs of the amygdala is brief, it suffices to demonstrate the importance of amygdala outputs in the formation of behaviour representative of depressive symptomatology.

4.5.1.5.3. Transmitter systems

While the majority of inputs to the amygdala are glutamatergic, with 20% being GABAergic and 17% a mixture of both (Barazangi and Role 2001), the amygdala itself contains a powerful inhibitory network that acts to prevent neurons firing in response to irrelevant stimuli (Pare, Royer et al. 2003). Thus, novel stimuli produce responses which quickly habituate but which may become more powerful if such a stimulus is presented concurrently with an event that has previously been stored in memory and which possesses emotional significance (LeDoux, 2007). Activation of the amygdala is accompanied by the release of various neurotransmitters (including noradrenalin, dopamine, serotonin and acetycholine) into the amygdala itself and the forebrain, although it may be that dopamine is the primary neurotransmitter responsible for determining the significance of a stimulus (Kienast, Hariri et al. 2008) and thence the emotional/mood response to it. After the significance of the stimulus has been ascertained, noradrenaline appears to be central in the consolidation of the memory of stimulus-consequence links, as indicated by the training effect present after infusion of noradrenaline into the lateral nuclei in mice and rats immediately after they had undergone an emotionally-arousing learning task (Galvez, Mesches et al. 1996), but not present when noradrenaline was infused into the central nuclei, thereby confirming the

role of the lateral nuclei in learning emotionally-significant associations. Activation of β-adrenoceptors in the lateral nuclei after conditioning also enhances memory consolidation, probably via stimulation of cyclic AMP-dependent protein kinase pathways (Ferry, Roozendaal et al. 1999). Recent data suggest a major role for the metabotropic glutamate receptor 7 (mGluR7) allosteric agonist AMN082 in the development of fear responses, as shown when treatment with that agonist prior to fear conditioning procedures effectively prevented the acquisition of conditioned fear, while also producing a significant decrease in Long Term Potentiation in lateral nuclei synapses (required for fear conditioning) (Fendt, Schmid et al. 2008).

4.5.1.5.4. Functions

Following several decades of animal studies of the amygdala (see review by Phelps and LeDoux 2005), imaging studies on humans have confirmed that the amygdala plays a major role in (i) determining the emotional significance of auditory, visual and olfactory signals (Adolphs, Tranel et al. 1995; Bonda, Petrides et al. 1996; Scott, Young et al. 1997), thus assisting the individual adjust to everyday environmental challenges (Adolphs, Tranel et al. 1995; Morris, Ohman et al. 1998), and (ii) helping establish memories for emotionally arousing events (Cahill and McGaugh 1998 ; Hamann, Ely et al. 1999; McGaugh 2004). Establishment of memories is accomplished by the amygdala sending information regarding the emotional significance of environmental stimuli and events to the hippocampus to form memories that will act to arouse the individual when those stimuli/events next occur (Abe 2001; Richardson, Strange et al. 2004).

The amygdala is also involved in comprehending the relationship between stimuli that have potentially pleasant consequences and those consequences themselves. For

example, Balleine, Killcross and Dickinson (2003) found that lesions to rats' lateral nuclei prevented them connecting the sensory qualities of food with the emotional consequences of consuming it, a finding supported by Hellemans, Everitt and Lee (2006). Further to the encoding of stimuli and consequence, Wang, Ostlund, Nader and Balleine (2005) reported that the injection of the protein synthesis blocker *anisomycin* to the lateral and basal nuclei of the amygdala effectively prevented rats from linking stimuli (food) with the consequences of obtaining it. More precisely, the blockage of NMDA receptors in the lateral nuclei prevented rats from encoding the relationship between food and the outcome of eating it (Yin, Knowlton et al. 2005; Tye, Stuber et al. 2008).

4.5.1.5.5. Overview of the amygdala's role in responding to threat.

Perhaps the first indication that the amygdala was involved in mood came from the work of Kluver and Bucy (1937), who removed the temporal lobes (including the amygdala) of a particularly aggressive rhesus female monkey which then became tame. Weiskrantz (1956) specifically identified the amygdala as the key part of the temporal lobe that was associated with the fear response (which had been eliminated in rhesus monkeys by Kluver & Bucy's surgery). This finding set the scene for a large amount of research into the links between the amygdala and the fear response via use of a Pavlovian fear conditioning response (LeDoux, 2003). The amygdala's role in the organism's response to fear has been well-documented (Davis 1997; Rosen and Donley 2006), particularly its involvement in assessment of the intensity of aversive stimuli, such as fearful facial expressions (Adolphs, Tranel et al. 1995) and high levels of CO_2 (Ziemann, Allen et al. 2009). The lateral amygdala is crucial for association of fear memories with specific stimuli (Maren and Quirk 2004), and (as might be expected) in the extinction of

conditioned fear (Barad, Gean et al. 2006). Damage to the amygdala reduces conditioned fear responses (Weiskrantz 1956) and impairs recognition of fearful facial expressions (Graham, Devinsky et al. 2007), as well as perception of emotionally salient events (Anderson and Phelps 2001).

Further evidence of the amygdala's important role in mood comes from its association with the regulation of personal space and social behaviour. Humans with lesions to their entire amygdala were unable to show a sense of personal space, and healthy individuals showed amygdala activity when their own personal space was violated, suggesting that the strong emotional reactions engendered by violations of personal space depend upon an intact amygdala (Kennedy, Glascher et al. 2009). Bickart and colleagues demonstrated a direct and positive correlation between the thickness of cortical connections to the amygdala and the size and complexity of social networks in humans (Bickart, Wright et al. 2011).

Also indicating the amygdala's central role in emotion, persons with bilateral damage to their amygdala were unable to recognize facial expressions of fear (Anderson, Spencer et al. 2000), the transition of facial expressions from anger to fear (Graham, Devinsky et al. 2007), or facial expressions of sadness (Adolphs and Tranel 2004). Similarly, Anderson and Phelps (2001) found that patients with bilateral lesions to their amygdala or only to their left amygdala were unable to detect the aversive content in verbalizations, but that those patients with right amygdala damage were able to correctly identify the aversive content, thus narrowing the neurobiological strata for this task.

While the amygdala responds most strongly to novel stimuli (ie, those which have not yet been classified for their potential threat to the organism: LeDoux, 2007), the

pairing of stored memories of the emotional significance of previously-encountered stimuli with the repeated presentation of those stimuli can produce 'learned' fear-based emotional responses which originate within the amygdala, are mediated by the PFC (Ochsner, Ray et al. 2004; Heinz, Braus et al. 2005) and lead to powerful hormonal and SNS responses when activated by the amygdala's connections to the hypothalamus (Tranel, Gullickson et al. 2006). This process can instigate behaviour aimed at maximizing the organism's survival in the face of threat and is a key component of the limbic system's responsiveness to aversive stimuli.

4.5.1.5.6. Cortisol and the amygdala.

By contrast with its apoptotic effects on hippocampal and PFC neurons, hypercortisolaemia can *increase* amygdala structure and function (Roozendaal, McEwan et al. 2009). That is, as well as *reducing* the volume and performance of the hippocampus and PFC, elevated cortisol can also *increase* dendritic growth in pyramidal and stellate basolateral amygdala neurons (Vyas, Mitra et al. 2002; Vyas, Bernal et al. 2003; Fuchs, Flugge et al. 2006), leading to enhanced synaptic connectivity (Vyas, Jadhav et al. 2006) and neuronal plasticity (Shekhar, Truitt et al. 2005), as well as increased amygdala volume. These changes are associated with increased anxious behaviour (Ferry, Roozendaal et al. 1999; Mitra, Jadhav et al. 2005), a symptom of MDD. Of interest, these increases in amygdala volume and connectivity in rats do not reverse after the stress is removed (Vyas, Pillai et al. 2004), but studies of the effect of stress-management training on humans have indicated that reductions in perceived stress correlated positively with decreases in right basolateral amygdala gray matter density (Hölzel, Carmody et al. 2010).

4.5.1.5.7. Depression and the amygdala

Although elevated anxious behaviour that follows increases in the amygdala's volumetric and synaptic plasticity that are brought about by stress-induced hypercortisolaemia have been demonstrated, the links between increased amygdala volume and depression are not so clear. For example, some studies have reported that patients with MDD have greater glucose metabolism in the amygdala than non-depressed control subjects (Drevets, Videen et al. 1992; Ho, Gillin et al. 1996) and also greater amygdala electrical activity during processing of emotionally-relevant material (Siegle, Thompson et al. 2007; de Almeida, Versace et al. 2009). Frodl, Meisenzahl et al. (2002) reported that 30 patients experiencing their first depressive episode had significantly greater amygdala volumes than 30 non-depressed and matched control subjects. These data were confirmed by Lange and Irle (2004) with depressed young women.

However, this finding was challenged by Hastings, Parsey et al. (2004), who noted that female MDD patients had smaller amygdala volumes than female non-depressed controls, and Caetano, Hatch et al. (2004) who reported no significant differences in amygdala volumes according to depressed status. In a meta-analysis of this issue, Hamilton, Siemer et al. (2008) reviewed 13 studies of amygdala volume comparisons between depressed and non-depressed individuals and concluded that, while four studies which reported data from medicated MDD patients showed fairly consistent amygdala volume increases, three studies which used unmedicated MDD patients showed the opposite effects. Those authors argued that antidepressant medication induces glial and neuron growth in the amygdala as well as in the hippocampus and that this may be responsible for the finding that depression is associated with enlarged amygdala in

some studies. They also commented that the functional outcome of amygdala volumetric reductions that were accompanied by increased metabolic activity in MDD patients needed further exploration.

Two subsequent studies argue against the findings and conclusions reported in Hamilton et al.'s review. The first of these (van Eijndhoven, van Wingen et al. 2009), compared 20 MDD patients experiencing their first episode and who were not taking antidepressant medication with 20 remitted and non-medicated MDD patients and 20 never-depressed controls. Although there were no significant differences in amygdala volumes between controls and remitted MDD patients, unmedicated MDD patients who were experiencing their first depressive episode had significantly larger amygdalae than the other two groups. Those authors concluded that amygdala enlargement is a state marker of depression in the early stages of the disorder and is independent of medication status. They also noted that the enlargement of the amygdalas of unmedicated MDD patients was significantly correlated with depression severity, further arguing that the enlargement of the amygdala in early-depressed patients is an outcome of higher neural activation levels there, but that this effect might be masked later in the course of the illness by neurotoxic effects of chronic corticosteroid therapy during longer illness. Secondly, Lorenzetti, Allen et al. (2009) compared 29 current MDD patients with 27 recovered MDD patients and 31 never-depressed controls matched for age and gender. Recovered MDD patients' mean left amygdala volumes (201.9mm^3) were significantly larger than those of the control subjects (M = 145.2mm^3) ($p < .005$), and also non-significantly ($p < .095$) larger than those in current MDD patients (M = 170.2mm^3). The difference between current MDD patients' and controls' amygdala volumes was not

significant (p = .25). However, the conclusions drawn from these data may suffer from a lack of statistical power (sample sizes were relatively small) and the relative sizes of the current MDD and control subjects' left amygdalae may warrant further investigation. There were no significant effects at all for the right amygdala of any group comparison, fitting the previous literature that indicates that the left amygdala is more often active than the right when processing negative emotions (Baas, Aleman et al. 2004) and is also more active in depressed patients than in non-depressed controls (Drevets, Price et al. 2002). Of greater interest in terms of Hamilton et al.'s conclusions regarding the effects of medication upon amygdala volume, there were no significant interaction effects due to medication status and disease state.

4.5.1.5.8. Summary of stress, amygdala volume changes and depression

Dysregulation of emotional processing is a core feature of MDD, inculcating the limbic region, particularly the amygdala. While the data reviewed here confirm that elevated cortisol increases amygdala volumes (unlike its effect upon the PFC or hippocampus), the link between depression and enlarged amygdala is less conclusive. However, the most recent data suggest that the left amygdala is enlarged during some period of depression, and that medication does not account for that enlargement in all cases.

Leaving aside the relative uncertainty regarding the relationship between amygdala volume and depression, it may be concluded that chronic stress and consequent hypercortisolaemia contribute to enlargement of the amygdala. Further, following from the literature reviewed above that demonstrates the causal role that cortisol has in depression, it may be accepted for the purposes of this discussion that stress, elevated

cortisol and enlarged (left) amygdalae are linked with depression. It is certain that, underlying this relationship, the sensitivity of the organism to negative emotions that is a hallmark of enlarged amygdala (perhaps contributing to pessimistic attitudes—another major symptom of depression), plus the central role of anxiety in MDD, provides at least a working hypothesis linking these factors.

4.5.2. Summary: How cortisol affects the hippocampus, PFC and amygdala and may link to depression

Gold, Drevets and Charney (2002) suggested that the impairment of PFC function and reductions in volume and function of the hippocampus, plus amygdala neurogenesis and consequent amygdala-driven hypothalamic hyperactivity, were all possible causal links between elevated cortisol and depression, a view supported by Nestler, et al. (2002). During stressful conditions, the amygdala overrides PFC control of its functions of rational evaluation of stressors and instead activates stress pathways in the hypothalamus and brainstem, thus increasing levels of noradrenaline and dopamine release (Arnsten 2009). These increased catecholamine levels then strengthen fear conditioning circuits within the amygdala, creating a self-serving circle (Debeic and Le Doux 2006), contributing to emotion-based decision-making during times of chronic stress (Yu, Holsboer et al. 2008). One way of conceptualizing these structural changes to these three important brain centres is that they reflect a move from rational ‘top-down’ PFC control of behaviour to reflexive and fear-based ‘bottom-up’ emotional amygdala responses (Arnsten 2009), which in turn engenders those behaviours characteristic of anxiety and depression (APA 2000; Mitra, Ferguson et al. 2009).

Maletic and colleagues (2007) raised an additional point of some significance—that of the comparative roles of the hippocampus and amygdala in moderating hypothalamus functioning and how this might contribute to depression. As briefly mentioned above, the ventral region of the hippocampus is involved in inhibition of the SNS and subsequent reduction of anxiety behaviours (Whittle, Allen et al. 2006). That is, unlike the amygdala which responds to threat and which then activates the hypothalamus for fight-or-flight responses, the hippocampus has an inhibitory effect upon the hypothalamus. Anxiety is not only often comorbid with depression (Coryell, Endicott et al. 1988), there is also major overlap in the symptomatology for both disorders (Zinbarg, Barlow et al. 1994). For example, several studies of depression and anxiety among prostate and breast cancer patients (Sharpley and Christie 2007; Sharpley, Bitsika et al. 2010) have shown that it is difficult to disentangle the two disorders, their factor structures and their underlying symptomatology. Therefore, the links between hippocampal inhibition of anxiety and the amygdaloid activation of fear may represent a 'balance' of efforts by these two regions that has the effect of allowing the individual to manage threat. This is particularly cogent when the associations of volume changes in these two regions are correlated with depression. These modifications to the PFC, hippocampus and amygdala in response to hypercortisolaemia due to stress may begin prenatally (Lupien, McEwan et al. 2009) and have been shown to predict early onset of depression in adolescents (Van den Bergh, Van Calster et al. 2008).

In terms of the mechanisms by which elevated cortisol brings about the changes to the hippocampus, PFC and amygdala described above, cortisol has also been shown to have a biphasic effect upon mitochondrial function, with low cortisol levels instigating a

neuroprotective effect in the hippocampus and high cortisol decreasing mitochondrial membrane potential, calcium-holding capacity and mitochondrial oxidation, all of which compromise the ability of mitochondria to synthesise ATP (Du, Wang et al. 2009). These fundamental influences upon the ability of neurons to grow and function may perhaps explain the mechanism whereby hypercortisolaemia inhibits cortical neural plasticity in the PFC and hippocampus (Charney 2004). Finally, another outcome of stress is the decrease in brain-derived neurotrophic factor (BDNF), with damaging effects upon processes which repair and maintain brain structures (Schmidt and Duman 2007). For example, Duman and Monteggia (2006) reviewed 17 studies where chronic and uncontrollable stress has been shown to decrease BDNF, thus contributing to the links between stress, HPA activity and depression via alterations to selected brain regions.

In conclusion, when it is chronic, severe or uncontrollable, stress is unpleasant, and the physiological sequelae themselves that are inherent within the stress response (eg, SNS activation) can cause distress to those who are experiencing them. Because stress occurs in response to major threats, it is similar to some of the ways in which the body responds to infection in that resources are mustered for short-term intense elevation or change of physiological functions. Those changes to physiological functions are adaptive, but may also be experienced as unpleasant, thus drawing a parallel between stress responsivity and immune system reactions to pathogens. The role of the immune system in depression has been suggested for some time, and will be discussed in the next section of this chapter.

4.6 Immune system links to depression

Illness is unpleasant, sometimes intensely so. Perhaps as a result of that unpleasantness, depression is the most common psychological disorder in medically ill persons, occurring in between 15% and 61% of patients (Creed and Dickens 2007), although the latter figure may be inflated by the potentially confounding effects of some depressive symptoms which may also be a result of the physical illness present. However the two sets of symptoms overlap, there are substantial data indicating that several major physical illnesses are associated with an elevated incidence of depression, such as coronary heart disease (Barefoot 1997), chronic pain (Fishbain, Cutler et al. 1997), cancer (McDaniel, Musselmen et al. 1995), and diabetes (Anderson, Freedland et al. 2001). Although there is substantial discussion regarding the identity of the primary antecedent in this relationship (i.e., whether depression causes some illness or whether illness causes depression), the former perspective is beyond the scope of this thesis. Instead, for the purposes of this discussion, depression will be considered in its occurrence in people who are firstly physically ill. More precisely, depression will be examined in terms of its links with the immune system's responses to infection.

4.6.1 Stress, inflammation and illness

Much has been written about the role of stress and the immune system, and how these may interact with depression. For example, McEwen (2000) commented that, whereas acute stress enhances immune function, chronic stress suppresses it, acting through the HPA axis and ANS (particularly the SNS), and affecting the production of adrenal steroids that have biphasic effects upon immune function. That is, under acute stress, the immune system acts to protect the organism by moving immune cells from the

bloodstream to immune tissues (McEwan 2000). Elevated glucocorticoids have been shown to have the effect of transferring lymphocytes, monocytes and NK cells from blood to the tissue that is the organism's front-line interaction with environmental infectious threat (ie., skin) (Dhabhar 2000). This is commonly called the 'delayed-type hypersensitivity' (DTH) response, and describes an inflammatory response that develops 24 to 72 hours after exposure to an antigen that the immune system recognizes as foreign. This type of immune response involves mainly T cells rather than antibodies (which are made by B cells), and may be used as a marker of organismic immunocompetence (Poulter, Seymour et al. 1982).

By contrast with the (beneficial) effects of acute stress, chronic stress acts to reduce this translocation response in an inverted-U fashion, so that, after several weeks of stress, the DTH is reduced (Dhabhar 2000). This occurs primarily via decreases in immune cell translocation from the bloodstream to tissues, which may (in some part) be a result of habituation of the HPA axis responsivity and lowered corticosteroid responsiveness to stress (McEwan 2000), although this hypothesis is challenged by data that show prolonged stress is associated with long-term elevations of serum cortisol (Ulrich-Lai and Herman 2009).

Perhaps via the reduced DTH response, chronic stress has been linked to increased vulnerability to illness in a range of studies using different kinds of stressors such as: exams, caring for ill relatives, public speaking, pain, maternal separation, and disease (Friedman and Lawrence 2002). Linking this finding with the previous paragraph, Segerstrom and Miller (2004) conducted a meta-analysis of over 300 studies performed during the preceding 30 years, and concluded that, whereas acute stressors upgraded

some aspects of natural immunity, they also downgraded some specific immunity functions. Further, chronic stressors suppressed both cellular and humoral immunity, although subjective reports of stress were not significantly associated with immune changes. That review clearly established the links between environmentally-induced HPA and ANS responses and immune status, with "chronic stressors (being) associated with the most global immunosuppression" (p. 618). However, the ways in which these stress-induced changes to the immune system are linked with depression requires further elaboration.

4.6.2 Stress-linked immunological changes and depression

Several major literature reviews of the connections between inflammation, cytokines and associated pro-inflammatory proteins and depression are of assistance in gaining an overview of the empirical research data that link stress-induced immunological changes to depression. Cytokines are soluble protein or peptide molecules that are secreted by lymphoid cells and act as signalers to other lymphoid cells. Cytokines fall into various groups, including *Interferons* (released by infected cells and induce antiviral resistance in uninfected tissue), *Interleukins* (denoted as IL, produced mostly by T cells and involved in directing other cells to divide and differentiate), *Colony stimulating factors* (which direct the division and differentiation of bone-marrow stem cells and precursors of blood leucocytes), and other *cytokines* such as tumour necrosis factors (TNF) that mediate inflammation and cytotoxic reactions (Roitt, Brostoff et al. 1996).

Cytokines are often referred to as *pro-inflammatory* (including IL-1, IL-6 and TNF) or *anti-inflammatory* (IL-4, IL-10, IL-13) (Dinan 2008). When an antigen is

detected by toll-like receptors (which recognize the molecular patterns of various pathogens), cytokines are released and communicate with other cells to instigate the immune response to infection. Bearing in mind this role of cytokines (i.e., as communicators of defense processes against pathogens), it is of interest that the majority of depressed patients who have undergone psychosocial stress as the 'trigger' for their depression also show activation of the inflammation response, as described above. That activation profile may continue during remission from depression, although it is suppressed by antidepressant treatment (Kling, Laesci et al. 2007).

In July, 2010, ten reviews were identified from literature searches of the five years prior to that date and conducted in PubMed, Science Direct and Google Scholar using the descriptors 'depression', 'immune system', cytokines', and by hand-searches of identified papers. Those 10 reviews described the links between inflammatory cytokines and depression. Taken chronologically, and examined for their particular comments that were relevant to the relationship between depression and cytokines, the first review was by Hayley, Poulter, Merali and Anisman (2005). Those authors noted that, although cortisol was clearly related to the development of depression, so were several pro-inflammatory cytokines, including IL-1, IL-6 and TNF, that acted via interfering with neuroplasticity processes and monoamine activity, drawing a parallel between the effects of stress and cytokines on depressive status. Hayley and colleagues also noted that melancholic depressed patients show elevated IL-1, IL-2, TMF and other cytokines, and that the magnitude of those elevations was directly related to the severity of the depression observed in patients. Further, when administered IL-2 as a treatment for hepatitis C, those non-depressed patients showed some of the cognitive disturbances,

fatigue, sleep disturbances, irritability, appetite suppression and depressed mood that are symptoms of MDD.

While conceding that depression had been conceptualized as a condition of immune hyperactivation similar to cardiovascular disease, diabetes and cancer, and listing over 20 studies in which depressed persons who were otherwise healthy had been shown to have increased pro-inflammatory cytokines such as IL-6, C-reactive protein, IL-1 and TNF in their cerebrospinal fluid as well as peripherally, with further data showing a correlation between plasma concentrations of those pro-inflammatory cytokines and depression severity, Raison, Capuron and Miller (2006) also noted several studies that had failed to find a relationship between inflammation and depression, and others in which that association had been a function of other factors such as gender, body mass index or personality. Some studies had also failed to report a direct correlation between depressive severity and pro-inflammatory cytokines, with others actually finding an inverse correlation between the two. These inconsistencies in the relationship between depression and inflammatory cytokines led Raison, et al. to question the hypothesized 'causal' role of cytokines in depression, instead arguing that hypersecretion of CRH is the "crucial biological substrate of the well-known link between psychosocial stress and depression" (p. 25). While acknowledging that the depressive effects of pro-inflammatory cytokines in patients with medical illnesses explained why depression was five times as prevalent among patients with a wide range of medical disorders than among healthy persons, Raison, et al. challenged the causal role of cytokines in those depressed patients who were otherwise healthy. They argued that psychosocial stress triggers depression via the effects of CRH to increase pro-inflammatory cytokine activity, and that the primary

causal role for depression should therefore be allocated to environmental stressors that might first act to increase CRH (and cortisol) serum concentrations, then lead to elevated pro-inflammatory responses that may be linked with depression. While plausible, that hypothesis also needs to incorporate the role that hypercortisolaemia has in altering hippocampal, PFC and amygdala structure and functions, as mentioned above.

Dantzer, O'Connor et al. (2007) identified "sickness behavior" (p. 46) (such as feeling feverish and nauseous, experiencing a lack of appetite, sleep disturbance, loss of interest in social and physical environments, anhedonia, and being easily fatigued) as a normal response to infection and one that is triggered by pro-inflammatory cytokines such as IL-1β and TNF-α. That is, as well as coordinating the local inflammatory response to infection, IL-1β and TNF-α also act on receptors spread throughout several regions of the brain (e.g., dentate gyrus, pyramidal cell layers of the hippocampus, anterior pituitary gland, hypothalamus and others (Parnet, Kelley et al. 2002; Konsman, Vigues et al. 2004)) to cause these sickness behaviours. These behaviours help infected individuals cope with their illness by changing their perceptions of their state and their reactions to it. However, in some cases, those sickness behaviours may be so severe as to constitute the necessary symptomatology for a diagnosis of MDD by way of the social withdrawal that characterizes cytokine-induced sickness behaviour and which also underlies all depressive symptomatology (Bolling, Kohlenberg et al. 1999). Dantzer, et al. reported that administration of IL-1β or TNF-α to rats induced sickness behaviour such as withdrawal from social activity, motor behaviour, reduced water and food intake, increased fatigue, altered cognition and changed sleep patterns. The rats "stay in a corner of their cage in hunched posture" (p. 48), reminiscent of the behaviour of many humans

with MDD (APA 2000). By contrast, IL-6 has none of these effects but does induce a fever response via its effect upon the hypothalamus, thus suggesting that the roles of these cytokines are relatively exclusive in terms of the kinds of sickness behaviour they instigate. Further, the sickness behaviour effects of IL-1β and TNF-α are regulated by anti-inflammatory cytokines such as IL-10 by inhibiting their production and signaling, thereby arguing for a balancing role for pro- and anti-inflammatory cytokines in maintenance of non-depressive states.

In terms of the specific causal links between cytokines and depression, Dantzer, et al. described two pathways in which elevated cytokines affected precursors of depressive behaviour. First, patients who receive immunotherapy treatments show decreased levels of tryptophan (a precursor of 5-HT) and thence serotonin itself. Second, pro-inflammatory cytokines significantly activate the HPA axis by increasing glucocorticoid receptor resistance, leading to a failure to down-regulate the production of CRH (and consequently, cortisol). Clearly, these are complex processes and may interact to produce the range of symptoms that constitute sickness behaviour and/or depressive behaviour.

Although sickness behaviour thus may have some adaptive benefits for the infected patient (e.g., by restricting the infected individual's activity levels and instituting a 'resting' regime), Dantzer and colleagues argued that depression does not have such an obvious benefit for the individual, and they hypothesised that depression might be a maladaptive form of cytokine-induced sickness behaviour that follows prolonged immune responses to ongoing antigen challenge. However, this interpretation of depressive behaviour may be challenged by data which demonstrate that this pattern of behaviour can have an immediate and highly-valued beneficial outcome for the person

expressing it, as will be seen later in this thesis. That position is supported by the original formulation of sickness behaviour by Hart (1988), who argued that "it is quite logical to expect that animals and people …have also evolved nonimmunological disease-fighting strategies, including behavioral patterns.." (p. 123), and went on to demonstrate the survival value of not only fever but also "sleepiness, depression, loss of appetite, reduction of water intake, and cessation of grooming" (p. 124) as ways in which the infected organism may conserve its energy and maintain the elevated body temperature that can kill pathogens. Loss of appetite reduces the need for the animal to search for food, thereby also conserving energy; sleepiness and depression (being characterized in animals as inactivity, lethargy and being uninterested in their environment) are apparent in humans who are infected by systemic illnesses such as influenza) and also function to conserve energy to fight the pathogen that has infected the organism. Decreased energy expenditure by eliminating self-grooming may also be listed among the symptomatology of sickness behaviour as well as MDD, supporting Hart's argument that these two sets of behaviours are not only congruent in their consistency but also in their functions. Thus, sickness behaviour may represent an older but still relevant behavioural response to threat that manifests itself in humans who encounter uncontrollable and unavoidable chronic stressors---resulting in behaviours that meet the criteria for MDD.

In their editorial on the link between depression and inflammation, Glassman and Miller (2007) noted that, whereas there were sufficient "multiple, large, well-controlled studies" that have found increases in CRP, IL-1, IL-6, TNF and vascular adhesion molecules in depressive samples for the relationship to be established, the "number of inconsistent observations implies that the relationship… is more complex than merely

that inflammatory markers are increased in depressed patients", and that a "consistent but regularly ignored finding is that inflammation occurs only among a subset of depressed patients" (p. 280). These somewhat reserved comments are elaborated in some of the following reviews. For example, Dinan (2008), in his brief review, raised the issue of what role was played by toll-like receptors (TLRs) in depression. TLRs are key pattern recognition receptors in the identification of pathogens, thus instigating immune responses by TNF, IL-1 and IL-2, but at the time of Dinan's comments, no studies had been conducted into their direct contribution to depressive behaviour. Dinan also pointed out that, whereas depressed patients with suicidal ideation showed decreased IL-2, depressed patients without suicidal ideation had elevations in IL-6; and that the interferon IFN-γ reduced the production of 5-HT by converting its precursor (tryptophan) so that 5-HT could not be synthesised.

The multiplicity of potential pathways between chronic immunological responses, sickness behaviour and depression is apparent from these few data, but hesitations clearly remain in conclusively inculcating cytokines as the *primary* cause of depression. Dunn (2008) urged caution regarding the attribution of cytokine-linked depression to a single cause, suggesting that it was difficult to distinguish between the direct influence of cytokines, the effects of disease upon a patient's mood, and a combination of these two, concluding that "it is not necessarily the case that the body's immune response to the disease caused the depression" (p. 486). Perhaps the most valuable contribution that Dunn made was the comparison of the DSM-IV symptoms of MDD and symptoms in patients treated with IL-2 or IFN-α (Table 2, p. 489). Of interest, both of the key symptoms of MDD (anhedonia, depressed mood), plus six of the remaining seven MDD

symptoms were present in patients treated with those cytokines for immunotherapy purposes, with only feelings of worthlessness not being present. In a purely arithmetical sense, the presence of the two key MDD symptoms plus at least four of the remaining symptoms qualifies for a diagnosis of MDD, thus clearly linking cytokines with the formal definition of depression. However, sickness behaviour that is induced by IL-1 and LPS includes other symptoms that are not present in MDD, including hyperthermia, hypomotility, hypophagia, decreased interest in exploring the environment, decreased libido in males and more time asleep (Kent, Bluthe et al. 1992), thus demonstrating that sickness behaviour may be a broader response to illness and that depression might function as a part of that broader response. Further confirmation of the non-equivalence of MDD and cytokine-induced sickness behaviour comes from studies of the ineffectiveness of anti-inflammatory drugs that inhibit COX (a key enzyme in the production of prostaglandins) as antidepressants, leading Dunn to conclude that "…the actions of cytokines are unlikely to account for all depressive illness.. (and that) …by activating CRF, the HPA axis, and noradrenergic and serotonergic mechanisms, cytokines may complement (or even synergize) other factors that induce depression" (p. 499).

That caution was supported by data from Howren, Lamkin et al.'s (2009) meta-analysis of 51 studies of depression and CRP, 62 for depression and IL-6, 14 for IL-1 and depression, and 9 for IL-1ra and depression. That review concluded that, although there were significant relationships between each of these inflammatory factors and depression, results were inconsistent with respect to age, medication, gender and body mass index, leading those authors to conclude that three causal pathways existed between

inflammation and depression: depression causing inflammation, inflammation causing depression, and a bi-directional relationship between the two. Similar limited results were found in Dowlati, Herrman et al.'s (2010) meta-analysis of 13 studies of depression and TNF-α, 9 studies of IL-1β and depression, 16 studies of IL-4, 5 for IL-2, 4 studies of IL-8, 6 studies of IL-0, and 4 studies of interferon-γ. Significantly higher concentrations of TNF-α were found in 438 depressed subjects compared to 350 non-depressed subjects, and also in IL-6 for 492 depressed subjects compared to 400 non-depressed subjects, but no significant differences were found in the other cytokines across depressed *vs* non-depressed subjects.

As well as the links between cytokines and serotonin mentioned by Dantzer, O'Connor et al. (2007) and Dinan (2008), McNally, Nhagwagar et al. (2008) built upon an emerging literature that links dysfunction of the GABA-glutamate system with depression (Sanacora, Mason et al. 1999; Mason, Sanacora et al. 2000; Sanacora, Mason et al. 2000; Mason, Anand et al. 2001; Sanacora, Mason et al. 2002; Sanacora, Mason et al. 2003; Sanacora, Gueorguieva et al. 2004; Kendall, Krystal et al. 2005; Kugaya and Sanacora 2005; Sanacora, Fenton et al. 2006; Bhagwagar, Wylezinaka et al. 2007; Bhagwagar, Wylezinska et al. 2007; Krystal, Sanacora et al. 2007; Sanacora and Saricicek 2007; Sanacora, Zarate et al. 2008), arguing that the glutamate system was also involved with the interaction between stress, inflammation and depression via cytokine activity and thus generalizing the effects of cytokines to disruption of this neurotransmitter system also, providing another avenue through which inflammation might interfere with cognition and contribute to one of the symptoms of MDD.

The final review that was published during the last five years and which adds to the information from those described above was by Miller, Maletic et al. (2009) who, as well as summarizing the links between stress, cytokines and depression that were described above, also extended that discussion into the possible translation of these findings to treatment for depression. Miller and colleagues noted that the inflammatory biomarkers mentioned above were particularly valuable in identifying those depressed patients who were most likely to be treatment-resistant to traditional models of care, such as antidepressants or lithium (Sluzewska, Sobieska et al. 1997; Lanquillon, Kerig et al. 2000), and that antidepressant treatment was associated with decreases in inflammatory cytokines in 11 of 20 studies reviewed by Miller, et al., although body mass was a confound in much of the data, possibly because of the increased propensity for adipose tissue to produce IL-6 and other cytokines (Kern, Ranganathan et al. 2001).

As well as these ten recent reviews of the field, eight papers that were published during the last three years and which reported empirical findings extending the conclusions from those reviews were identified from the literature search. These papers were chosen because they give an indication of the breadth of this field, as well as suggestions of how it might move forward. For example, Capuron, Su et al. (2008) found that, in patients with metabolic syndrome (who have higher incidences of depression than healthy individuals), depression was associated with elevated C-reactive protein and IL-6, perhaps suggesting how metabolic syndrome acts upon the moods of sufferers of that condition and opening the way for investigations of the inflammatory links between a range of diseases and depression. The potent role of IL-1 in depression that is triggered by a prolonged period of stress was reported by Goshen, Kreisel et al. (2008) in their

study of the effects of chronic mild stress in mice, leading those authors to comment that "elevation in brain IL-1 levels…is both necessary and sufficient for producing the high incidence of depression that is found in these conditions" (i.e., chronic mild stress) (p. 717). Cizza, Marques et al. (2008) collected sweat from skin patches on 19 depressed women and 17 women who were in remission from depression. By identifying significantly higher levels of IL-1α, IL-1β, IL-6, TNFα and IL-8 in currently depressed persons than in those subjects who were in remission from remission, Cizza and colleagues presented a strong argument to support their hypothesis that non-invasive biomarkers of depression might be developed. Dhabhar, Burke et al. (2009) examined the relationship between IL-6 and Il-10 in depressed and non-depressed subjects and found that increased IL-6 and the absence of an immunoregulatory increase in IL-10 were associated with the presence of depression, suggesting that this imbalance between these two cytokines may contribute to the development of depression. The damaging effect of childhood maltreatment upon incidence of depression in adulthood was emphasized by Danese, Moffitt et al. (2008), who found that current depression alone was less likely to be associated with elevated cytokines (C-reactive protein) than the presence of current depression and childhood maltreatment, suggesting an interaction between childhood experience and inflammation that is linked to depression. Also concerned with the interaction of age and inflammation, Milaneschi, Corsi et al. (2009) found that, among persons aged 65 years or older, presence of high serum IL1-ra was significantly associated with incidence of depression. In the first of two studies of opposite intent, Raison, Borisov et al. (2009) peripherally administered the pro-inflammatory IFN-α to adults and noted a significant increase in CNS inflammatory responses and depression.

Conversely, in a study aimed to reduce depression and inflammation, Thornton, Andersen et al. (2009) provided psychological antidepressant treatment to breast cancer patients and found that it significantly reduced not only depression but also white cell blood count and neutrophil count (which may be used as indicators of inflammation). There are many studies of the relationship between inflammatory cytokines and depression, and this small selection represents the wide range of issues and topics that are being investigated in this field.

4.6.3 Cytokines and depression: summary

Thus, as suggested by these reviews and the sample of empirical studies, several specific cytokines have been: (a) reliably linked with almost all aspects of MDD symptomatology; (b) observed to be elevated in MDD patients compared to non-depressed subjects; (c) seen to possess several potential pathways linking stress and depression, including activation of the HPA axis, interference with 5-HT production, and also have a reciprocal interaction with depression; (d) may be used to induce a depressive-like state when injected peripherally; and (e) reduce in concentration when psychotherapy for depression is successful.

Chronic stress appears to induce elevated cytokine activity, but may do so via increases in CRH production rather than directly. While acute stress acts to increase immunocompetence in the short term, prolonged stress has the reverse effect, probably via decreased CRH receptor sensitivity, thus reinforcing the intermediary role of the HPA axis between stress and immune system function, leaving the individual more vulnerable to illness.

Although IL-1, IL-6 and TNF plus C-reactive protein have the most supportive data linking them with depression, the balancing role of IL-10 also requires inclusion in any equation describing this relationship, and sufficient other cytokines have been implicated with depressive symptomatology as to warrant further investigation. The lack of consistent findings requires attention, particularly as they interact with other factors such as adiposity and age.

However, probably the most relevant aspect of inflammation that connects it with depression is sickness behaviour. While there is a clear overlap between symptoms of sickness behaviour and MDD symptomatology, emphasizing behavioural withdrawal from social and other activities, plus the links between elevated cytokines, hyperactivation of the HPA axis and interference in the synthesis of 5-HT, there is a plausible amount of evidence and hypothetical pathways between stress, HPA axis-induced cytokine activity and inflammation, and a set of sickness behaviours that reflect much of depressive symptomatology, to assume that cytokines are an important link between stress and depression. The indication that childhood trauma may figure in this relationship is consistent with data reviewed earlier in this chapter regarding HPA axis hyper-responsivity, hypercortisolaemia and alterations to the PFC, hippocampus and amygdala that accompany affective disturbance and depression. Therefore, it remains to posit a model of how cytokines (and the other factors reviewed in this chapter) interact to produce depressive symptomatology.

4.7 Overview of neurobiological factors in depression.

Several genetic factors have been implicated in depression by establishing a vulnerability for development of the disorder. That vulnerability may be evident in what

was once referred to as ‘endogenous’ depression, perhaps via genetic factors setting up the carrier for depression almost regardless of environmental pressures. In such cases, the depressive state will persevere most of the time, perhaps accompanied by melancholic features as a result of its relative long-term nature.

Alternatively, in ‘exogenous’ depression (where the impact of environmental stressors is more apparent), specific sensitivity-to-environment genetic-based predispositions such as the well-researched 5-HTTLPR polymorphism may combine with aversive life events or stressors to trigger depressive symptomatology which may be transient. Although the descriptors ‘exogenous’ and ‘endogenous’ are no longer in such wide usage as they once were, having been replaced by a focus upon depression severity instead, that concept does help to illuminate the combination of genes and environment which has received a great deal of research support as a model of depression and which can help explain why the disorder occurs. Figure 9 (p. 151) presents such a model which, while simplistic, captures the interaction between ‘genetic factors’ (including gender) and environmental stressors in the development of depressive symptomatology. Different factors are shown in different colours.

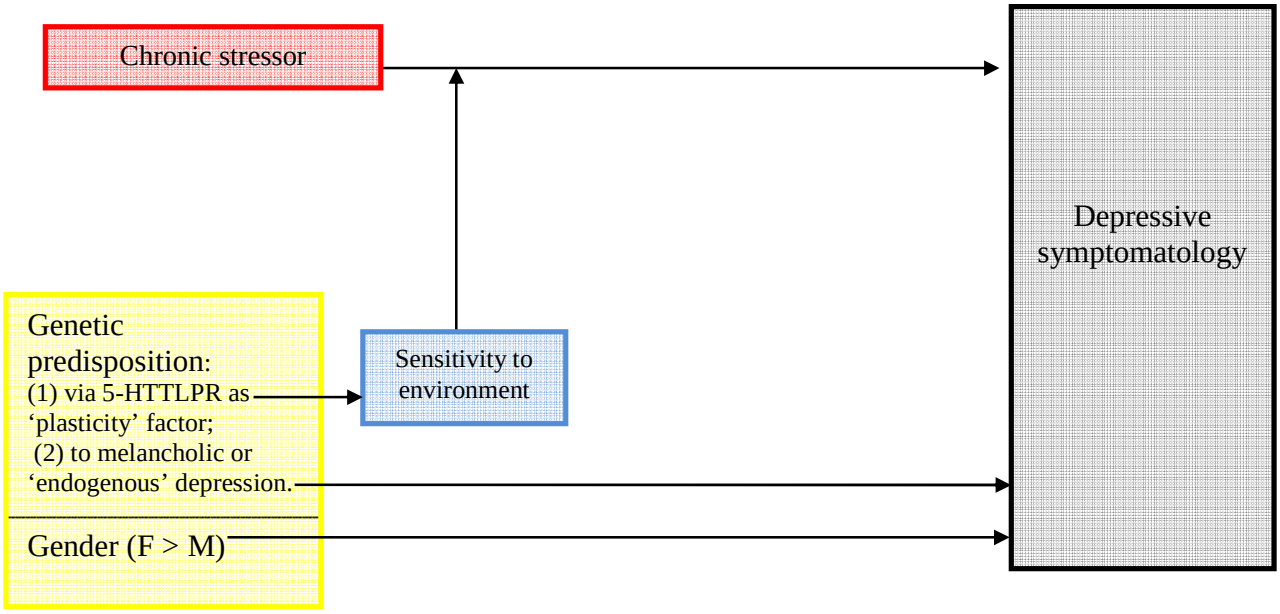

Figure 9: Genetic factors, stressors, and depressive symptomatology.

However, although these genetic factors establish the necessary conditions for depression, they do not explain *how* the depressive symptomatology actually develops, and *why* this particular form of behaviour is the result of chronic stressful events. That role may be a function of several concurrent and/or intermingling neurobiological sequelae of the gene-environment interaction, but one of those sequelae may be a deficiency in major neurotransmitters, principally serotonin, dopamine and noradrenalin.

Despite the data which link at least some genetic factors to reduced concentrations of these neurotransmitters, which indicate that MDD patients often show such reduced concentrations of 5-HT, NA and DO, and which also demonstrate that application of MOAIs and related agents to inhibit the reuptake of those neurotransmitters from the synapse act to reduce depression in some patients, the Monoamine model of depression is

not strongly supported by the data reviewed above. Further, the delay in the anti-depressive effects of increased concentrations of neurotransmitters which is occasioned by antidepressant medication challenges their direct 'causal' connectivity to depression. When added to the finding that, even among those MDD patients who do eventually show improvement, the change on scales of depressive symptomatology is clinically negligible, the link between neurotransmitter deprivation and depression is weak. Antidepressants that increase neurotransmitter concentrations do appear to be effective with patients who suffer from severe depression (melancholic depression) but not for most other patients. Figure 10 depicts the possible place of lowered neurotransmitter concentrations in the development of depression, the uncertain causal role of this factor (and genetic predisposition) being indicated by the dashed lines.

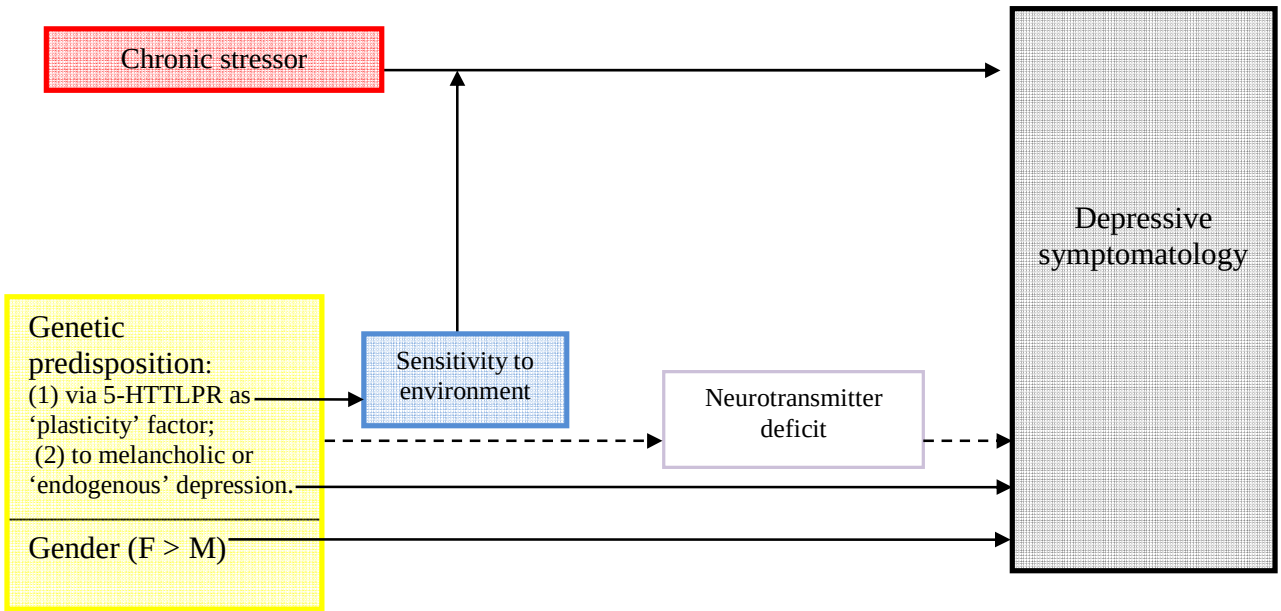

Figure 10: Genetic factors, stressors, neurotransmitters, and depressive symptomatology.

The way in which environmental stressors reciprocally interact with genetic vulnerability, reduce neurotransmitter concentrations (to the extent that they do), and influence depressive behaviour is clearly central to any understanding of depression. The hyperactivation of the HPA axis, elevated CRH and ACTH, and the consequence of hypercortisolaemia, have been reliably linked with the presence of depressive symptomatology. CRH and cortisol are well-established as instigators of depression, and the way in which cortisol in particular achieves this is of potentially most value in explaining how (and why) depressive behaviour emerges in the repertoire of the genetically-vulnerable person who undergoes chronic and uncontrollable stress. Figure 11 adds CRH and cortisol to the overall model, including the effect that genetic predisposition to HPA axis hyperesponsivity may have.

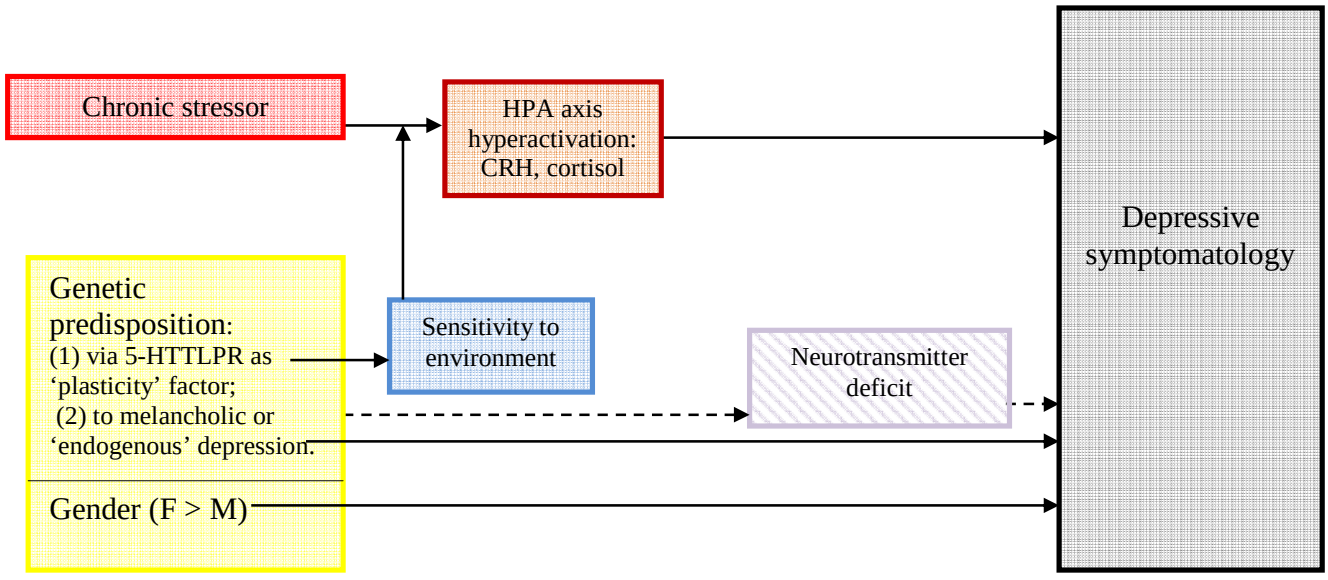

Figure 11: Genetic factors, stressors, HPA-axis responses, neurotransmitters, depressive symptomatology.

The prominent role played by cortisol in depression has been described as occurring via a number of intermediary factors, one of which is alterations to specific brain regions-–the hippocampus, PFC and amygdala in particular. The reductions in volume and functionality (whether via cell apoptosis or reduced neurogenesis) in the hippocampus and PFC that are brought about by elevated cortisol produce cognitive confusion, memory problems and reduced hippocampus/PFC control of hypothalamic reactions to environmental threats. By contrast, the dendritic arborization and increased functioning by the amygdala that are caused by elevated cortisol enhance fear responses and produce hypothalamic reactions that reflect this. Overall, the cortisol-induced down-regulation of the 'rationale' decision-making that is primarily a function of the PFC and hippocampus, plus the up-regulation of the 'emotional' (primarily fear) functions of the amygdala, establish a response regimen that fits the survival needs of the organism when it is in a major life-threatening situation by instigating enhanced flight-or-fight behaviour response patterns. Should this situation continue indefinitely (as when the organism is under chronic and uncontrollable stress), then these changes to brain regions, plus their alteration of the response systems (hypothalamus, SNS) to that situation, may induce depressive symptomatology. Figure 12 (p. 155) shows the link between genes, stress, HPA-axis responses, cortisolaemia, brain region changes and depression.

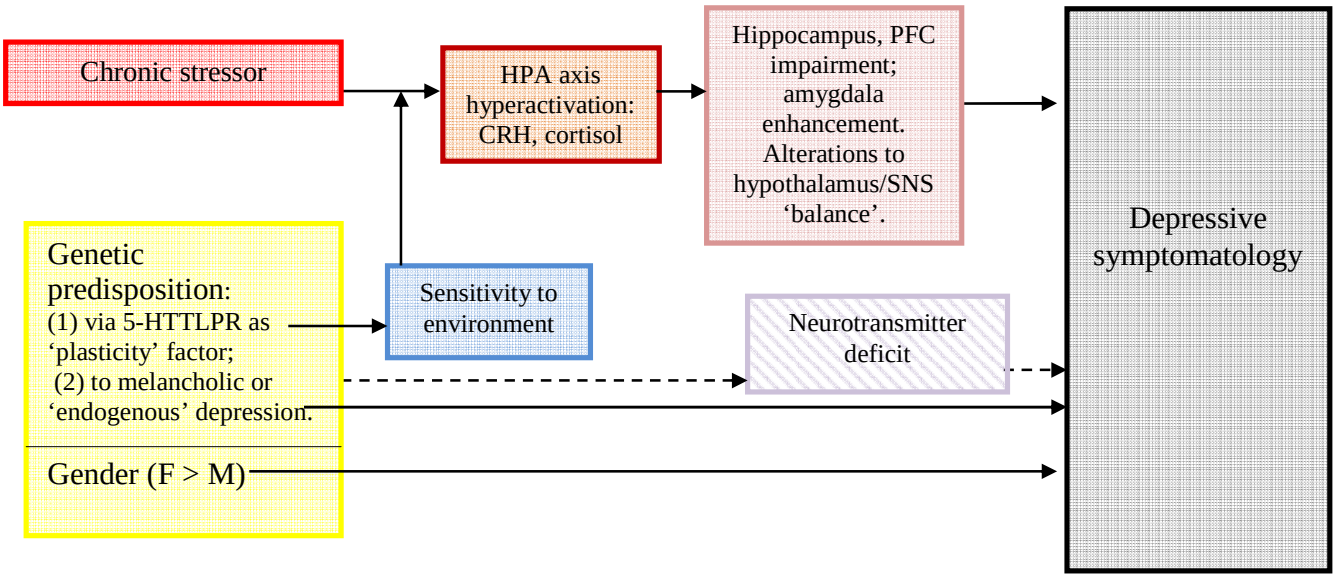

Figure 12: Genetic factors, stressors, HPA-axis responses, brain region changes, neurotransmitters, depressive symptomatology.

The fact that these changes to the hippocampus, PFC and amygdala begin prenatally, predict early onset depression, are a direct outcome of cortisol and its damaging effect upon mitochondrial function, and are accompanied by reductions to BDNF, all indicate that the HPA-axis responsivity to chronic and uncontrollable stressors (that has a major effect upon those brain regions responsible for the balance between rational and hypothalamic/SNS fear-based responsivity) is more than simply dysregulation of those systems. This sequence of actions, from genetically-influenced HPA-based response to a stressor, changes in brain region form and function and (perhaps) reductions in neurotransmitters necessary for cognitive clarity and problem-

solving, produce behaviour that may be perceived as adaptive in that it helps the organism deal with a major threat from the environment.

One further aspect of that potentially adaptive functioning is the response of the immune system to stress, and how this might contribute to depression. Several cytokines have been linked with depression, and the imbalance between pro-inflammatory and anti-inflammatory cytokines may be the central core of this relationship. Moreover, those cytokines have been shown to respond to HPA axis activation, interfere with production of serotonin, and interaction reciprocally with depression. Administration of cytokines can induce depressive-like behaviours, and cytokine concentrations decrease under psychotherapy. The links between cytokines and depression are firmly grounded in the stress reactivity of the organism, principally via the effects of CRH, which may decrease immunocompetence during prolonged stressor demand.

However, the most relevant (and potentially illuminating) aspect of the relationship between cytokines and depression is via the phenomenon that has been termed ‘sickness behaviour’. Because of the significant overlap between sickness behaviour and depression, with the latter being a subset of the former according to Hart (1988), Dunn (2008) and Dantzer, et al. (2007), the hypothesis that depression may be part of an organism-wide response to pathological influences arises. Certainly, sickness behaviour is mainly characterized by behavioural withdrawal from threat, a commonly-cited underlying theme of depressive symptomatology (Bolling, Kohlenberg et al. 1999). As such, cytokine links with depression via elevated HPA axis responses fit within the model developed above, and which is re-presented in Figure 13 (p. 157) to include cytokines and sickness behaviour.

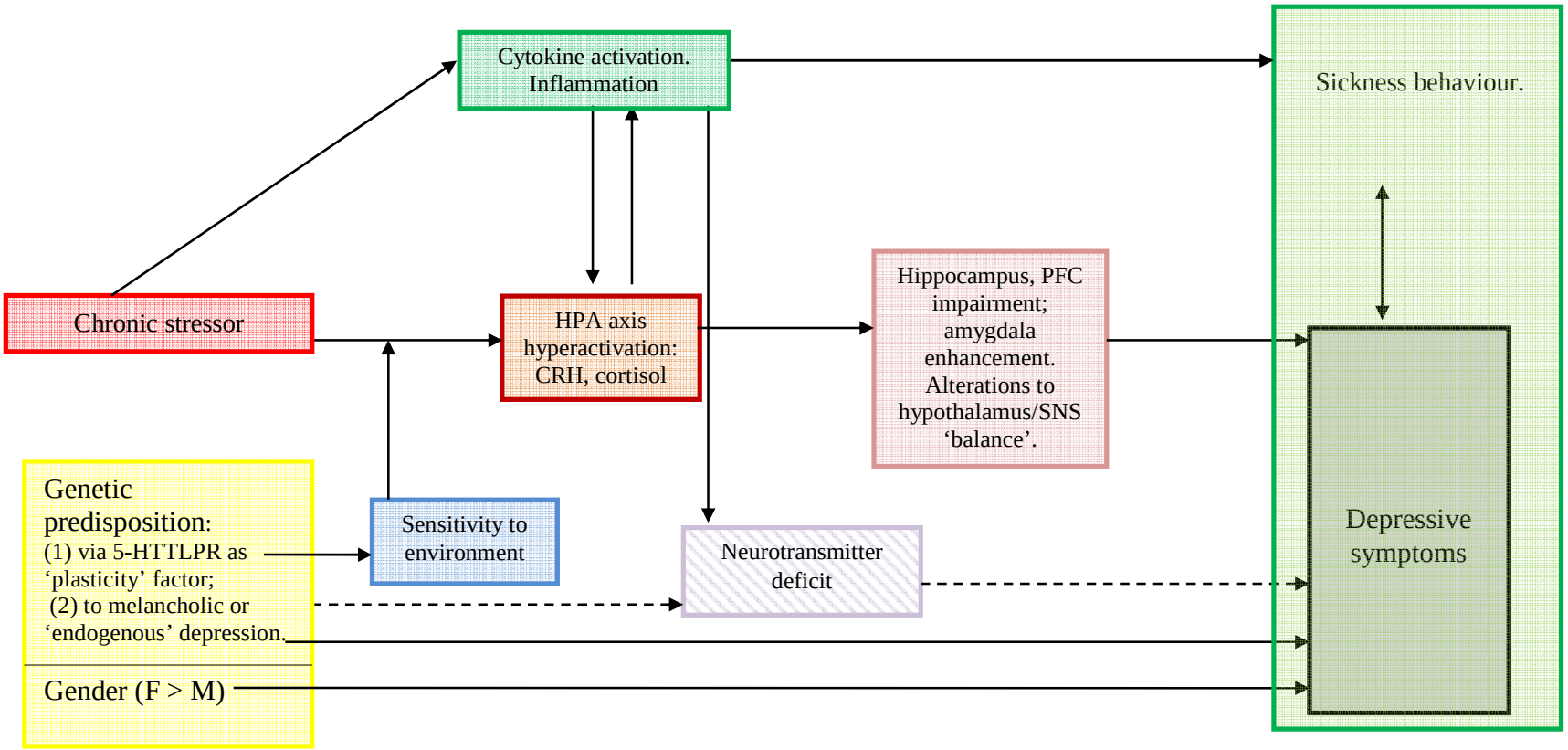

Figure 13: Genetic factors, stressors, HPA-axis responses, neurological sequelae, neurotransmitters, cytokines, sickness behaviour, depressive symptomatology.

4.8 Explanations of causality

As explained above, some 'depressive' symptomatology may be subsumed within a 'sickness behaviour' model, wherein the organism is seeking to cope with, or adapt to, an uncontrollable aversive environmental stressor by instigating exaggerated HPA responses, cytokine activity, and replacement of rational decision-making by fear-based strategies. Because the depressive/sickness behaviour may have 'adaptive' qualities in that it assists the organism to cope effectively with a threatening environment, these responses to stressors may be conceptualized as not simply 'dysregulation' of the various bodily systems involved, but may instead represent purposeful (or at least adaptive) physiological/neurobiological and behavioural changes in the face of overwhelming aversive environmental demands.

While the suggestion that depression can be 'useful' or 'functional' to the sufferer may be unusual, it is very close to the rationale for sickness behaviour being functional for the ill animal, as posited by Hart (1988) and Dantzer et al. (2007). That is, just as fever, runny nose, diarrhea and vomiting are the unpleasant but functional *responses of the organism* to invasive pathogens (rather than the pathogen itself), so also may the unpleasant symptoms of depression (such as anhedonia, loss of interest in activities, social withdrawal, eating and sleeping disturbances, etc) be functional *responses by the organism* to combat the 'pathogen' that is represented by uncontrollable aversive environmental stressors. Bearing in mind that sickness behaviour (including some depressive symptomatology) evolved in other animals well before the emergence of *homo sapiens sapiens*, the hypothesis that depressive symptomatology represents a generalization of the organism's attempt to escape from threat is plausible. One step in understanding this model of depressive behaviour is consideration of the kinds of threats that are seen to instigate depressive behaviour. That is, what

are the environmental stressors that trigger HPA axis hyperesponsiveness in people who carry the 'sensitivity to environment' *s* form of the 5-HTTLPR polymorphism, and any other similar genetic factors that may predispose carriers to have exaggerated stress reactions to stressors.

To discuss that issue, it is necessary to consider (1) the types of events that befall people and which act as 'triggers' for depressive responses, (2) how those events interact with genetic and other neurobiological factors that were set out in Figure 13, and (3) how the consequent depressive behaviour acts to provide some kind of benefit to the person exhibiting it and who is faced with those 'trigger' events. The next two chapters deal with these issues.

CHAPTER 5: AVERSIVE EVENTS THAT 'TRIGGER' DEPRESSION

5.1 Types of adversity

All animals strive to exist within an environment that is not always hospitable. During that existence, most animals experience some adversity, whether it is minor or severe, and respond to it in ways that maximize their chances of survival. Because this thesis is focussed upon depression in humans, this chapter will review the literature which links depressive behaviour with preceding aversive events in humans where possible, but with reference to studies on other mammals where human data are not available. Two particular areas of research which serve to illustrate the links between adversity and depression are physical illness and childhood mistreatment.

5.2 Physical illness as a trigger for depression

In a discussion of the links between anxiety, depression and chronic medical illness, Katon, Lin et al. (2007) reviewed 31 randomised controlled trials (each of which had more than 100 participants) that included a total of 16,922 patients across a range of illnesses including diabetes, coronary artery disease, congestive heart failure, asthma, and arthritis. Somatic symptoms were at least as strongly associated with depression and anxiety as objective physiological measures, leading those authors to argue that diagnoses of anxiety and depression were "essential in understanding the cause …of somatic symptom burden" (p. 147). Although that review did not tease out the 'triggering' effects of disease on depression *per se*, it did emphatically show the association between physical illness and depression.

Data from Australian patients do, however, indicate that depression is worse when disease is more severe, and complement WHO data which recognize "the interaction between depression and physical illness" (Clarke 2009, p. S52). Of interest to discussions of the causal relationship between disease and depression, Clarke and Currie (2009) summarised other reviews of this

phenomenon. For example, from 32 previous reviews of the links between heart disease and depression, it was found that 60% to 70% of patients were experiencing depression at the time of follow-up (1 to 4 months) after their myocardial infarction. From 23 previous reviews, up to 36% of stroke patients were also depressed at six months after their stroke. Incidence of depression among diabetes Type 1 patients was 12%, and between 8% and 52% for Type 2 patients (based on 19 reviews). Major depression was found in 14.4% of patients with asthma (12 reviews), and in up to 80% of patients with rheumatoid arthritis (24 reviews). Between 20% and 35% of patients with cancer experienced ongoing depression (36 reviews). In some of the author's own research, depression following a diagnosis of prostate cancer was found in between 13% (Sharpley and Christie 2007) and nearly 40% (Sharpley, Christie et al. 2010) of samples, depending on the time after diagnosis and the lack of success of treatment. As an indicator of the ongoing link between disease and depression, a study by Shah, Gupchup et al. (2008) found that 72% of 201 non-hospitalised male and female Type 2 diabetes patients were clinically depressed up to 10 years after initial diagnosis.

Although there are data which indicate that the presence of depression following a heart attack significantly predicts further heart disease (Davidson, Burg et al. 2010), the studies reviewed above support the hypothesis that the presence of major diseases is strongly associated with the development of depression. As noted by Creed and Dickens (2006), "Psychiatric disorders of all types are more common in people with physical illness compared with the general population. Depression is the most common disorder, accounting for approximately 50% of psychopathology in the medically ill" (p. 3).

These physical illnesses act as stressors for the people who are experiencing them. There is no doubt that *receiving a diagnosis* of a major illness such as cancer, diabetes, cardiovascular

disease, etc, will act as stressors that will trigger anxiety, HPA axis responsivity, and the sequence of neurobiological changes shown in Figure 13 (p. 157) that culminate in sickness behaviour, including depressive symptomatology. That aspect of physical illness (ie, receiving the diagnosis and reflecting upon the life-threatening aspects of such severe illnesses) is a *psychogenic stressor* that can act to elevate HPA responses, but the illness itself is a *physiological stressor* (which will cause cytokine activation and inflammation, leading to the development of sickness behaviour). Because of the ongoing nature of these aspects of major physical illness, they constitute the characteristics of being a 'chronic stressor' as depicted in Figure 13 and described above (p. 85) and may be inserted into the diagrammatic structure shown in Figure 13 as examples of chronic stressors. However, even prior to the onset of major physical illness, adversity during early childhood may affect mood later in life, and the next section of this chapter describes that influence.

5.3 Childhood maltreatment as a trigger for depression

The damaging effects of childhood maltreatment upon later psychological functioning have been observed for some time. For example, the concept of the 'Battered Child Syndrome' was described in the nineteenth century by French Forensic Medicine specialist, Taedieu (Tardieu 1860) and translated by Roche (2005). More currently, depressive symptoms as a result of mistreatment have been recorded in children as young as three years of age (Côté, Boivin et al. 2009; Luby, Si et al. 2009). It is of note that the depressive symptomatology noted in these very young children was not developmentally transient, but chronic over the 24-month period of observations undertaken in the study (Luby, Si et al. 2009), suggesting that depression was not typical of other illnesses that usually occur in response to a specific pathogen during the early years of life. In fact, other data suggest that the frequency of depression *increases* during the first five years of age, and that the strongest predictors of depression in infants are the child having a difficult temperament at six

months of age, plus incidence of lifetime maternal depression (Côté, Boivin et al. 2009), reflecting the strong familial association factor in depression that was discussed earlier in this thesis.

While the unpleasant and even traumatic effects of being mistreated by those adults upon whom one is dependent for safety and survival may easily lead to a child feeling a sense of powerlessness and fear of the future, intellectual conceptualization of those experiences (and their emotional sequelae) is usually done by adults. That is, children do not usually have the ability to consider or communicate about the mistreatment they experience from a clinical or scientific perspective *at the time they are experiencing it*---they are simply too deeply immersed within the immediate unpleasant environment that is dominated by a sense of unpredictability and insecurity to do so. As such, and because of their relative powerlessness to alter the unpleasant environment, children have few options to escape from that environment or to rationalize its presence. Further, if the mistreatment they experience is intermittent with periods of non-aversive parental interactions (even sometimes caring), the unpredictability of the environment becomes even more pronounced. Under these circumstances, it may be that the only recourse available to a child in this situation is to cognitively and emotionally withdraw from the environment, but to do so in an appeasing manner so as to avoid annoying their parents. This type of withdrawal is noted in the symptoms of appeasement and submission shown by adults who undergo prolonged periods of unpredictable and aversive treatment by others who hold them 'captive', such as in prison or hostage situations (Price, Gardner et al. 2004).

Evidence to support the hypothesis that aversive early life experiences can predict later mood disorders is shown in two large studies of 9,282 and 5,692 adults respectively (Green, McLaughlin et al. 2010; McLaughlin, Green et al. 2010). In the second of those studies, it was found that childhood adversities were associated with 44.6% of all psychiatric disorders that

occurred during childhood and up to 32.0% of those that occurred during adulthood. Carballo, Chibuikem et al. (2008) emphasized the damaging effects of early childhood abuse by showing that the risk of suicide in adults was ten times as strong for people who had experienced abuse during childhood compared to adults who had not experienced childhood abuse.

In terms of specific adversities, the death of a parent more than quadruples the risk for depression in children, adolescents and young adults (Brent, Melhem et al. 2009). Less severe, but nevertheless significant in its effects upon childhood mood, postpartum depression among mothers (and consequent reduced nurturing for their infants) has been causally linked with an exaggerated fear response, poor social engagement behaviour and elevated cortisol in their nine-month old infant children (Feldman, Granat et al. 2009). Variations in maternal care have also been shown to alter the expression of genes that regulate behavioural and endocrinal responses to stress in offspring, and even hippocampal synaptic development in humans (Meaney 2001) and alterations to the PFC and cingulate cortex in primates (Spinelli, Chefer et al. 2009). All of these experiences are (i) aversive to the child experiencing them, (ii) uncontrollable by that child, and (iii) ongoing. Therefore, they constitute a chronic stressor to the child who suffers them, as shown in Figure 14 (p. 165), which also includes physical illness as a chronic stressor with links to sickness behaviour via cytokine activation.

It is also valuable to explain *how* these aversive experiences during childhood can influence HPA-axis responses, and the next section will deal with that issue.

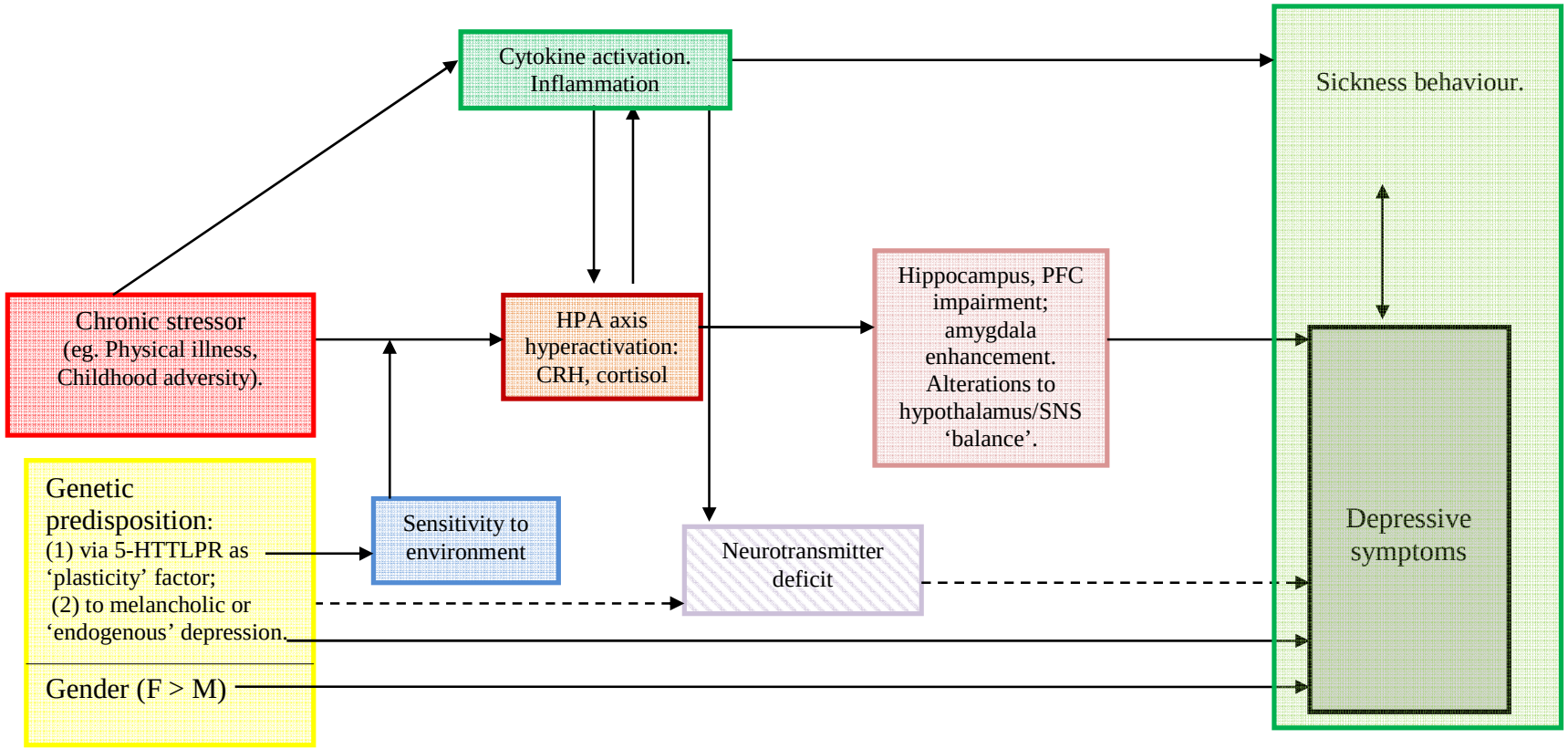

Figure 14: Genetic factors, stressors (with some examples), HPA-axis responses, neurological sequelae, neurotransmitters, cytokines, sickness behaviour, and depressive symptomatology.

5.3.1 How childhood adversity leads to decreased glucocorticoid receptor expression and elevated HPA-axis responsivity to stress

The elevated HPA-axis responsivity to stressors that is significantly and consistently associated with depression (described above) occurs via *decreased expression* of the glucocorticoid receptor (GR) gene, which makes the HPA-axis feedback system less sensitive to levels of circulating glucocorticoids, and hence increases the release of CRF from the hypothalamus, ACTH from the pituitary and cortisol from the adrenal glands. Conversely, *increased expression* of the GR gene is associated with decreased responsivity of the HPA-axis to stressors and consequent lower levels of anxiety and depression.

The central role of the HPA axis as a link between mothers' antenatal anxiety and later depression in their children has been demonstrated in a prospective study (Van den Bergh, Van Calster et al. 2008), which reported that HPA axis dysregulation in mothers mediated the incidence of depressive symptoms in their teenage daughters. O'Connor, Ben-Shlomo et al. (2005) demonstrated that prenatal anxiety in mothers was directly and significantly associated with elevated cortisol in their 10-year old children. In an explanation of how this process occurs, Oberlander, Weinberg et al. (2008) suggested that it was due to methylation of the glucocorticoid receptor gene *NR3C1* in newborns and (resulting) elevated cortisol at three-months of age. This is an 'epigenetic' process.

An 'epigenetic' process is one in which environmental events influence the expression of particular genes by forming a heritable phenotype that is not coded by a change in DNA sequence (Nestler 2009). While this process occurs across many cell types and is necessary for normal healthy physiological functioning, studies in rats have demonstrated that a lack of maternal nurturance (in the form of licking and grooming of offspring) can epigenetically alter the expression

of genes responsible for the efficiency of glucocorticoid receptors (GR), which in turn influence the development of HPA-axis responses to stress (as explained above).

Rat pups with mothers that engaged in low levels of licking and grooming had elevated HPA responses to stress than offspring with mothers that showed higher levels of licking and grooming (Liu and Meaney 1997; Fish, Shahrokh et al. 2004). Further, this effect was due to the higher levels of DNA methylation and increased histone acetylation of individual cytosines within the CpG dinucleotides of the exon 1_7 GR promoter gene (which is the equivalent of the *NR3C1* gene in humans) in offspring of rat mothers that gave low levels of licking and grooming (Weaver, Cervoni et al. 2004). DNA methylation is the process of adding a methyl group to the 5 position of the cytosine pyramine ring or the 6 position of the adenine purine ring. This modification can be inherited through cell division and is a critical aspect of normal cell organisation among animals. DNA methylation therefore acts to stabilise the pattern of gene expression in cells over time, so that they continue to respond in adulthood as they did in infancy. Methylation varies across tissues, even in different brain regions such as the hippocampus, amygdala and PFC (Xin, Chanrion et al. 2010). In the case of stress reactivity, methylation of infant rats' GR genes is responsible for the continued sensitivity to stress shown by those rats which received low levels of licking and grooming from their mothers, so that they exhibit exaggerated HPA-axis responsivity for the rest of their lives.

Glucocorticoids play an important role in the formation of memory storage and consequent behavioural adaptation by altering synaptic transmission and plasticity (Krugers, Hoogenraad et al. 2010) so that memory of stressful stimuli is associated with fear responses when the same stimulus is presented in future (Martin, Henley et al. 2009). There are also data which indicate that this 'priming' of synapses sensitizes the HPA-axis to respond to new stressors when they are presented, thus not only conditioning the initial stress response to a particular stressor stimulus, but also

increasing the likelihood of the organism responding in similar (stressful) ways when new stressors are encountered (Kuzmiski, Marty et al. 2010).

There are some data which indicate that the effects of methylation of the exon 1_7 GR promoter gene in rat pups can be reversed by later transfer of the pup to another mother that engages in higher levels of licking and grooming during infancy (Weaver, Cervoni et al. 2004), and even during adulthood by infusion of the histone deacetylase inhibitor trichostatin A (TSA), which eliminates the damaging effect of maternal mistreatment on offspring histone acetylation and DNA methylation, consequently reducing GR expression and HPA responses to stress in the adult offspring of mothers that engaged in low levels of licking and grooming (Weaver, Meaney et al. 2006). These effects on the GR gene have also been shown in the BDNF gene in rats exposed to stressed carers, and even in the offspring of those rats, demonstrating not only lifelong but also "transgenerational perpetuation of changes in gene expression and behavior incited by early abuse and neglect" (Roth, Lubin et al. 2009, p. 408). Similar alterations to the DNA methylation status of mice offspring that were subject to unpredictable maternal separation were noted during adulthood, and these affects persisted into their own (non-stressed) offspring (Franklin, Russig et al. 2010). In addition, higher levels of methylation of the 5HTT promoter have been associated with increased risk of unsuccessful responses to prior adversity in humans, and thus are also suggested to be the interface between aversive environmental stressors, the 5-HTTLPR *ss* polymorphism, and psychological problems (van Ijzendoorn, Caspers et al. 2010).

Together, these studies on rats, mice and humans demonstrate that early life experience can establish an epigenetic state in at least the exon 1_7 GR promoter gene and the BDNF gene in rats, and the *NR3C1* and 5-HTTLPR genes in humans, which are variously associated with HPA axis activation, neuronal maintenance and repair, and serotonin reuptake, all of which have been shown

earlier in this thesis to be linked with depression. These epigenetic effects can persist over the lifetime of the deprived rat offspring and even be transmitted to their own offspring. Some data with rats suggest that the epigenetic effects that arise from the experience of adversity during infancy can be reversed during infancy by replacement caring, or later in life via biochemical means (Weaver 2009). However, data regarding these phenomena in humans are less detailed.

Although the interaction between genes and environmental experiences in humans has been discussed elsewhere (e.g., Phillips 2005), and at least one model has been developed (which suggests that the process of early life adversity causes epigenetic changes that disturb gene regulation in a long-term manner, act through alterations to the methylation and oxidation status within the promoter of specific genes so that psychopathology emerges later in life (Lahiri, Maloney et al. 2009; Nestler 2009)), only a few studies have been published to date. For example, *NR3C1* is highly expressed in the human hippocampus (Turner and Muller 2005). Following the logic postulated for the studies in rodents that were described above, decreased hippocampal glucocorticoid receptor expression would increase HPA-axis responsivity to stressors and (hypothetically) lead to depression. In support of this hypothesis, in their study of 12 suicide victims with a history of childhood abuse *vs* 12 suicide victims without a history of child abuse *vs* 12 non-suicide deceased control subjects without a history of childhood abuse, McGowan, Sasaki et al. (2009) found that the suicide victims who had been abused as children showed decreased hippocampal *NR3C1* gene expression compared to controls. However, they did not find any significant differences between the hippocampal *NR3C1* gene expression of non-abused suicide victims and controls, thus supporting the hypothesis that levels of hippocampal *NR3C1* gene expression reflect the presence of childhood abuse rather than suicide. Although suicide is often associated with depression (and these data do not indicate that hippocampal *NR3C1* gene expression

is significantly associated with depression *per se*), previous data reviewed earlier in this thesis strongly link the presence of elevated HPA-axis responses (occasioned by decreased hippocampal *NR3C1* gene expression) with depression. This limitation in McGowan et al.'s study is a result of not being able to ascertain the precise depressive state of the suicide victims and reflects some of the logistic problems in research of this nature.

In the first of two recent studies which helped to bridge the gap between animal and human responses to early adversity, Frodl, Reinhold et al. (2010) reported that (as expected) the hippocampal volumes of 43 MDD patients were significantly smaller than those in non-depressed control subjects, and that the presence of childhood adversity in either MDD or healthy subjects was significantly associated with smaller hippocampal volumes. In their second study, Frodl, Reinhold et al. (2010) found that the hippocampal volumes of 25 MDD inpatient children who had experienced stressful childhood experiences and who possessed the *ss* variant of the 5-HTTLPR polymorphism (shown earlier to be significantly associated with depression) were significantly smaller than those in 27 healthy control subjects. Of note, there was no significant difference between the hippocampal volumes of MDD patients who had the *ll* form of 5-HTTLPR and healthy controls.

In another recent study, van Harmelen, van Tol et al. (2010) found that self-reported maltreatment during childhood was significantly associated with reduction in PFC volume, regardless of current depressive state (i.e., the effect was found in both healthy as well as depressed subjects). Of interest, while the presence of physical (Tomoda, Suzuki et al. 2009) and sexual (Vithilingam, Heim et al. 2002) abuse during childhood has previously been associated with depression and reductions in hippocampus and PFC volumes, the data reported by van Harmelen and colleagues showed that even emotional maltreatment (defined as "people at home didn't listen

to you, your problems were ignored, and you felt unable to find any attention or support from the people in your house": van Harmelen, van Tol, et al., p. 2) was sufficient to be significantly associated with reduced hippocampal or PFC volumes. Taken overall, these data suggest an interaction between genetic and epigenetic factors during childhood to produce vulnerability to depression in adulthood, and may be added to the flowchart of neurobiological factors in depression, as shown in Figure 15 (p. 172).

Despite the focus of this thesis upon the neurobiological factors that are associated with depression, both physical illness and childhood adversity have 'psychological' impacts upon humans (if not other animals). Therefore, it is relevant to briefly summarise some of the 'psychological' factors that have been associated with depression, and to attempt to incorporate them into the model set out in Figure 15, and the next section of this chapter will deal with that issue.

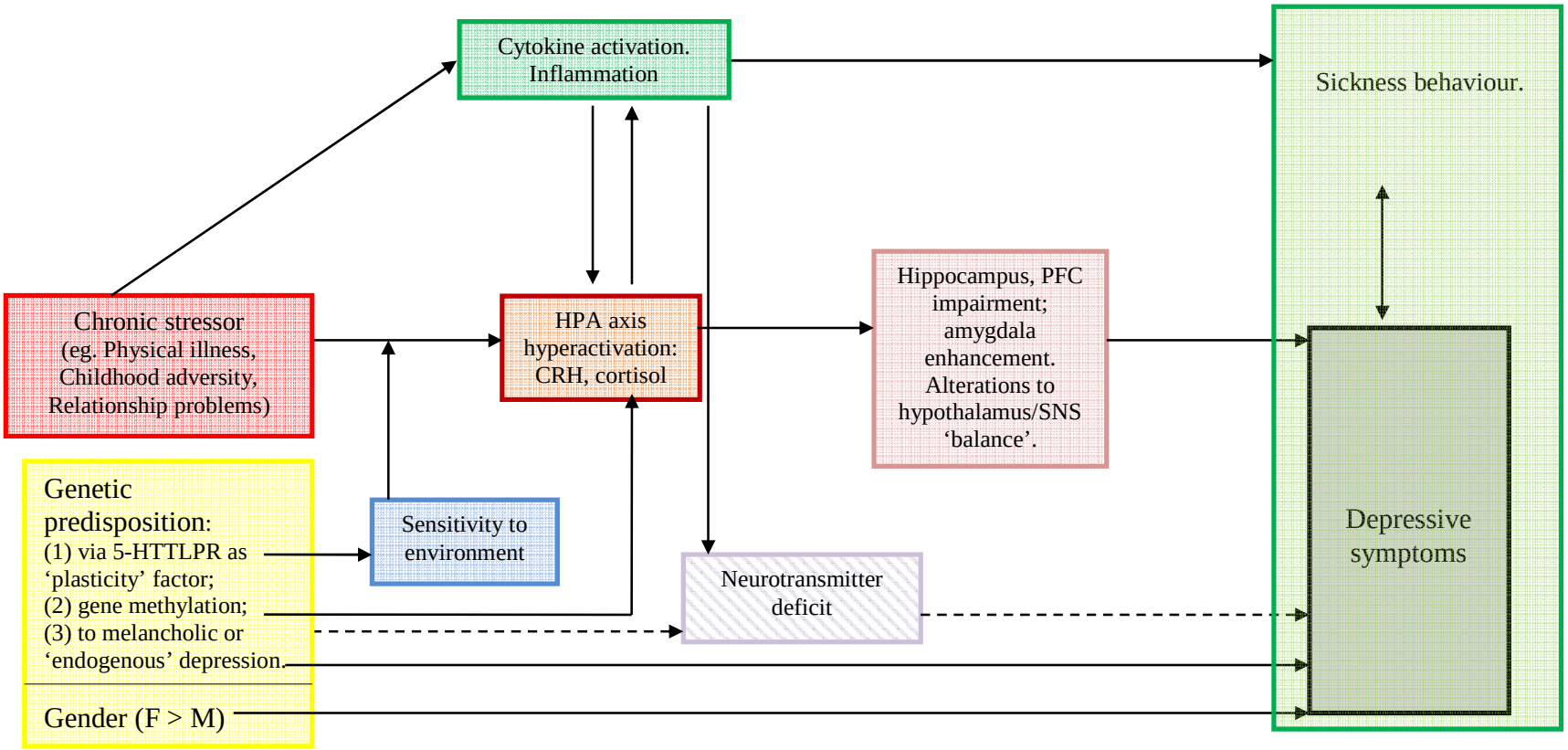

Figure 15: Genetic factors (including methylation), stressors (with some examples), HPA-axis responses, neurological sequelae, neurotransmitters, cytokines, sickness behaviour and depressive symptomatology.

5.4 How do 'psychological' factors fit into an epigenetic model of vulnerability to depression?

Several 'psychological' factors have been associated with depression. For example, neuroticism (Kendler, Neale et al. 1993; Duggan, Sham et al. 1995; Clara, Cox et al. 2003; Jylhä and Isometsä 2006; Song, Huang et al. 2008), introversion (Akiskal, Hirschfeld et al. 1983), submission, passivity and interpersonal dependency (Hirschfeld, Klerman et al. 1983), need for control (Mazure, Bruce et al. 2000), hostility (Roy 1990; Harkness, Bagby et al. 2002) and avoidance of harm (Stewart, Ebmeier et al. 2005) have all been significantly linked with depression, but some studies failed to find any significant relationships between a range of personality factors and depression (Bagby, Bindseil et al. 1997). Other psychological factors that have been associated with an increased risk of depression include having a pessimistic attitude (Seligman 1975; Seligman, Abramson et al. 1979), focussing upon recalling unpleasant or unsuccessful life experiences, thinking about oneself as inadequate or worthless (Beck, Ward et al. 1961; Beck, Rush et al. 1979; Beck 2008), or solving problems in an ineffective way (Nezu 1985; Nezu 2004).

Of interest, many of the factors that have been associated with depression are, in fact, identical or very similar to, the actual symptoms of MDD themselves. For example, neuroticism, avoidance of harm, having a pessimistic attitude, recall of unpleasant or unsuccessful life experiences and thinking of oneself as inadequate, may all relate very closely to anxiety and pessimism (both of which are key aspects of MDD: Chapter 2, p. 9); introversion, submission, passivity and avoidance of harm may be seen as congruent with the construct of withdrawal from others and life events that is a characteristic of depression (and which is discussed in more detail in the next chapter). That is, there may be some circularity present in the identification of these psychological factors as being associated with depression. This thesis is not focussed upon a

detailed examination of that hypothesis, and it is not proposed here with any firm intent, but rather as a way of explaining the linkages between these psychological factors and depression. Bearing in mind that further exploration of the neurobiological aspects of these psychological factors and depression may inform their relationships with depression, it is relevant to reflect upon the ways in which *positive* psychological factors are related to a *lack* of depression.

For example, approaching life with an optimistic attitude (Seligman 1991; Seligman 2002; Seligman, Schulman et al. 2006), and being able to adapt and renew one's sense of purpose via the presence of *resilience* (Luthar and Cicchetti 2000) appear to buffer against depression. Resilience is defined as "the ability to successfully adapt to stressors, maintaining psychological well-being in the face of adversity" (Haglund, Nestadt et al. 2007, p. 889), and is particularly relevant to this thesis because neurobiological and molecular bases have been found for the presence of this psychological/behavioural trait (Charney 2004; Krishnan, Han et al. 2007; Feder, Nestler et al. 2009). Although initially investigated as a psychological variable, resilience has been shown to have a biological basis that relies upon plasticity of the reward and fear circuits in the brain (Bergstrom, Jayatissa et al. 2007; Feder, Nestler et al. 2009), with 11 possible neurological mediators of the resilient response to extreme stress having been identified (Charney 2004). A recent study also indicated that adults who showed resilience over childhood stress also had larger fibre volumes to and from the frontal cortices (that are associated with rational decision-making in the face of stress) (Frodl, Carballedo et al. 2010). As well as having been shown to intervene between the experience of traumatic events and the individual's development of depression in the face of such aversive life events as old age (Jopp and Rott 2006), terrorist attacks (Bonanno, Galea et al. 2007), and chronic pain (Karoly and Reuhlman 2006), resilience assists individuals to overcome the experience of trauma during early childhood and to progress to normal and satisfying

lives (Watt, David et al. 1995), thus suggesting a link with the kinds of changes to the methylation and oxidation status of the *NR3C1* gene that were occasioned by childhood trauma and noted in the preceding pages.

Some data also indicate an association between other aversive life events that are commonly experienced during adulthood and consequent development of depression. For example, marital discord has been shown to increase the risk of depression (Whisman 2001), and the importance of general social support and personal relationships as a buffer against depression has also been demonstrated (Lakey and Cronin 2008). These data fall into the model suggested above of depression arising from the experience of a major negative event (ie, a stressor) or a series of minor but irritating daily life 'hassles' (Harkness, Bagby et al. 2002; Sharpley, Tanti et al. 2004) over which the individual has little or no control. Thus, the various negative psychological factors described above that are associated with depression may represent the behavioural manifestations of an epigenetic influence upon (at least) the *NR3C1* gene and consequent ongoing exaggerated HPA-axis responsivity to environmental stressors. That is, neuroticism, hostility and need for control may be 'active' behavioural strategies by which individuals attempt to protect themselves against the events that befall them and which (because of their genetic propensity for elevated HPA-axis responsivity) may represent potential threats to survival. Concurrently, submission, passivity and interpersonal dependency and seeking to avoid harm may represent 'passive' behavioural attempts to avoid stressors. Negative attitudes and cognitive styles may also fall into this category of (ineffective) self-protective behaviours. That is, as well as perhaps being symptoms of depression itself, these negative psychological factors may also reflect the behavioural manifestations of withdrawal that are shown in sickness behaviour. Figure 16 (p. 175) shows these factors.

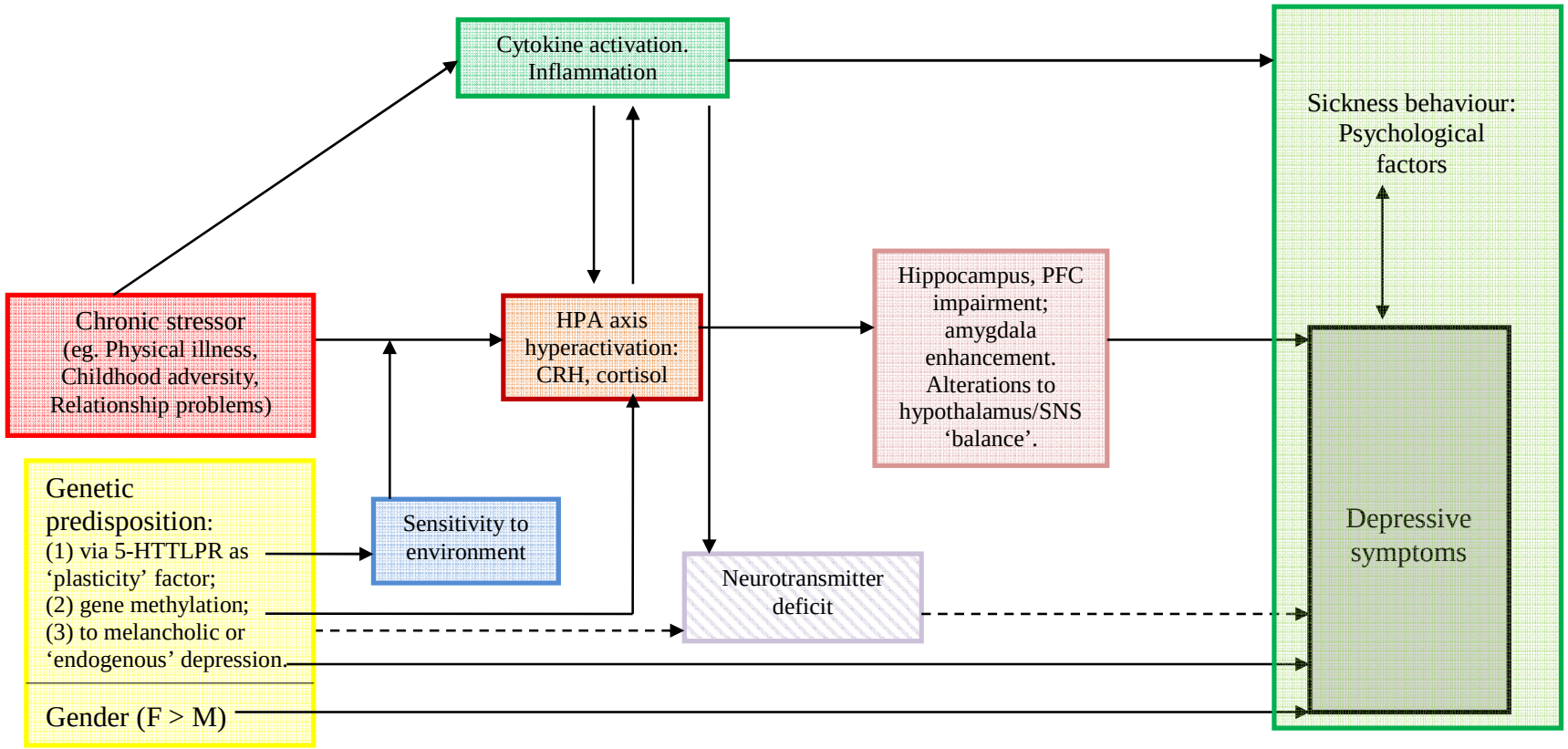

Figure 16: Genetic factors (including methylation), stressors (with some examples), HPA-axis responses, neurological sequelae, neurotransmitters, cytokines, sickness behaviour, depressive symptomatology, and psychological factors.

Conversely, being optimistic or possessing resilience may allow the individual to experience life stressors, not have exaggerated HPA axis responses and consequent changes to the PFC, hippocampus and amygdala and downstream manifestations of depression. As such, these positive 'psychological' responses (which also have biological bases) may represent self-initiated protective mechanisms against depression in the face of aversive events. The finding that resilience can assist individuals to overcome childhood trauma and lead non-depressed lives supports this hypothesis. However, while logically attractive, this hypothesis has yet to be empirically investigated. An hypothetical representation of the place of resilience in the flowchart shown previously is presented in Figure 17, p. 179. Because the exact neurological way in which resilience buffers against depression has not been clarified as yet, the exact point at which it interferes with the production of cytokines and/or elevated HPA axis responsivity is also unclear. Therefore, the action of resilience as a buffer against the effects of chronic stressors has been set between the stressor and these two consequences, and shown as a dashed line to indicate the hypothetical stage at which resilience assists the individual to avoid depression. The possibility that resilience may have a genetic basis is also shown as a dashed line between genetic factors and resilience to represent the hypothetical nature of this link.

Rather than being an alternative set of explanations of how depression occurs, these 'psychological' factors may represent behavioural withdrawal manifestations of biological (i.e., genetic or epigenetic) aspects of the organism's responsivity to stressors via the HPA-axis. If that position is accepted for the purpose of this thesis, and the neurobiological bases and pathways to depression described in the previous chapter

remain as the principal way in which depression comes about, then the question which remains to be addressed is *why* depressive behaviour occurs in the face of uncontrollable adverse events and *why* it is maintained after the passing of those events. The discussion of a possible answer to those questions represents the synthesis of the preceding content of this thesis and will be presented in the next chapter.

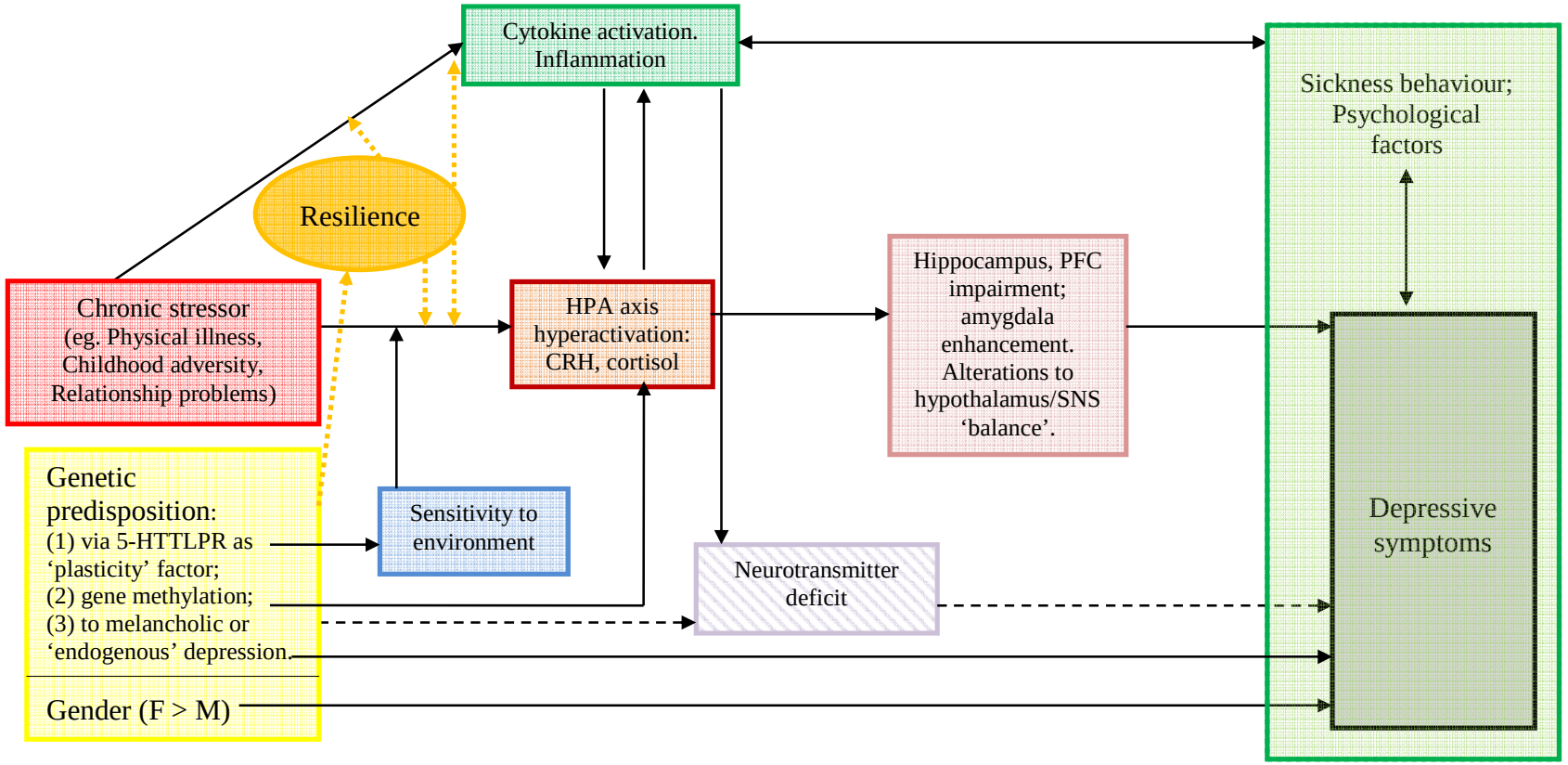

Figure 17: Genetic factors (including methylation), stressors (with some examples), HPA-axis responses, neurological sequelae, neurotransmitters, cytokines and immune-suppression, sickness behaviour, depressive symptomatology, some psychological factors and resilience.

CHAPTER 6: A UNIFIED MODEL OF DEPRESSION: LINKING BEHAVIOUR WITH PHYSIOLOGY

6.1 Is Depression 'Evolutionary', or just 'Adaptive'?[1]

6.1.1 Depression as 'evolutionary'

To explain the widespread incidence of depression, plus the presence of genetic- and epigenetic-based factors which predispose certain individuals to depression, several authors have hypothesised an 'evolutionary' model for depression which focuses upon the apparent benefits that depression has for the individual suffering from it (e.g., Gilbert 1998; Gilbert 1998; Nesse 1998; Price 1998; Nesse and Young 2000; Nesse 2000; Gilbert 2001; Allen and Badcock 2006; Gilbert 2006; Keller 2008; Nettle 2009). This evolutionary model posits that depression brings two benefits to the individual: (1) withdrawal from the stressor environment to allow the depressed individual time to analyse the stressful situation they find themselves in, and (2) eliciting assistance from partners and others who may solve the problem for the depression-sufferer (Watson and Andrews 2002). However, as well as being criticised by some (e.g., Burns 2009; Hendrie and Pickles 2009), this model may not, in fact, be 'evolutionary' at all.

From a biological perspective, for a trait (such as a predisposition to depression) to be considered as 'evolutionary', it must fulfil several criteria. Following Darwin's (1859) postulates and more recent developments (Dobzhansky, Ayala et al. 1977; Lewontin 2003), different traits naturally exist between individuals within a population and, if those different traits are passed on to offspring *and* confer a survival or

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[1] Portions of this section are drawn from Sharpley and Bitsika (2010).

reproductive advantage to those offspring, then the traits will be naturally selected and will become more common. When this process occurs, it may be said that evolutionary processes are at work (Bell 1997). Presented as a series of steps: (1) the trait or attribute in question must be present in one generation and passed on to the next generation via genetic inheritance, and (2) the trait or attribute that is passed on must confer some reproductive advantage to the offspring of the parent with the trait (Mayr 1942; Lewontin 1970). Of particular importance to the current discussion, the trait in question cannot be *developed* (e.g., in response to environmental stressors) during the parent's lifetime, because that would be Lamarckism rather than Darwinian evolution. Therefore, to be an evolutionary-based behaviour, depression in parents would (a) somehow enhance their chances of reproducing successfully, (b) be passed on to their children, and (c) enhance their children's chances of also reproducing successfully. As will be explained below, only one of these three requirements is met by depression.

Taking the first of these requirements, while being depressed may have some *immediate* beneficial outcome for the depressed person (e.g., withdrawal from uncontrollable aversive environmental stressors and/or enlisting others' help in dealing with those stressors), it is not clear that being depressed actually increases the depressed person's chances of reproducing successfully. To the contrary, data regarding the career success of people with depression indicate that they are less productive at work (Stewart, Ricci et al. 2003) and earn between 13% and 18% less than their non-depressed colleagues (Ettner, Frank et al. 1997), thus providing them with less of the income which may be used to provide for a family and for their own health and well-being. Depression may also prevent patients from earning at all, with 34% of unemployed people in the UK

being excluded from work by depression (Kemp and Davidson 2007). In addition, being depressed increases the likelihood of suicide (Blair-West, Cantor et al. 1999). These are not the likely hallmarks of individuals who will reproduce and have successful offspring, at least within recorded history. Nor are the underlying behaviour patterns of these people likely to have been beneficial to their archeological ancestors, consisting as they do of low occupational success, inability to perform tasks when under demand, and absence of the kinds of behaviours which lead to material wealth, health and well-being. Even if being depressed interacted with a particular environmental situation and thereby provided a hypothetical reproductive advantage for the depressed person within such an environment, such an advantage has not been reported in the wider literature to date. In fact, and as mentioned in the beginning of this thesis, depression's parallel risk status with smoking as a predictor of mortality (even when related health factors such as blood pressure, alcohol intake, cholesterol and social status are taken into account) argues against there being any demonstrated reproductive or survival value for depression (Mykletun, Bjerkeset et al. 2009). Thus, the likelihood of depression having any (previously hidden) beneficial and compensatory effects on reproductive survival remains to be demonstrated, at best.

The second requirement of an evolutionary trait (i.e., that the trait of being depressed is passed on to offspring genetically) is met, as indicated by the review of familial risk status for depression that was reported earlier in this thesis. Parent-child links are robust for Major Depressive Disorder (MDD), with children whose both parents had MDD having a 74% chance of developing the same disorder and children with one

parent with MDD having a 27% chance of becoming severely depressed, compared to 7% for children with neither parent meeting the criteria for MDD.

The third requirement (i.e., being the child of depressed parents enhances a child's own survival and reproductive success) is not met. There are multiple studies which have reported that children of depressed parents react more negatively to stressors, are delayed in their acquisition of self-regulation strategies, have more educational difficulties, a higher incidence of behaviour problems, and lower self-esteem (Cummings and Davies 1994 ; Goodman and Gotlib 1999; Gotlib and Goodman 1999). Even though the construct of antagonistic pleiotropy, (i.e., that a gene may transmit beneficial as well as damaging traits) might be raised as a possible way in which depression holds an evolutionary advantage for the later offspring of depressed parents (ie, that the benefit might not emerge in the first generation of the depressed parents' offspring but may be apparent in later generations), there are no data extant in the literature which support this hypothesis. To the contrary, as well as the presence of psychological disorders in children of depressed parents, the presence of these problems has been noted in grandchildren of depressed parents (Weissman, Wickramratne et al. 2005), arguing against the antagonistic pleiotropy hypothesis in this case. The surmise that these children are likely to succeed at school, become career successful and amass the resources that are characteristic of individuals whose offspring have the greatest chance of reproducing themselves and managing their lives effectively (i.e., show reproductive fitness) is not supported by fact (Weissman, Wickramaratne et al. 2006). Again, the kinds of behaviours shown by children of depressed parents and listed above would not be likely to confer a reproductive advantage for the ancestors of *H. sapiens sapiens.*

Thus, the ‘depression as evolutionary’ model does not possess sufficient validity to be accepted. It remains to be considered whether depressive behaviour may be considered to be adaptive in any other way, and that issue will be discussed below.

6.1.2 Is there a real distinction between ‘Depression’ and ‘Depressive Behaviour’?

The research findings reviewed throughout the earlier chapters of this thesis purposely focused on MDD or similarly severe depression, as this is the disorder which is of major concern. However, the data presented on pp. 16 and 17 regarding the unpleasantness and disease burden represented by subsyndromal depression showed that presence of almost any of the MDD symptoms could be considered as a ‘depressive’ illness. This suggests that the term ‘depressive behaviour’ might be substituted for ‘depression’ or MDD because it includes any or all of the required symptoms for MDD, subsyndromal depression, or simply ‘feeling blue’, all of which have aversive effects on humans and all of which are related to the kinds of adaptive responses to overwhelming aversive environmental events that trigger the sickness behaviour discussed above and shown in Figure 17.

As a subset of sickness behaviour, depressive behaviour also helps to explain how the kinds of withdrawal responses described above that characterize depression may hold some advantage for the individual and how that kind of response might indeed be seen as evolutionary (even if full MDD is not). Therefore, the next section will deal with depressive behaviour rather than MDD or similar severe diagnoses of depression.

6.1.3 Does depressive behaviour provide an 'advantage'?

The 'depression as evolutionary' argument might be modified to explain one set of *immediate* benefits of depressive behaviour to those individuals who exhibit a tendency to respond to adversity by behavioural withdrawal because those withdrawal behaviours provide *an immediate adaptive advantage for the individual in the current environment*. One theory of depressive behaviour which is based upon the assumption that it bestows some adaptive benefit upon the person exhibiting it has been described by several authors (e.g., Ferster 1973; Dougher and Hackbert 1994; Kanter, Callaghan et al. 2004; Kanter, Cautilli et al. 2005; Kanter, Busch et al. 2008). As noted by Bolling, Kohlenberg and Parker (1999), "Identified features of the depressive syndrome are all in the spectrum of a withdrawal from contact with the world and the consequences of activity" (p. 127). Applied to the specific symptomatology of depression, sadness, anhedonia, sleep and appetite change and cognitive disturbances are part of a "biological response pattern …identified as the conservation-withdrawal response to excesses or deficits of stimulation" (p. 127) that includes low self-esteem, hopelessness and helplessness. This withdrawal from aversive stimuli and environments has been described as 'adaptive' in that it reduces the quantum of the noxious stimuli state (via either too much aversive stimuli or too little positive stimuli) to which the person is exposed (Gilbert 1998; Gilbert 2006). Such withdrawal may help the person who is experiencing such a noxious state to adjust to their feelings of hopelessness and helplessness in the face of the aversive events, and may provide an opportunity for others to take control of the individual's environment (Price 1998). An important aspect of the mechanism underlying this withdrawal is the conviction on the part of the depressed person that

he/she has no real control over the unpleasant experience that is occurring (Gilbert 1998; Gilbert 2006) and therefore is left with a single response that will reduce distress---withdrawal from the environment that is causing the unpleasantness. This immediate benefit from depressive behaviour is what Darwin (1876/2002, p. 51) referred to when he commented that "But pain or suffering of any kind, if long continued, causes depression and lessens the power of action; yet it is well adapted to make a creature guard itself against any great or sudden evil".

Evidence supporting the 'adaptation' model of depression comes from studies of the kinds of antecedent events that precede depression. For example, Keller and Nesse (Keller and Nesse 2005; Keller and Nesse 2005; Keller and Nesse 2006; Keller, Neale et al. 2007) found that social losses such as death of a loved one, relationship breakdown and social isolation were associated with more crying and physiological arousal, whereas failure to reach a goal, stress and winter season were associated with more fatigue and pessimism. Similar work by the author and colleagues on samples of university students, and breast and prostate cancer patients has identified the particular aversive antecedents that these populations undergo and which trigger depressive behaviour (Sharpley, Bitsika et al. 2009; Bitsika, Sharpley et al. 2010; Bitsika, Sharpley et al. 2010; Sharpley, Bitsika et al. 2010). These findings challenge the perception of depression as an illness, and instead suggest that depressive behaviour may represent a series of adaptive responses to overwhelming environmental adversity. That series of responses may hold some advantage (eg., withdrawal from the aversive environment, eliciting others' assistance, reducing noxious emotional intensity), and the tendency to exhibit those responses may be transmitted genetically, and even provide some survival advantage. This challenge to

the model of depressive behaviour as always being an ‘illness’ is supported by Greenberg’s (2010) comment that conceptualizing depression as a disease is as much a matter of history as it is of science. In fact, while MDD is certainly a disorder, some of the depressive behaviours that an individual may learn to show in response to environmental stressors may be adaptive.

6.1.4 Depression as an adaptive sickness behaviour

As well as the range of sickness behaviours mentioned above that may be adaptive when the organism is infected by various pathogens (e.g., fever, runny nose, diahhroea, vomiting), a more extreme parallel of the withdrawal from environmental stimuli that characterizes depressive behaviour may be seen in the concept of multi-organ failure which occurs when the organism is in a life-threatening situation. Although this carries the negative connotation of severe malfunction (like MDD), it has recently been suggested that multi-organ failure may actually be a survival strategy that enables the organism to decrease the demand upon its cellular functioning by modifying the cell’s metabolic rate, thus adapting to reduced ATP production. This is supported by the finding that cell death is rare during multi-organ failure and that survivors show organ recovery. Thus, multi-organ failure may be seen as a “transient state of metabolic shutdown analogous to hibernation” (Mongardon, Dyson et al. 2009, p. 431) that enables the organism to survive.

As part of the application of this adaptive process model to depressive behaviour, anhedonia may result from reductions in cognitive and emotional processing of salient pleasant environmental reinforcers, plus increases in focussing upon negative information to guide behaviour. This corresponds with abnormalities noted in reward-processing

brain systems (such as the PFC and hippocampus) and elevation of the role of the amygdala in judging environmental stimuli from an emotional perspective. Evidence for this model comes from data showing that persons who exhibit depressive behaviour also have been shown to be immediately *hyporesponsive* to rewards and *hyperresponsive* to punishment for laboratory tasks (Eshel and Roiser 2010). Depressed persons also have an impaired ability to modify their behaviour on the basis of prior reinforcement history, thus demonstrating impaired longterm hyporesponsiveness to rewards and a lack of access to learnt responses that were based upon previous positive environmental stimuli. This impairment may directly contribute to reduced engagement in pleasurable activities and (thence) exacerbation of the major depressive symptom of anhedonia (Pizzagalli, Iosifescu et al. 2008). It is of note that inhibition of general behaviour among adolescents is an antecedent to depression (Muris, Merckelbach et al. 2001), perhaps acting via the same behavioural withdrawal mechanisms as described above. One dramatic aspect of the depressed person's withdrawal from an aversive environment is the finding that MDD patients show significantly lower retinal contrast sensitivity to a standard visual stimulus compared to non-depressed controls (Bubl, Tebartz Van Elst et al. 2009; Bubl, Kern et al. 2010). That is, depressed patients 'see' less clearly than non-depressed persons. This is withdrawal of more than a simply psychological, emotional or behavioural nature, and suggests powerful biological processes underlying the more obvious behavioural withdrawal that is a characteristic of depressive behaviour.

A parallel withdrawal mechanism in the face of threat may be seen in catatonia, which has been described as "a common end state response to feelings of imminent doom" (Maskowitz 2004). From that perspective, catatonia is a form of tonic immobility

or ‘arrested flight’ displayed when an organism is faced with an inescapable threat. This strategy serves to deflect attack from a predator (and by doing so, also reduces the organism’s own arousal levels) because many predators will cease their attack when their prey appears to be dead. Dixon (1998) maintained that arrested flight is linked with some depressive symptomatology such as social withdrawal, reduced eye contact and psychomotor retardation and is “the behavioral hallmark of the severely depressed individual” (p. 436).

6.2 Linking adaptive depressive behaviour with neurobiological pathways: a synthesised biological-behavioural model of depression

Arising from the discussions above, it may be posited that at least some forms and incidences of depression represent an adaptive process by the organism when it is faced with uncontrollable and enduring aversive environmental stimuli. While this hypothesis in no way seeks to reduce the sheer unpleasantness of the symptoms of depression, it does argue that depression may be like some other aspects of sickness behaviour such as fever, vomiting and diarrhea, in that it may be seen to act as (an uncomfortable) self-preservation mechanism in the same way as these other self-preservation mechanisms. Although classifying depression as an adaptive process may challenge the conventional wisdom, other serious self-preservation responses such as extreme fever, life-threatening diarrhea and even multi-organ failure also have been shown to possess benefits to the organism and therefore the ‘depression as adaptive behaviour’ hypothesis thus holds at least some face validity. Of greater interest to the focus of this thesis, however, is how this process of adaptation in the face of overwhelming adversity occurs, and for that explanation, it is necessary to return to the models developed in Chapter 4 that described

the neurobiological and structural changes that accompanied depression. Figure 17, p. 179 showed that model most comprehensively, and is reproduced on p. 191 as Figure 18 to expand the argument being made in this part of the thesis. Further development of that model in the light of the content of the last two chapters is shown by the demarking of the events and processes in Figure 18 into a 'Pre-adaptation' stage, a 'Physiological adaptation' stage and a 'Behavioural adaptation' stage (where 'behaviour' includes cognitive and emotional brain activity).

The conceptualization of depression and depressive behaviour as a subset of sickness behaviour, with identifiable beneficial outcomes for the organism (e.g., withdrawal from aversive stimuli, inactivity to allow others to help and/or for the aversive stimuli to just 'go away', and conservation of resources for problem-solving in the future when the immediate negative emotional impact has reduced in intensity), allows the physiological and neurobiological concomitants of depression described in this thesis to be conceptualized as *adaptive processes* by which the organism responds to an overwhelming aversive environmental stimulus. That is, the neurobiological precursors to depression may be viewed as 'normal' or 'healthy' *physiological* responses in that they function in the same way as many other sickness behaviours such as vomiting and running a temperature. The later *behavioural* adaptation responses also fit this adaptive process. However, just as the adaptive sickness behaviours of a continual high temperature, vomiting or organ failure will become self-defeating if repeated for long enough, causing longterm damage to the organism and even death, so the adaptive physiological and behavioural responses shown in Figure 18 will also become debilitating for the person suffering them if they persist long enough—ie, MDD.

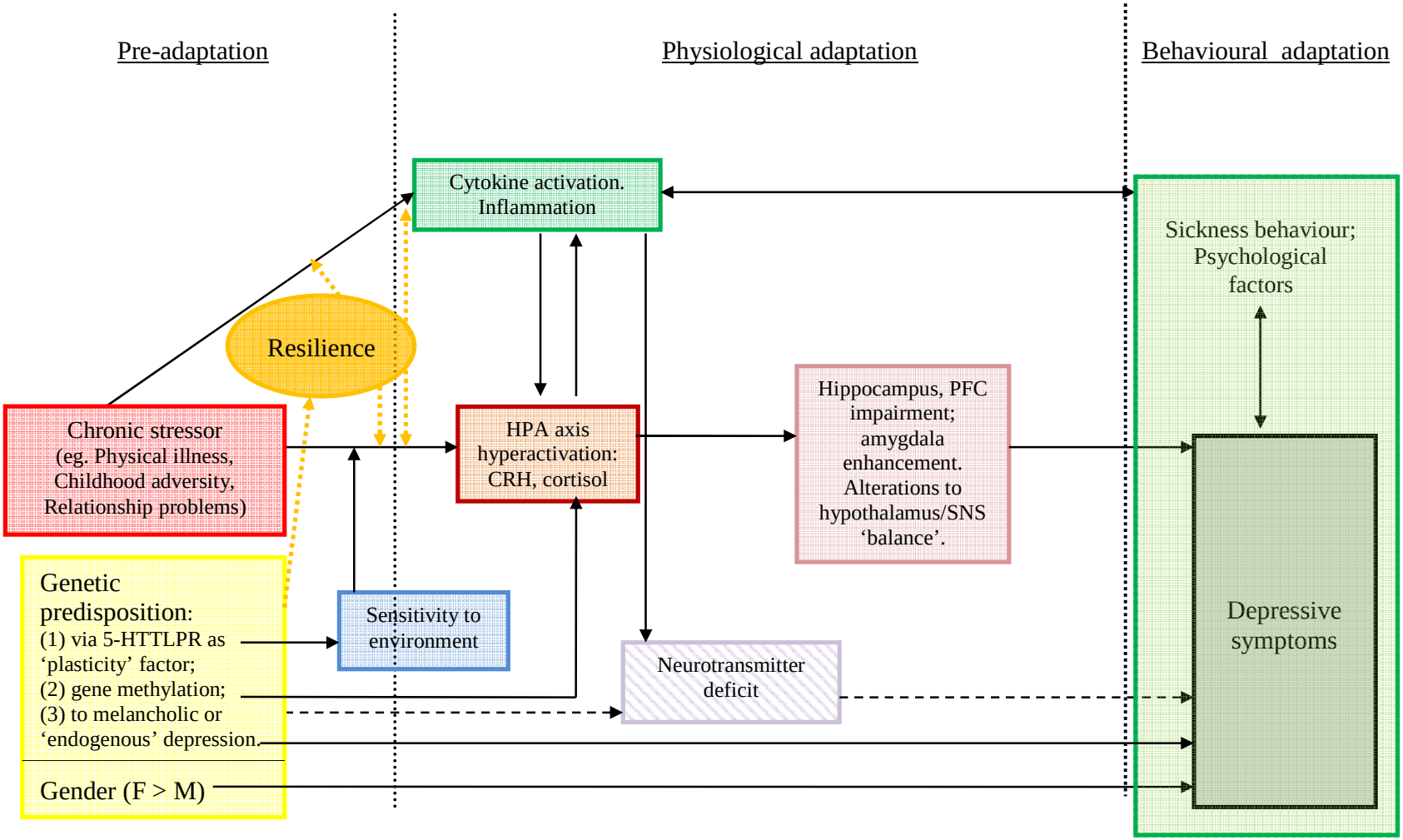

Figure 18: Genetic factors (including methylation), stressors (with some examples), HPA-axis responses, neurological sequelae, neurotransmitters, cytokines, sickness behaviour, depressive symptomatology, some psychological factors and resilience, plus demarcation into 'Pre-adaptation', 'Physiological adaptation' and 'Behavioural adaptation' stages.

Figure 18 functions to explain how and why depressive behaviour occurs to assist the individual cope with uncontrollable aversive environmental stimuli. During the 'Pre-adaptation' stage, several antecedents are established in the individual's life. These may include gender, genetic susceptibility to melancholic depression, presence of the 'sensitivity to environment' 5-HTTLPR polymorphism, methylation of the glucocorticoid receptor gene *NR3C1*, and also other genetic factors that are associated with depression. Secondly, the presence of a chronic stressor (such as childhood maltreatment, a major illness, relationship problems, and many other similar aversive events) will combine with genetic factors to predispose the individual to commence the kinds of physiological adaptations shown in the second stage of the model in Figure 18. Resilience may act at this stage to *prevent* those physiological adaptation responses to genetic factors and chronic stressors, or it may act later during the physiological adaptation stage to *reduce* them, and the uncertainty of the exact timing of the effects of resilience is indicated in Figure 18 by dashed lines into both stages.

During the 'Physiological adaptation' stage, the organism seeks to cope with the combined genetic predisposition and chronic stressor factors by several mechanisms. First, immune system responses (cytokines, inflammation) initiate sickness behaviour in response to the 'pathogen' of the chronic stressor and aimed at isolating and killing it. Second, elevated HPA axis responses occur as a general response to threat, to specifically activate various mechanisms that ensure adequate energy levels, and to instigate phagocytosis of the pathogen and it extermination within the lysosomes. Third, hypercortisolaemia causes changes to the PFC and hippocampus (apoptosis) and the amygdala (neurogenesis) in order to establish a fear-based response pattern rather than a

reason-based way of dealing with the chronic stressors, because of the selective advantage of fear-based responses in preserving the organism in the face of life-threatening environmental stressors. Perhaps the availability of neurotransmitters will decrease, reducing cognitive clarity and rendering decision-making more emotional than rational.

The third stage, the 'Behavioural adaptation' stage (including cognitive, emotional and physical behaviour) entails 'sickness behaviour' (sleep and inactivity to help the organism withdraw from the stressor and conserve its resources, and raised temperature, vomiting, diarrhea to combat/evacuate the infection), some psychological/emotional responses (such as sadness, pessimism, anhedonia, loss of interest and concentration, low self-esteem, guilt, anxiety, thoughts of death or suicide—all of which are designed to help the organism withdraw from an environment that is overwhelmingly aversive and also to elicit the help of others), and behavioural responses (including social isolation, fatigue, sleep disturbances, loss of appetite, psychomotor agitation or retardation). The organism will not be able to function effectively socially or occupationally while in this state. Thus, the symptoms of depression shown in Table 3 (p. 20) are enacted during this stage.

6.3 Limitations of the model and suggestions for further research

Figure 18 represents a model of depression that includes all stages of its development, the 'reasons' or functions for the various aspects of adaptation, and the consequences that occur and which take the form of MDD. However, there are some limitations to it at this point in time.

From the material presented regarding genetic factors, it is clear that this is an emerging field, and therefore no final comment can be made about which genes are

active in depression, and how they work. That is a work in progress and the data presented above and incorporated into the model in Figure 18 should be considered to be current, but by no means complete. The data able to be presented on the kinds of stressors which initiate physiological responses have been restricted in this thesis by word limit restrictions, and there are many other stressors which could also be included here, such as occupational stressors, socioeconomic stressors (i.e., poor standard of living), physiological stressors (poor physical fitness, drug addiction, insufficient diet) and 'meaning of life' stressors. Similarly, although a great deal has been reported in terms of how cortisol affects the brain, more research is being published on this issue almost on a weekly basis, and so this is also a field in flux. However, bearing in mind the restrictions of space (word limit) and time (published data to early 2011), the most salient aspects of the literature have been covered here.

Although all of the earlier neurobiological material reviewed and synthesised may be accepted as confirmed in the literature, the later section on the psychobiological nature of resilience is not so well established. Therefore, while the 'causal' model of depression shown in Figure 16 is the sum of that research, the role of resilience in the final models shown in Figures 17 and 18 is hypothetical in that the point where resilience intervenes to buffer the individual against depression is not yet established. Research into the physiological responses of persons with high *vs* low resilience (as determined by questionnaires and behavioural observations of responses to major life stressors previously experienced) via laboratory presentation of standardised stressors, and measurement of the HPA-axis and cytokine reactions of the two types of persons, would enable testing of the point where resilience intervenes in the flow between genes and

depression. Similarly, investigation of the presence of a 'resilience' gene would help fix the source of resilience in the flowchart, as would examination of the effects of maternal non-grooming and care upon methylation of particular genes that are linked with depression in organisms which carry the resilience gene compared to those that do not carry it. Third, diagnosis of the psychological/behavioural responses of high *vs* low resilience individuals to commonly-experienced major stressors (eg, civil conflict, extreme weather) could also assist in determining how resilience intervenes in the development of depression in persons who have experienced such stressors.

6.4 Implications for treatment

A detailed review of the effectiveness of various treatments for depression in the light of the material presented here is a major undertaking, and beyond the scope of this thesis. The author has written a paper on the role that hypercortisolaemia plays in development of depression, and the use of treatments such as psychotherapy, medication, combinations of psychotherapy and medication, ECT, transcranial magnetic stimulation, and functional magnetic resonance imaging neurofeedback for depression, and a copy of that paper is bound with this thesis (Sharpley 2010), plus a paper that examined the links between the nurturing relationship established in psychotherapy and reductions in hypercortisolaemia and depression (Sharpley 2010). However, those papers were focussed upon the specific role of hypercortisolaemia and depression, and did not include genetic or immunological factors, nor a discussion of the role that various environmental chronic stressors might have. Therefore, it is relevant to make some brief comments here regarding the implications that the more comprehensive model of depression that is shown in Figure 18 has for the current range of antidepressant treatments available, and

how they might be implemented, but with no discussion of the efficacy of those treatments.

By reference to the three stages depicted in Figure 18, several comments may be made regarding treatment options that are focussed upon the factors and processes described in each of those stages. For example, taking the 'Pre-adaptation' stage first, several initial suggestions might be made, based upon the roles of genetic factors, the presence of chronic stressors, and whether or not a person is resilient. First, it appears likely that some genetic factors play a major role in the likelihood of depression *if* aversive life circumstances are also present for a particular individual. Therefore, as well as considering the individual's gender and the depressive status of the individual's parents', the presence of genes which may predispose to melancholic depression, and/or genetic factors that may increase the individual's sensitivity to environmental events (such as the *ss* 5-HTTLPR polymorphism) should be determined. As other genetic markers of vulnerability to depression emerge from research, it may be that genetic testing could include these in the same way that screening might be done for the presence of a genetic predilection for other diseases. Other screening at a later date might include the methylation state of the *NR3C1* and the *BNDF* genes as indicators of increased risk of hypercortisolaemia and impaired brain function. As well as these screening procedures, prevention via treatment modalities aimed at changing the genetic profile of individuals at risk for depression may be useful, although they are beyond current medical technologies. If it can be identified, screening for the 'resilience' gene may also be profitable in identifying at risk infants.

Similarly, the presence of environmental stressors is clearly a major causal factor for depression. Although the provision of sound and nurturing care for infants and young children is a firmly-held value within all societies, the relative importance of such experiences that the infant undergoes during the very early months of life following birth may sometimes be overlooked because of the perceived plasticity of the newborn (i.e., its physical ability to thrive despite some environmental stressors). That is, a lack of maternal (or even paternal?) comforting physical contact and nurturance may have little obvious effect on the infant's physiological health compared to the provision of adequate diet, warmth and physical security, but may also be sufficient to lead to methylation of the glucocorticoid gene, resulting in lifelong hyperresponsiveness to stressors and consequent effects upon the PFC, hippocampus and amygdala that instigate a reliance upon fear-based decision-making rather than rational evaluation of environmental demands. Infant care policies might include regular screening for the presence of a lack of nurtiring-parental-care-based stressors which elevate the likelihood of the child becoming depressed. In addition, child-raising philosophies and infant care procedures might incorporate the presence of significant and consistent nurturing physical contact by parents or other persons who play a caring role in the life of the newborn.

During the second stage ('Physiological adaptation'), screening may be replaced by treatments aimed at (i) decreasing hypercortisolaemia, (ii) modifying the influence of cortisol upon the PFC, hippocampus and amygdala, (iii) increasing resilience, and (iv) modifying the responses of the immune system. (Although pharmacological treatments appear to be justified by some of the data, they are not clearly effective in reducing depressive symptoms for all patients.) The first of these four avenues for reducing

physiological responses during stage 2 may be accomplished by a range of treatments, including anticortisolaemic drugs, psychotherapies that have been shown to reduce cortisol levels in depressive patients (Sharpley 2010), exercise (Maniam and Morris in press) and diet (Maniam and Morris 2010).

Treatments that may counteract the effects of hypercortisolaemia upon the PFC, hippocampus and amygdala may include bioelectric procedures that have been shown to have anti-depressive effects, such as deep brain stimulation (Mayberg 1997; Mayberg 2003; Mayberg, Lozano et al. 2005; Lozano, Mayberg et al. 2008) and cranial magnetic stimulation (George, Wassermann et al. 1997; George, Nahas et al. 2000; O'Reardon, Solvason et al. 2007; George and Sackeim 2008; George and Aston-Jones 2010; George, Lisanby et al. 2010). These may prove effective where pharmacological treatments have not, but are in their very early stages at present. Other methods of stimulating neurogenesis in the PFC and hippocampus and reducing amygdaloid growth, may be chemical (Anacker, Zunszain et al. 2011), exercise-based (Fabel and Kempermann 2008) or focus upon environmental enrichment (DeCarolis and Eisch 2010).

Resilience has genetic and neurological components, but is also amenable to psychological interventions, such as those developed by Seligman (Seligman, Schulman et al. 2006; Seligman, Schulman et al. 2007) and shown to be efficacious in the workplace (Steensma, Den Heijer et al. 2007), schools (Gillham, Reivich et al. 2006) and the armed forces (Reivich, Seligman et al. 2011). Although the bidirectional links between depleted immune function and depression have been established for some time (Kiecolt-Glaser and Glaser 2002), and there are data which show that meditation can increase immune function (Davidson, Kabat-Zinn et al. 2003), at present, there are few

data which explain whether *increased* immune function would result in greater or lesser sickness behaviour (and thence, depressive symptomatology). This issue remains to be elucidated.

Finally, during stage 3 of the model (ie, the 'Psychological adaptation' stage) a range of psychological and behavioural therapies might be indicated, including those which focus upon building a close rapport between patients and therapist and thereby provide a nurturing environment for the patient and decreasing cortisol levels (Sharpley 2010), a focus upon explaining depression as an adaptive response to overwhelming stressors (and therefore not an indication of mental illness), and the establishment of alternative behavioural responses to those aversive events (Hayes, Masuda et al. 2004; Hayes, Luoma et al. 2006).

6.5 Conclusion

Depression is a complex phenomenon, and this thesis has touched upon one aspect of its nature—some of the major neurobiological 'causal' steps in its development. As such, the model produced in Figure 18 should be seen as an account of depression which is based upon solely those factors that have been reviewed herein. However, allowing for that caveat, the combination of the factors that have been reviewed into the model shown in Figure 18 represents a stage in understanding depression that was not previously achieved.

Depression is widespread in the Western world, almost too widespread to remain considered as a 'disease', particularly since there are no obvious 'pathogens' that initiate it in the high incidence rates that are common in Western societies. As an alternative explanation, this thesis suggests that depression may be similar to several other defense

and adjustment mechanisms which were selected for their survival well before human consciousness evolved, and which function to assist the organism to adapt to its environment. As such, the model of depression posited here may help to understand why so many people in the relatively affluent Western societies report that they are depressed. The consideration of which aspects of those societies are represented in the overwhelming aversive stressors that trigger the stages of depression shown in Figure 18, and what to do about them, is the subject matter of another thesis.

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