KØBENHAVNS UNIVERSITET

INSTITUT FOR PSYKOLOGI

Neuropsychological Research on Depression
Towards a Synergy between
Cognitive and Neurobiological Theories and Methods

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Af Kamilla Miskowiak

BA.psych., MSc

"Soul and body, I suggest, react sympathetically upon each other: a change in the state of the soul produces a change in the shape of the body, and conversely: a change in the shape of the body produces a change in the state of the soul."

(Aristotle in Popper & Eccles, 1977, p.176)

1 Introduction and outline of the dissertation

Depression is a common, life-disrupting, highly recurrent, and potentially lethal affective disorder, and is the fourth-largest contributor to the global burden of disease, thus causing profound suffering as well as high costs to health care systems and society (Thase, 2003). The disorder has estimated lifetime prevalence rates of 13% and 21% for men and women, respectively (Kessler *et al.,* 1994). Milder sub-clinical forms of depressive disorder involving too few symptoms to meet diagnostic criteria for major depressive disorder are even more common. According to the American Psychiatric Association (2000), up to 15% of individuals suffering from severe depression die by suicide. Epidemiological and family studies report that onset of depression occurs primarily in young adults (Klerman & Weisman, 1989), and as the course of depression is often chronic and recurring, the disorder causes long-term impairment in social, occupational, and personal functioning. Recent studies show that less than one in twenty depressed persons are correctly diagnosed and adequately treated (Mourilhe & Stokes, 1998). Thus, research into the causes, perseverance, and treatment of affective disorders represents a major challenge facing the contemporary scientific community, and is of particular importance to any national mental health research strategy.

Over the last few decades, research on depression has been dominated by two major approaches: the paradigms of cognitive psychology and neurobiology (psychopharmacology). In both fields a continuing effort has been made to improve the treatment of depressive disorder. Cognitive theories, of which Beck's Cognitive Theory (1979) has been the most influential, suggest that *negative* biases in the cognitive processing and memory of self-referent information are key features in the development and maintenance of depression. Conversely, the neurobiological view is that depression is caused by imbalance in key neurotransmitter systems and by structural and functional abnormalities within the central nervous system (CNS). According to this view, the disorder can be fully accounted for in a biological pharmacological framework and treatments of the disorder should be designed to target the biological CNS abnormalities in depression. From the neurobiological perspective it remains uncertain how structural and functional alterations within the CNS lead to depressive symptoms and how the neural mechanisms of antidepressants can be used

efficiently in clinical practice. We do not yet understand how molecular and cellular mechanisms summate to affect subjective experience and behaviour. From the perspective of cognitive psychology, on the other hand, depression is explained in terms of cognitive, social, and behavioural malfunction. This leaves unanswered the question of why genetics and the neurobiology of the brain also seem to play an important role in both the aetiology and remission of depression. There is a fundamental difference between paradigms used in cognitive and neurobiological conceptions of depression, and this has profound implications for research strategies on depression as well as on its treatment.

A new approach to depression research has emerged, aiming to integrate neurobiological and psychological perspectives into a *neuropsychological* account of depression. Technological advances now offer an array of neuroimaging techniques which have made possible a neuroscientific examination of how brain function supports cognitive processing, shedding light over the link between the workings of the mind and brain. These developments in neuroscientific methodology have altered the conceptualisation of mental disorder, increasing the awareness of the subtle interactions between biological and psychological factors in the aetiology and maintenance of the disorder as well as remission from it. This neuropsychological paradigm has become an attractive line of research. It has yielded a number of new findings on the relation between the neurobiology and psychology of depression. The approach combines traditionally opposing conceptualisations. It may thus create a more versatile understanding of depression and suggest new strategies in the treatment of the disorder.

The aim of this dissertation is to review the cognitive and neurobiological theories and methods in research on depression to explore the possibilities of creating a synergy between the two approaches in a new approach, which I choose to call the neuropsychological approach to depression. The objective is further to present the findings of a neuropsychological study performed by the author and colleagues and to discuss the implications of this new approach to depression. The dissertation is structured into four major sections. The first section will discuss the meta-theoretical relation between the cognitive, neurobiological, and neuropsychological approaches to depression. A framework will be presented to place the approaches at their respective theoretical levels of analysis. These are not mutually exclusive, but together form an exhaustive account of depression. A following brief review of the principal historical schools of thought within the philosophy of mind provides a philosophical perspective for a consideration of the different implicit understandings of the relation between mind and brain in each approach to depression. An understanding of the fundamental conceptions that are embedded in the different paradigms is of great value for the understanding of their respective arguments and research strategies. The second

section will define depression and provide a review and discussion of the cognitive, neurobiological, and neuropsychological theories and methods in depression research as well the as empirical evidence for each of them. These theoretical sections form the background for the third major section, which presents the empirical findings of a neuropsychological study by Miskowiak and colleagues (submitted): "Acute antidepressant administration modulates the neural processing of positive versus negative self-referent personality characteristics". This event-related functional magnetic resonance imaging (ER-fMRI) study tested the hypothesis that administration of a selective noradrenaline reuptake inhibitor reboxetine affects both neural and cognitive processing of emotional information in healthy volunteers. The final section discusses the contributions and limitations of the present study in the context of neuropsychological research on depression in general, and evaluates the implications for research strategies on and the theoretical conception and treatment of depression.

2 Philosophical foundations of scientific approaches to mind disorder

Historically, mental disorders have been dealt with separately from other medical illnesses because they influence the mind. Because of the multi-factorial nature of mental disorder, in which neurobiology and psychology interact, a complete scientific account necessitates an explanation of a number of factors: the *subjectively experienced* aspects (i.e. the depressed mood, loss of interest or feelings of worthlessness in depression), the *neurobiological* processes underlying these symptoms, and the *relation* or interaction between the two. In affective sciences, the troublesome questions of how the mental and neurophysiological manifestations of the disorders relate to each other, as well as whether and how we can fit the subjective feelings (e.g. depressed mood, low self-esteem) into a scientific account are therefore of crucial importance. These issues derive from the more fundamental issue and represent a great challenge for science today: how it is possible to study the conscious mind and include mental phenomena in a scientific world view? Should we acknowledge the existence of a non-physical mind or can it be reduced to a material process, exactly like all other natural phenomena? Whether physical and mental phenomena are two fundamentally different substances, and whether they interact or are otherwise related, are known as the mind-brain problem (Popper & Eccles, 1977).

The foundation of a building is the invisible part of the architecture supporting the visible part of the building. Analogously, the foundations of a scientific paradigm consist of a largely invisible set of assumptions, upon which the visible part of paradigm depends. These

'enabling assumptions' provide a conception of the target domain in question, which gives meaning to the theories, methodologies and effects that make up the special content of the discipline (Cummins & Cummins, 2000). In order to understand the foundations of the different concepts, methodologies and arguments in research on depression, it is important to uncover the enabling assumptions about the mind-brain problem that are implicit in the different paradigms.

The mind or consciousness is at the same time a fascinating, intense, and fleeting phenomenon, which has been defined as "*... that which thinks and experiences*" (Graham, 1993) and "*The having of perceptions, thoughts, and feelings; awareness*" (Sutherland, 1989). We are all familiar with the state of consciousness as it is with our conscious awareness that we experience the world. At the same time, conscious phenomena are still a profound mystery to philosophers and scientists, as consciousness cannot be directly assessed by existing scientific methods. It is invisible, intangible, and fundamentally different from all other natural phenomena in the world. The roots of the enabling assumptions of the different approaches to depression reach far back into the history of western European philosophy of mind, *"...the area of philosophy which strives for comprehensive and systematic understanding of that which thinks and experiences, namely the mind*" (Graham, 1993). In the following, central positions in the philosophy of mind are therefore presented and discussed to provide an understanding of how these conceptualisations influence scientific research in mental disorder today.

2.1 The mind-brain-problem

"It must be confessed ... that perception, and that which depends on it, are inexplicable by mechanical causes… And, supposing that there were a mechanism so constructed as to think, feel and have perception, we might enter it as into a mill. And this is granted, we should only find on visiting it, pieces which push one against another, but never anything by which to explain a perception."

(Leibniz, *monology*, sec.17. In Cummins & Cummins, 2000, p.4)

In this famous passage, Leibniz points out the essence of the mind-brain problem: the fundamental gap between the concepts describing the mind and those describing the brain. Although we know that mind and brain are closely linked, physical observation of the brain provides data in a seemingly wrong vocabulary: neurons and synapses rather than thoughts and feelings. This gap between mind and brain is the centre topic for centuries of philosophical debate, which has been dominated by two principal movements; *dualism* and *monism*. While dualists claim that the mind and brain are two fundamentally different metaphysical entities, the view proposed by the monists is that mind can be explained within the frames of the physical world. "*Dualism and monism have*

long represented a dichotomy that offers opposing answers to one of man's most critical and enduring concerns, namely, can conscious experience exist apart form the brain?" (Sperry, 1990, p.143).

The father of dualism as a philosophical position, René Descartes (1596-1650), argued that there are two fundamentally different substances or essences in the world: a physical substance with spatial properties and placement, as well as a mental substance without any of the properties of the physical world. Descartes' argument against monism, serving to support his *substance dualism,* was: "*I can conceive of myself as lacking a brain, but I cannot conceive of myself as lacking a mind. If I try to doubt that I have a mind, I will discover myself with thoughts like 'I doubt I have a mind', and so must admit that I have a mind – for the activity of doubting is mental. Hence, brain and mind must be distinct.*" (in Graham, 1993). However, from the fact that one can assess the mind but not the brain, it does not necessarily follow that mind and brain are distinct; one and the same thing could be known or accessed in different ways (ibid.). Another of Descartes' ideas is the existence of an interaction between the mind and body, taking place in a small organ in the brain – the pineal gland. Many important thinkers that followed Descartes rejected this *interactionism*, pointing out that if the soul and body are substances of fundamentally different natures, then how could there be an interaction between them? A form of dualism, formulated by the critics of Cartesian interactionism, was *parallelism.* The parallelists 'dissolved' the mind-brain-problem by postulating that mental and physical events are only apparently related. In reality these two entities merely exist in parallel without influencing each other, like two pendulums side by side, whose movement is initiated simultaneously and for the observer seem to engage in a causal relationship. This form of dualism seems rather implausible today, with a substantial body of neuroscientific evidence pointing to a close dependence of the mind on the brain. The questions are rather, what is the *exact* causal relation between the mind and brain, i.e., how intimately does the functioning of the mind depend upon the functioning of the brain (and *vice versa*), and what sort of dependence is it? A final form of dualism, *property dualism,* which can be divided into *epiphenomenalism* and *emergentism*, acknowledges the dependence of the mind on the brain. The epiphenomenalist stand is that the mind and brain are related by a one-way causality, in which the physical properties of the brain give rise to mental phenomena. In this way the mind can be conceived of as *supervening* on the brain[1]. This conception fosters the view that the mind has no causal power on the brain. Emergentism, on the other hand, claims that physical substance can give rise to new properties in the cases where the physical substance meets certain criteria. These emergent properties cannot be

[1] The concept of supervenience formalises the idea that one set of facts can fully determine another set of facts (e.g. physical facts appear to determine biological facts) (Chalmers, 1996).

reduced to or predicted from the properties of the physical constituents, so they seem to be fundamentally different from the properties from which they arise.

In contrast with dualists, monists claim that both the mind and brain can be accounted for within the frames of one single ontology. Despite the disparate appearances of the mind and brain, they are of the same fundamental substance. Monism comprises *Idealism* and *Materialism,* of which the former states that all phenomena in the world are fundamentally mental, and the latter that everything is physical. Materialism, the main grouping within monism*,* is the most popular contemporary view among neuroscientists studying the relation between mind and brain, and can be traced back to Thomas Hobbes in the 17th century. The main motive of all materialist theories is to eliminate or reduce the mind to something physical, which results from the reductionistic belief that there can be no influence of the mind on the brain (no 'downwards causation') because of the 'causal closedness' of the physical world (Popper & Eccles, 1977). *Reductive materialism* argues that mental events like experiences and feelings can ultimately be reduced to material events – that is to physical events in the brain. In line with this, it is argued that mental experiences will be mapped onto brain states once sufficient progress has taken place in the neurosciences. In contrast, *eliminative materialism* claims that this kind of translation is superfluous. The whole terminology of mental phenomena and processes should be eliminated and replaced by the more 'precise' neurobiological descriptions of the brain states that generate experience. *Functionalism,* a reductionistic view within cognitive science, argues that this elimination is too strict. According to the functionalist view, a conscious state is a certain function, so that every conscious state equals a certain function. As identical functions can be performed in various different materials, it is not the physical substance which is the determining factor, but rather the function that is performed. In this way, functionalism argues that conscious experiences are logically possible in other types of 'hard ware' than the neurobiological brain. The theoretical position of materialism can be summarised in three theses: *The identification thesis*, which states that the mind is nothing but matter, i.e. that mental states and processes are nothing more than physical states and processes - the mind *is* the brain. *The explanation thesis,* which claims that behaviour is best accounted for by physical neurochemistry and neurophysiology. Finally, *the exclusion thesis* states that humans have no powers or properties not possessed by all other physical systems. The mind is therefore excluded from existence; "*Man is nothing but a material object having none but physical properties*" (D.M. Armstrong in Graham, 1993, p.137).

Materialism has certain advantages over dualism. Its first virtue is the simplicity achieved by asserting that anything mental can be explained as something that is material or physical. The second advantage is the unified conception of the world presented by materialism in the

explanation of all phenomena as ultimately physical. Materialism also excludes the supernatural from the understanding of human behaviour in clearly denying all sorts of supernatural phenomena. Finally, materialism allows the entry of the mind in physical science; it claims that studying the mind is no different from studying the brain, and we can therefore use our scientific knowledge of the brain to understand mental processes. There are numerous disadvantages of materialism of which the most convincing is evident in Franz Brentano's (1838-1917) thesis stating that the mental can be distinguished from the physical in virtue of its *intentionality* or *aboutness* (ibid.). Believing and experiencing are mental activities that are *about* an object or state of affairs and thereby *represent* something (their objects) as existing in certain ways. The same is not true for physical processes, which cannot be conceived of as having intentionality or being about anything at all. Thus in this view the mental and physical are fundamentally different phenomena.

Brentano's thesis constitutes one of the most serious fault lines in materialism. In order to save the materialist doctrine, D.M. Armstrong declared that the materialist theory of mind must account for intentionality in material terms: "*No materialist can claim that intentionality is a unique, unanalysable property of mental processes and still be consistent with his Materialism. A materialist is forced to attempt an* analysis *of intentionality*" (Armstrong, 1968). The candidate materialist accounts of aboutness are 'the resemblance analysis' and 'the causal analysis' (Graham, 1993). The idea of the resemblance analysis is that one thing is about something else when it *resembles* it. The mind is about an object or situation when it contains mental images or pictures of that object or situation. The materialist form of this view is that the images or pictures are physical - maybe even geometrical - patterns of activity in the brain corresponding to the external object or situation. This analysis is valid only if resemblance really can constitute aboutness. However, resemblance is very different from aboutness: while resemblance is 'symmetrical', aboutness is 'asymmetrical'. This means that aboutness moves in one direction – from the object or situation to the subject, which experiences it – while resemblance moves forth and back – from the object or situation resembled to the resembling object or situation and back again. Thus, the fact that two things resemble one another does not mean that one is *about* the other. A second problem with the resemblance analysis is that aboutness can occur in the absence of resemblance and can therefore not be accounted for by resemblance. A final setback is that the resemblance analysis hinges on the presumption that there are physical pictures or patterns in the brain resembling things in the outside world. It is then necessary to specify the exact configurations of brain activity that constitute the image, leaving the remaining properties of the mental state as irrelevant. We thus need a materialist criterion for resemblance that interprets the brain as the seat for resemblances of objects. However,

no one has a clear idea of how to develop such a criterion, which makes this approach rather dubious.

The second materialist candidate of aboutness is the causal analysis, which holds that something physically internal to the brain is *about* an (external) object, when the object *causes* that exact internal activity. In other words, something external causes the internal activity in the brain. An advantage of the causal analysis compared to the resemblance analysis is that it respects the asymmetry of aboutness. X can be about Y, without Y being about X (Graham, 1993). A pitfall of the causal analysis is, however, that is does not account for mental phenomena that are about objects, which really do not exist (e.g. hallucinations), since in the material world something non-existing cannot cause anything. Taken together it would seem that materialism so far fails to explain Brentano's intentionality or aboutness in physical terms. Without this explanation, the materialist doctrine should be resisted. While providing a good explanation of the physical mechanisms in the brain, materialism yields no insights into why these processes are accompanied by feelings, thoughts or perceptions.

2.2 The entry of the mind in science

Historically the roots of the mind-brain-problem reach centuries back in European Philosophy; although it is only recently that the problem has become a legitimate object of scientific research. The entry of conscious phenomena in science is underlined by the molecular biologist and geneticist Francis Crick (1916-): "*No longer need one spend time enduring the tedium of philosophers perpetually disagreeing with one another. Consciousness is now largely a scientific problem.*" (in Carter, 2002, p.103). The 'mind-brain-problem' is thus no longer a topic for philosophy alone, but is now also a focus area of scientific research across a number of disciplines. There is, however, a profound methodological problem in research on conscious phenomena, which is highlighted by the philosopher of mind David Chalmers in the following: *"The problem of consciousness lies uneasily at the border of science and philosophy… it is not open to investigation by usual scientific methods… not least because of the difficulties in observing the phenomenon. Outside the first-person case, data are hard to come by*" (Chalmers, 1996, p.xiv). The methodological problem is thus the dichotomy between *subjectivity* and *objectivity* in science.

Modern scientific opinions on which phenomena are susceptible to scientific investigation originate from Galilee's *criteria of scientific objects*. According to Galilee (*Il Saggiatore*, 1623) an object of scientific study has to be observable from a third-person perspective, which means that scientists must be able to assess the object independently of the individual observer. This is

impossible in the study of conscious phenomena as the very nature of consciousness is private and subjective. Galilee's scientific criteria thereby leave us with only two possibilities: Either that consciousness cannot be investigated scientifically as it is impossible to reach an *objective* understanding of something that is by nature *subjective*; or that consciousness must be regarded as a phenomenon accompanying the physical object (the brain) but with no claim of naturalisation (epiphenomenalism). In the light of these strict scientific criteria of objectivity, the massive scientific interest today in mental phenomena and their relation to the brain could seem rather surprising. Three principal factors are presumably responsible for the entry of the mind in science: firstly, the entry of the cognitive paradigm in psychology and the view that subjective introspection can be verbalised and the words regarded as objectively observable behaviour has made the study of the mind scientifically legitimate; secondly, technological advances have enabled an 'objective' neuroscientific exploration of the conscious brain; and third, there is a growing recognition of the limitations of classical physics in accounting for all natural phenomena.

2.2.1 The development of paradigms in psychology

The first component enabling scientific exploration of mental phenomena is the development of paradigms in experimental psychology, which has brought forth the cognitive paradigm that is dominant today. The first time the mind became an object of scientific study was in 1879, when Wilhelm Wundt established the first laboratory of experimental psychology, thereby marking the birth of psychology as a scientific experimental discipline. The primary objective of this new paradigm was to initiate a scientific study of the *structure* of the mind and of mental processes. In order to keep psychology as compatible with traditional conceptions of natural science, the goal of *structuralism* was to explain the mind in physical terms. The strategy was therefore to search for fundamental elements of thought such as sensations and reflexes as well as laws that governed their combination, which leads to the more complex forms of thought experienced by humans. The simple physical sensations that underlie our everyday experiences were identified though the use of introspection, defined as the "examination or observation of one's own mental processes". Tichener, a student of Wundt, puts it like this: "*When I am thinking about anything, my consciousness consists of a number of ideas… But every idea can be resolved into elements… and these elements are sensations*" (Cummins, 1988, p.33). The use of introspection as an analytical technique was, however, the downfall of the structuralist school. The method was doomed from the start, as it was based on the assumption that one could discern the elements of thought merely by introspecting them. An analogy could be that one tried to discern the elements of water by observing a drop of water. The attempt would fail, because the perceived qualities of water are

nothing like those of its components (i.e. hydrogen and oxygen). Another reason that introspection failed as a scientific method was its violation of the fundamental rule for scientific investigation: that of independent access to the phenomenon (the third person perspective).

While structuralism began to collapse under the weight of this fundamental difficulty, some events occurred that led to a change of paradigm to that of behaviourism in the 1920s. Among these was the discovery of how *quantitative* laws govern the forming of associations among stimuli by Hermann Ebbinghaus in his work on the mechanisms underlying learning and memory. This led to a replacement of the structuralist focus on the qualitative aspects of mental processes (i.e. structure) by emphasis on the quantitative laws of mental phenomena. An other important event was the discovery of *stimulus substitution* by Ivan Pavlov, which suggested that 'reflexes' could be described solely in terms of associations among stimuli and responses, making reference to associations among thoughts or other mental constructs superfluous. Finally, the rise of pragmatism in academics and social policy, which stressed the relation between events and action, fostered the view that structuralists were overemphasizing the internal responses to stimuli (which could not be observed anyway) and neglecting (observable) external responses and actions (Cummins & Cummins, 2000). In the 1920s the revolution of behaviourism took place as a result of an accumulation of problems with structuralism. The behaviourists overthrew the structuralist paradigm by asserting that observable behaviour was the true object of psychological study and that environmental influences were the sole determinants of behaviour. Concepts like mind or mental processes were therefore excommunicated and the study of cognition was considered impossible because cognition was conceived as a mental process and therefore did not exist. Although some behaviourists went so far as to deny the existence of the mind, others considered it an epiphenomenon that was irrelevant as it could not cause or explain behaviour. Through the elimination of the mind from psychology, behaviourism avoided the problem the mind and its relation to the brain.

The cognitive revolution in the 1960s was a result of some discoveries made in a variety of disciplines in the 1940s and 1950s that came together in the mid-1960s to form a new psychology, in which the mind and mental processes were again subjected to scientific study. Cognitive psychology became a part of the larger discipline of cognitive science, including researchers from the disparate fields of philosophy, artificial intelligence, psycholinguistics, and neuroscience, whose principal goal was to understand the mind. One of the major foundations of cognitive science was mathematician Allen Turing's work on 'finite state automata' or the 'Turing machine', which could in principle carry out any recursive function, just like humans (Cummins & Cummins, 2000, p.14). This led to the suggestion that machines could perform reasoning processes,

that the states and processes of mechanical systems could be described in information-processing terms, and that information-processing models could be applied to the brain to simulate human thought processes. The idea that human cognition resembles the functioning of computers made the information-processing paradigm the main approach within cognitive psychology at the end of the 1970s. The seven central main assumptions underlying this are, that people are autonomous intentional individuals who interact with the external world; that the mind, through which they interact with the world, is a general-purpose, symbol-processing system; that there are some processes that translate these symbols into other symbols that ultimately relate to the world and that the aim of psychological research is to uncover these symbolic processes and representations; cognitive processes are extended over time, which makes measures of reaction times possible and valuable; the mind is a processor subjected to structural and resource limitations; and finally the symbol system depends on a neurobiological substrate, but is not determined by it (Eysenck & Keane, 2000). The empirical methods of cognitive psychology are not only collection of behavioural data, but also making use of introspection, which is regarded as useful information about mental processes. Taken together, the replacement of behaviourism by cognitive psychology has opened up for the possibility of placing mental processes in a scientific framework again and of initiating various lines of research with the mutual goal of clarifying the workings of the mind.

2.2.2 Technological and methodological advances

The second factor contributing to the entry of the mind in science is the great technological development that has taken place in the last decades, which permits an 'objective' *in vivo* neuroscientific exploration of the intact conscious brain. The current strategy within cognitive neuroscience is to explore the neurobiological correlates of the mental states and processes by means of various neuroimaging techniques in order to clarify how brain function supports cognitive processing. This strategy agrees with the traditional criterion for scientific objects: through imaging, the neural processing is observable from a third-person perspective, and is thus independent of the individual observer. This *quantification* of 'conscious' neural activity is an important reason for the great enthusiasm for neuroimaging and for the central position of cognitive neuroscience in research on the relation between mind and brain. By providing insights into the neurobiological basis for mental processes and emotional states, neuroimaging has become an important tool for investigating the *relation* between the mind and the brain and which brain functions, structures, and activity play a crucial role for conscious phenomena.

Since the introduction of x-ray computed tomography (CT) in the 1970s there has been great development in scientific technology, giving birth to the techniques of positron emission

tomography (PET), single photon emission computerised tomography (SPECT) as well as magnetic and functional magnetic resonance imaging (MRI and fMRI) (Posner & Raichle, 1999). These advances allow the examination of subtle changes in both regional structure and function that are associated with the pathophysiology of mental disorder. Roughly described, CT, PET, SPECT, MRI, and fMRI provide important insights into the anatomical and functional organisation of the brain through imaging of brain structures (CT and MRI) and of the changing blood flow and metabolism in these structures during sensory stimulation, cognitive operations and emotional states (PET, SPECT and fMRI). Ongoing advances in MRI image reconstruction techniques now provide spatial resolution of less than $1mm^3$ so that the activity occurring even in small brain structures can be visualised and measured volumetrically, which provides a unique advantage over older cross-sectional area measurements using CT (Strakowski, Adler & DelBello, 2002). This high resolution method makes it possible to examine the often subtle structural changes associated with mental disorders like depression. However, structural imaging cannot identify the functional significance of a structural component and must therefore be completed by dynamic functional imaging techniques like PET, SPECT, and fMRI, which visualise the changes in regional cerebral blood flow (rCBF) and glucose metabolism in various structures of the brain (ibid.). Identification of rCBF related to a certain mental activity of interest is obtained by using a subtractive method, which consists of producing an average image of brain activity in a particular subject during relaxation and subtracting this image from an image of brain activity during the mental activity under investigation. In this way the background activity is eliminated to provide a picture of changes in blood flow due to the specific mental activity or emotional state measured. As functional (biochemical and molecular) changes presumably precede structural alterations, functional imaging is important for accurate definition of the pathophysiology of mental disorder, better predictions of appropriate treatments, and advances in our understanding of emotional processing in the human brain. While imaging a detailed functional anatomy of the brain, these techniques provide little information about the sequencing and duration of neural processes because of a relatively low time resolution[2]. In order to study rapid changes in neural activity, neuroscience employs electrophysiological techniques with high time resolution, such as EEG and ERP. EEG enables us to track the course of the mental processing following a stimulus by recording electrical brain activity from the scalp of a human subject. By use of the subtractive method it is possible to obtain a recording of the electrical activity produced by a specific stimulus - also called the event-

2Neural communication takes place within milliseconds while the time to construct for instance a PET image of cerebral blood flow is about 40 seconds, which makes PET inadequate to capture fluctuations in neuronal activity. Although fMRI has a higher time resolution, this technique is also too slow to provide information about moment-to-moment changes in neural activity.

related potential (ERP). Thus, recordings of the ERP are a valuable method of obtaining information about the duration and sequence of neural activity related to a conscious event. The limitation of this method, however, is its imprecise spatial resolution and the consequent difficulty of locating the electrical generating cell assemblies in the brain.

The combination of structural and functional imaging techniques and electrophysiological measures is a strong tool for research on mental disorder, as it improves the localisation of abnormalities in blood flow, metabolism, neurotransmitter receptor function, and neurophysiological function. Moreover, functional and structural mapping provides a bridge between the hypotheses stemming from rapidly growing knowledge in the related fields of molecular biology, psychopharmacology, and clinical treatment applications. In summary, brain research on mental disorder has made substantial advances within the last three decades, supported by conceptual developments as well as by technological advances. The possibility of performing objective scientific investigations of the neural structures and processes underlying the subjective conscious phenomena has allowed studies of the mind to take place within the natural sciences.

2.2.3 Broadening of the scientific world view

The third and last factor of major importance for the acceptance of mental phenomena in science today is that scientists have become increasingly aware that all phenomena in the world cannot be explained in the framework of classical physics. In order to explain phenomena at micro and macro levels we have to make use of quantum mechanics and non-linear dynamics.

With the birth of quantum mechanics the scientific world view was profoundly changed. Its interpretation of the atomic nucleus as a system of particles in rapid motion and the surrounding electrons as an electron cloud replaced Bohr's deterministic model of orbiting electrons that obeyed Newton's classical physics with mechanical determinism. In quantum mechanics the interaction between atoms and wave motion has a random or chance aspect, and is subject to the probabilistic theory of random events rather than to exact mechanical laws as previously thought. As all physical systems are, in reality, clouds of particles interacting randomly, the traditional conception of physical systems as subjected to the mechanical laws of classical physics has turned out to be an approximation. Sufficiently large systems consisting of thousands of atoms like large macromolecules, which form systems of crystals (the objects we perceive as solid), interact *approximately* according to Newton's laws of mechanics. We can thus conclude that the 'solid' objects, which constitute the main furniture of our environment, are in fact various forms of energy, governed by electrical and other forces (Popper & Eccles, 1977). Furthermore, quantum mechanics has demonstrated that certain phenomena are affected by the process of observation, which

illustrates the fact that there is *always* some degree of interaction between different systems (here the observer and the observed system) (Hameroff & Penrose, 1999). With these discoveries scientists are beginning to understand that no system is completely isolated and objective in traditional terms, and that the strict demarcations between objectivity and subjectivity begin to blur. The insights provided by quantum mechanics call in question the universal value of Galilee's criterion for scientific objects and opens up for the possibility of studying subjective mental phenomena like consciousness that cannot be explained by the classical physical laws within a natural scientific paradigm (Carter, 2002, p.6ff).

The example of the interaction between temperature and individual atoms or molecules has been employed to illustrate how no physical system is completely isolated but always takes part in some sort of interaction with other systems. Temperature is a phenomenon *caused* by the movement of the *individual* atoms, but is at the same time defined by the *average* velocity of *all* atoms: This means that temperature is defined on a level *different* from that of individual atoms in motion – an emergent or holistic level (Popper & Eccles, 1977, p.34). However, these levels are not isolated from one another: On one hand the temperature of a physical object is defined by the average speed of its vibrating particles; on the other hand the object can be heated up by being placed in warm surroundings. Thereby the vibration of the single particle influences the 'global' temperature of the object (upwards causation), and is at the same time affected by the temperature (downwards causation). There is thus an *interaction* between the different levels or layers; the emergent higher level (temperature) and the lower level (movement of individual atoms) influence one another in both 'upwards' and 'downwards' causations. This suggests an *emergence* of hierarchical levels in the natural world and the presence of an interaction between them through bidirectional causations. The emergence hypothesis introduces a fundamental indeterminism of the physical universe, which cannot be regarded as an objective 'closed' system in the traditional scientific sense; physical and 'non-physical' or emergent phenomena do, in reality, interact and affect one another (ibid.). In relation to the mind-brain debate, this is an important insight as it introduces the possibility of an interaction between mind and brain despite their existence at different levels or layers in the natural world. This provides an interesting way out of the polarisation between monists and dualists in the mind-brain-debate, as it avoids opposing the mind and brain as two fundamentally different substances (dualism) on one hand, and a *reduction* of mind facts to brain facts on the other (materialism). Instead it proposes an understanding of the mind as an *emergent* phenomenon arising from the lower level 'physical' brain processes and suggests the existence of an *interaction* between mind and brain characterised by both upwards and downwards causations. Thus the mind and brain are both natural phenomena that exist at different

conceptual levels and must, accordingly, be analysed and described with terminologies belonging to their particular level. It would thus be a fallacy to explain mental phenomena with concepts belonging to the brain-level like neural oscillations or signal transmission between synapses. According to this view, an account of any mental phenomenon, e.g. affective disorders, should include both mind facts and brain facts and their mutual relations. It is not enough to account for either the neurobiological or the psychological aspects – we need to understand both aspects as well as how they interact.

2.3 Depression: answers from the different approaches

In order to illustrate the way depression is conceptualised and treated within the cognitive, neurobiological, and neuropsychological approaches, imagining a fictive case may be valuable. Imagine that you are a psychologist and have been contacted by a severely depressed young man who has barely survived a suicide attempt. In order to find an explanation you can distinguish between two sets of facts that may contribute to his disorder: the mental or 'mind facts' and the neurophysiological or 'brain facts'. The mind set of facts includes the following: the man suffers from a severe clinical depression; for several months after being left by his fiancée he has been feeling depressed, has lost interest in the world, sees the future as threatening and hopeless, feels worthless, has lost appetite, has problems concentrating, and has been haunted by thoughts of bringing an end to it all by taking his own life. The brain set of facts incorporates that the man has imbalances in the monoamine systems as well as functional and structural CNS abnormalities, and that there is a genetic factor involved with a family history of depression. The aspects you will focus on and the treatments you will suggest to the young man are of course profoundly influenced by the conceptualisation of depression inherent in your particular approach. The neurobiological, the psychological, and the neuropsychological approaches derive from different philosophical positions in the mind-brain-debate. They thus provide divergent answers as to how the mind and brain relate and how depression should be conceived, what factors are central in an explanation of the disorder, and finally which type of treatment(s) should be initiated. Clarifying how the philosophical affiliations of the paradigms in depression research affect the different conceptions of depression within these paradigms is therefore of central value. In the case of depression, the central question is: How do the brain facts and mind facts relate? How do these two sets of facts fit together to form a unified explanation of the young man's severe depression?

One response, provided by adherents of the dualist position *parallelism*, is that there is *no* link between mind and brain facts. Brain facts have nothing to do with mind facts, as they are

wholly independent and do not engage in any causal relation. However, this response is somewhat absurd. For if the mind and brain were absolute independent of one another then we should expect the mind to be invulnerable to pathology or damage to the brain as well as no influence of the mind on the brain whatsoever. In fact, recent neuroscientific evidence has proved the opposite to be true in both cases, which will be discussed at a later point in this dissertation. Thus, the question is not *if* mind and brain relate, but rather *how intimately*?

Materialists argue for the most intimate fit between mind and brain by combining the two sets of facts into one set: Mind facts are identical to brain facts, wherefore the materialist answer to the question is that: "*The Mind fact of severe depression just is identical to the Brain fact of depleted biogenic amines. To be severely depressed is to have depleted biogenic amines*." (Graham, 1993, p.145). This materialist claim is represented within the majority of neurobiological approaches, in which a distinctive feature is that it views depression as a neurobiological brain disorder characterised by neurotransmitter imbalances and other brain abnormalities that can be reversed by means of antidepressant drug or electroconvulsive therapy. Although some neurobiologists do acknowledge that there is a mind, they still put off its explanation according to the assumption that something non-physical cannot influence the physical brain. This reflects an epiphenomenalist view of the mind-brain-relation and the assumption of closedness of the physical systems. The neurobiological framework thereby provides unequivocal answers to the aetiology as well as treatment strategies of depression: the disorder is caused by neurobiological dysfunctions and any treatment should be designed to target and reverse these brain abnormalities.

Assuming materialism, what is then the role of the mind facts in the case of depression? Suppose that our young patient tells you that the reason for his suicide attempt was that he was left by his fiancée and now feels like he has lost everything worth living for. From the materialist perspective of the neurobiological approach, depression is altogether located physically in the brain, which leaves no place for such psychological or social factors. Assuming Brentano's thesis of intentionality, the materialist explanation is thus ill-advised. Intentionality or aboutness is a central aspect in the young man's depression and suicide attempt. His feeling of worthlessness, failure of love, loss of interest in the world and the threat he perceives in the future are all mental states that possess *intentionality*. The inability of materialists to provide any physical analysis of intentionality means that the mental phenomena are not physical states or processes, although they are indeed linked to the physical brain abnormalities. While the contributions from the neurobiological approach are crucial to the understanding of depressive disorder, the explanation of the young man's depression and self-destructive actions cannot occur strictly within the confines of materialism. By solely investigating the neurobiological aspects that underlie the subjective

intentional symptoms of depression, we will never obtain an exhaustive account of the disorder. Put in other words, the *objective* facts about the neurobiology of the brain cannot explain the nature of the *subjective* intentional aspects of depression. This is highlighted by philosopher Colin McGinn in the following: "*... the property of consciousness itself (or specific conscious states) is not an observable or perceptible property of the brain*" (McGinn, 1995, p.10-11). Taken together, the neurobiological approach to depression must therefore be supplemented with other approaches that encounter the psychosocial factors that contribute to depression.

If materialism is not true, could the explanation then be that mind facts are vulnerable to brain facts without being identical to them? This view is represented by advocates of property dualism such as the epiphenomenalists and emergentists who, as we have seen, describe the relationship between the mind and brain as on of mind/brain *supervenience.* But if mind supervenes on or arises from the brain, could reference to the brain not suffice to explain depression? A number of supporters of the supervenience hypothesis argue that reference to brain facts would suffice, as all psychological phenomena arise from the brain facts and are thus best and most correctly explained with reference to these. However, this reasoning is guilty of a fallacy; from the fact that the mind somehow *arises* from the brain it does not follow that the mind can be *reduced* to the brain processes. As with all emergent phenomena, the unity of the mind is more that just the sum of its physical constituents. The subjective aspects of depression conceptually surpass the material neurobiological bases on which they supervene. According to this view, we can conclude that even if the young man's depression does supervene on neurobiological abnormalities, the depression itself cannot be equated with these brain abnormalities.

Considering the diverse psychosocial phenomena surrounding the young man's depression – his own feelings of worthlessness, hopelessness, loss of interest in the world around him, and the fact that he was left by his fiancée – the mind facts seem to be necessary for understanding his symptoms and suicide attempt. The conception of depression as a purely mental disorder having a psychological aetiology is evident within the cognitive approach. According to the cognitive perspective, depression is caused by psychological factors, such as selective processing and memory of negative information, which is what is believed to be the key mechanism in maintaining the disorder. Thus within the cognitive framework, the treatment that would be initiated for our young depressed patient would be a form of cognitive therapy. To determine the enabling assumptions of the cognitive approach in the light of the mind-brain-debate, it is important to notice that the approach is concerned only with mind facts. Brain facts and the relation between mind and brain are assigned no importance whatsoever, but the brain facts are still not refuted altogether. Underlying the cognitive approach may therefore be a dualist view on the

relation between mind and brain, although the main emphasis is given to the workings of the mind. The cognitive understanding of depression does, however, leave one with a feeling that something essential is left out. For in this account, is any role assigned to the neurobiology of the brain, and if so, what might that role be? In the case of the young patient, we must not overlook the fact that he had a predisposition to depression; there was a clear genetic factor (family history of depression). Furthermore, neuroimaging of his brain demonstrated functional and structural abnormalities in various limbic and frontal areas. Within the confines of cognitive psychology, no explanation is given of the involvement of these genetic and neurobiological factors, which must be considered a serious lacuna in the cognitive approach. In summary, the neurobiological approach places the entire focus on the brain facts, while the cognitive approach acknowledges only the mind facts. Although both approaches, as we shall see, contribute with central insights to the disorder, neither of them is fully adequate in accounting for depression. From both perspectives something of crucial value for understanding the disorder is left out. But is it really necessary to dismiss brain facts in order to acknowledge the relevance of the mind facts? Or is there an available framework that can accommodate both sets of facts in a more exhaustive multi-factorial account of depression?

The neuropsychological approach is a more recent approach to depression, in which both mind and brain facts as well as their mutual influences are acknowledged. In this way the approach is highly compatible with the philosophical view of the mind-brain-relation as levels of emergence interacting with one another by means of both upwards and downwards causations. The precise causal relations between the two sets of facts or levels of emergence remain uncertain so far, but converging neuropsychological evidence is beginning to disclose this relation to form a more complete and integrated account of the disorder. Returning for the last time to our young depressed man, we would from a neuropsychological perspective appreciate the role of his neurobiological abnormalities and the influence of the genetic factors as well as the way these biological factors *interact* with the psychological factors like his subjective state, behaviour, and social environment. The acknowledgement of both mind and brain facts has the strong advantage over the two former approaches of being able to provide a multi-factorial account of depression. The neuropsychological understanding of depression is consistent with the fact that many authorities today draw attention the complexities involved in the establishment of an exhaustive explanatory framework for depression. The view, which has recently been gaining ground is that depression is best accounted for in terms of minds facts, including both psychological and social factors as well as the family history of the depressed person, supplemented (but surely not displaced) by reference to brain facts. There is thus recognition that the conceptual and explanatory complexity of depressive disorder necessitates an understanding that encounters the neurobiological,

psychological and social aspects of the disorder as well as their mutual interactions. To reach this goal, the new neuropsychological line of research appears to be the most promising candidate approach.

2.4 Different levels of analysis in research on depression

Although both the cognitive and the neurobiological approaches provide important insights into the nature of the disorder, their radically different conceptual frameworks, employing either mind or brain terminologies, produce conflicting accounts that together draw a rather incoherent picture of depression. An important question is therefore: How can we understand these scientific approaches to depression in relation to one another within a meta-theoretical framework? And is it possible to combine the disparate accounts of depression into a coherent whole?

A complete scientific understanding of any phenomenon requires contemplation of different kinds of explanation at different levels of description, which (at least in principle) are linked into a cohesive whole; "*Almost never can a complex system of any kind be understood as a simple extrapolation from the properties of its elementary components… the effort is to show that in principle the microscopic and macroscopic descriptions are consistent with one another.*" (Marr, 1982). According to Marr (1982), there are three levels at which an information processing device such as the brain must be described. At the top level is the *abstract computational theory* of the phenomenon, involving a description of the function or the purpose of the computation and its appropriateness. The questions that Marr have highlighted as central at this level of description are: What is the goal of the computation, why is it appropriate, and what is the logic of the strategy by which it can be carried out? The second level entails the choice of input-output *representation* and the implemented *algorithm* that specifies how the system combines and transforms the pieces of information in the computations. Questions to be answered at this intermediate level are: How can this computational theory be implemented? What is the representation for the input and output – and what is the algorithm for the transformation? Finally, there is the lowest level of description, the *hardware level,* at which details are specified as to how the algorithm and representation are realised physically. Here, the central question is therefore: How can the representation and algorithm be realised physically?

Although the description at one level of a phenomenon engages issues that are quite independent of the other two levels, all levels are both logically and causally related. Thereby they each have an important place in an eventual understanding of a phenomenon. Marr stresses the fact that it is not all phenomena that require descriptions at all three levels. Depending on their

complexity some phenomena may be explained at only one or two levels; neuroanatomy or synaptic mechanisms, for instance, can be tied to the third level, the physical realisation of the computation. In contrast, psychophysics is more related to the level of algorithm or representation. It is thus important to have the idea of different levels of description in mind when accounting for different phenomena. Lack of awareness of these different levels has led to category errors in many scientific arguments and thus to the dubious validity of claims made by otherwise serious neuroscience research programs[3]. Marr uses the following analogy to underline the importance of being aware of these levels when forming a theory of any given phenomenon: "*...trying to understand perception by studying only neurons is like trying to understand bird flight by studying only feathers: It just cannot be done*" (Marr, 1982). Understanding the differences between the neurobiological and cognitive perspectives on depression in the light of Marr's distinction between different levels of description provides a unifying theoretical framework for the relation between them.

We saw that the enabling assumption of the neurobiological approach is that the mind can be fully accounted for through understanding the neurophysiological processes, which has long allowed neuroscientists to ignore the need for an explanation of the influence of psychosocial factors in depression. Thus, from the neurobiological perspective, depression is conceptualised within the confines of the physical world. The principal question of the neurobiological approach is therefore: how is depression realised physically? The level of analysis, to which the approach belongs, is thus the *hardware level*. In contrast, the focus of the cognitive perspective is primarily on how the processing of emotional information is performed as well as on the function or purpose of this processing. More specifically, the questions addressed are: how does the privileged processing and memory of negative emotional information occur in the mind of the depressed person and what is the function or effects of the negative biases characterising perception and memory? From this, we can infer that the aspects of depression addressed by the cognitive approach are concentrated on the two top levels of description – the representational and computational levels – while nothing is said about the hardware level of depression. The distinction between different levels of analysis in the research on depression is thus valuable, placing the neurobiological and cognitive approaches each on their own levels to constitute a complete picture of the disorder. The multiple-level framework provides a basis for assessing the validity of the different kinds of objections that are raised by the two approaches.

The scientific *criterion of homogeneity* states that we cannot explain phenomena belonging to one level of analysis with concepts belonging to another level. According to this

[3] Category errors: explaining phenomena at one level of description by using a vocabulary belonging to another level.

criterion, it is scientifically correct to formulate *intra-level* - but not *inter-level* explanations. Explaining a phenomenon at one level of analysis with concepts belonging to another level is a scientific fallacy. This is highlighted by philosopher Colin McGinn (1995), who argues that neurobiological accounts cannot explain conscious phenomena, because neural processes and conscious experiences are phenomena that belong to two distinct levels of analysis. Following the criterion of homogeneity it is thus a fundamental mistake to argue that the neurobiological or cognitive understanding is superior or could replace the other. The apparent conflict and incompatibility between the accounts of depression proposed by the different paradigms is thus caused by the failure to recognise the existence of different levels of scientific analysis in the account of depression.

There is increasing awareness that important insights are provided both by the cognitive and by the neurobiological perspectives at their respective levels of description and that the two approaches can be synthesised to form a multifactor or multilevel understanding of depression that constitutes a neuropsychological approach to depression. The neuropsychological research program aims to integrate all three levels of description to create a unified non-reductionistic understanding of depression including both mind and brain facts as well as the mechanisms by which they interact.

3 Theories and methods in research on depression

3.1 Definition of depression

The diagnosis of depression or 'major depressive disorder' is based on the symptomatic criteria set out in the Diagnostic and Statistical Manual (DSM-IV-TR) (American Psychiatric Association, 2000). According to the manual, the diagnosis depends on the presence of one of the two core symptoms depressed mood or loss of interest or pleasure in nearly all activities, accompanied by four or more symptoms of depression for most of the day, nearly every day, for at least two consecutive weeks. The list of symptoms include: changes in appetite or weight; sleep and psychomotor disturbances; decreased energy; feelings of worthlessness or excessive guilt; difficulty thinking, concentrating, and making decisions; recurrent thoughts of death or suicidal ideation, plans or attempts. The diagnosis of a major depressive episode also requires that the symptoms are associated with considerable distress and impairment in social, occupational or other important areas of functioning. The importance of both the duration and impairment criteria is supported by studies which report that major depression is likely to take a chronic, recurring course in a majority of patients seeking treatment (Coryell *et al.,* 1991; Gotlib & Hammen, 1992; Keller *et al.*, 1982).

Empirical studies have reported that either depressed mood or loss of interest is present in almost all cases of significant clinical depression (Beck, 1967, Depression Guideline Panel, 1993). Although there is a strong emphasis on the somatic symptoms of depression in the DSM-IV-TR, it has been reported that the more subjective symptoms of depression like depressed mood, hopelessness, and feelings of worthlessness are as essential or even more central to the definition of depression (Beck, 1967; Coulehan, *et al.,* 1988; Goldberg *et al.*, 1987; Lovibond & Lovibond, 1995). A diagnosis of major depressive disorder is ruled out in the case when symptoms are associated with a mixed episode of mania and depression, when they are caused by the direct physiological effects of drugs or when they are better explained as being due to bereavement.

Despite these universal symptoms, depression is characterised by considerable symptom variability, which has prompted an acknowledgement that clinical depression consists of a heterogeneous set of disorders. According to the DSM-IV-TR the central subtypes of depression are: depression without psychotic features; severe depression with psychotic features; and chronic depression with catatonic, melancholic or atypical features, or with postpartum onset (American Psychiatric Association, 2000). The severity of depression is judged to be mild, moderate or severe on the basis of the number of criteria symptoms present, the severity of these, and the degree of functional disability and distress. At one end of the spectrum are the mild episodes that are characterised by the presence of only five or six clinical symptoms and mild disability. At the other end is severe depression without psychotic symptoms, which is characterised by the presence of most of the criteria symptoms and profound disability in all aspects of social and occupational functioning. Severe depression with psychotic symptoms is the subtype in which there are delusions or hallucinations congruent with depressive themes, such as delusions of guilt or punishment or nihilistic delusions (e.g. personal or world destruction). Hallucinations are typically auditory, such as a voice reprimanding the person for sin or insufficiency. Chronic depression is diagnosed when all the criteria for a major depressive episode have been met continuously for at least two years. Chronic depression with catatonic features is characterised by distinct psychomotor disturbances involving motoric immobility (e.g. stupor) or excessive motor activity, mutism, disturbances of voluntary movements (e.g. bizarre postures or grimaces), echolalia (parrot-like repetition of words spoken by another person), echopraxia (repetitive imitation of the movements of another person), or extreme negativism (the maintenance of rigid postures against attempts to be moved). In chronic depression with melancholic features, the central feature is loss of interest or pleasure in all, or almost all, activities or lack of reactivity to stimuli that are usually pleasurable. This diagnosis is made if the depressed mood remains unaltered even when something good happens, with three of the following additional symptoms: a distinct quality of the depressed mood,

worsening of the mood in the morning, early morning awakening, psychomotor abnormalities, significant weight loss, or excessive feelings of guilt. Finally, atypical depression is recognisable by the existence of mood reactivity, such as brightening of mood in response to positive events as well as at least two of the following features: significant weight gain or increased appetite, hypersomnia, leaden paralysis (heavy sensation in arms or legs), and an enduring pattern of interpersonal rejection sensitivity. In summary, it is clear that depression is not a unitary construct, but is rather characterized by an immense variability in severity, chronicity, and clinical presentation.

3.2 The cognitive perspective on depression

3.2.1 From behaviourist models to a cognitive theory of depression

Cognitive theories provide central insights into key mechanisms of depression, addressing both the content of cognitions and differences in how emotional information is processed as a function of the presence or absence of pathology. Through the last three decades, the cognitive theory (CT) and therapy of depression by Aaron Beck has become increasingly influential and is currently recognised as the leading theory in the cognitive approach to depression. The growth of CT followed the previously described shift of paradigms within psychology from behaviourism to cognitivism in the 1960s.

Behaviourist models of depression in the 1960s and early 1970s were based on principles of operant conditioning and learning, conceptualising depression as an over-generalised response triggered by a specific stimulus or event and claimed that the depressive symptoms of anhedonia, withdrawal, fatigue, and psychomotor retardation were caused by a high rate of aversive experience. The most influential behaviourist theory of depression was the Learned Helplessness Model by Martin Seligman (1967, 1975), which was based on laboratory experiments on dogs. Selingman found that given an inescapable shock while restrained in a Pavlovian hammock, the dogs subsequently demonstrated a ‘depressed’ behaviour; they gave up escaping, failed to learn new response-relief contingencies and were extremely passive. He proposed that learned helplessness could be an analogue for clinical depression, in which the typical deficits in motivation, learning, and emotion could be explained as the responses to overwhelmingly aversive experiences. There were, however, a number of limitations of the original learned helplessness model of which the most important ones were its inability to demonstrate a unique relation between learned helplessness and depressive states, to explain the generality, persistence or recurrence of depression, and to account for *subjectively* experienced symptoms of depression. The limitations of the learned helplessness model and other behaviourist theories led to considerable theoretical

change with rejection of the sole reliance on behavioural concepts and addition of cognitive constructs in the account of depression. Increased recognition of the importance of a cognitive approach for understanding and treating affective disorders provided increased momentum for the propagation of cognitive theory and therapy.

Although the cognitive zeitgeist in the 1960s was part of the success of cognitive theory and therapy, it was not the only background for Beck's adoption of the cognitive approach to depression. The greatest influence came from Beck's own clinical observations and experimentation with depressed individuals. In accordance with his training in psychoanalysis, Beck originally operated with psychoanalytical ideas of depression, of which a central one was that inner directed anger (anger directed against oneself) is a core psychological process in depressive disorders. During therapy sessions, however, he noted another central feature that was inconsistent with the psychoanalytical theory: the majority of his patients had dreams in which they were the victims of some sort of rejection, criticism or disappointment (Clark, *et al.* 1999). This inconsistency led to the hypothesis that the core symptom of depression could be a need to suffer masochism. In order to investigate this, Beck developed a scheme for scoring masochistic dreams to be completed by clinically depressed and non-depressed subjects. However, Beck needed a reliable and valid method for diagnosing depression and determining its severity. A number of systematic studies on clinical ratings of depressive symptoms were therefore carried out, which led to the development of the Beck Depression Inventory (BDI), a self-report instrument for measuring the severity of depression (Beck *et al.*, 1961; Beck, 1967). In the large clinical study performed after the accomplishment of this reliable and valid measure of depression, Beck found that depressed individuals had significantly more masochistic dreams than healthy individuals, and that there was a considerable correlation between the content of the masochistic dreams and the attitudes and behaviour of the depressed individuals in the waking state (Beck *et al.*, 1961). Additional studies indicated that depressed patients were more negative and pessimistic about themselves and their performance compared to non-depressed individuals, which led Beck to suggest that "…*certain cognitive patterns could be responsible for the patients' tendency to make negatively biased judgements of themselves, their environment, and their future*." (Beck, 1967, p.185). This cognitive hypothesis was supported by additional studies, which together provided the basis for Beck's formulation of the cognitive theory and therapy of depression.

3.2.2 The cognitive theory and therapy of depression

Beck's cognitive theory and therapy of depression was considered a breakthrough in research on affective disorders and represented a fundamental shift in conceptualising depression in terms of

'thought disorder' as opposed to pure affective disturbance. The theory resulted in vigorous widespread research initiatives and still provides the foundation for the cognitive model of depression, 30 years later.

An assumption underlying the cognitive theory of depression is that affect or emotion is "*…a subjective state resulting from the appraisal or evaluation of internal or external stimuli*" (Beck, 1976). While the term 'affect' has a broad meaning covering experiences such as emotions, moods, and preferences, the term 'emotion' is often used to refer to rather brief but intense experiences (though it has also been used in a broader sense) (Eysenck & Keane, 2000). Four emotions are highlighted as fundamental for the motivation and adaptive behaviour involved in the attainment of basic human needs such as survival, security, reproduction and sociability (Beck & Clark, 1997): *sadness*, which is evoked by feelings of loss, defeat or deprivation, *happiness,* involving appraisals of gain, *fear* (and anxiety), which occurs as a result of appraisals of danger or vulnerability, and *anger*, which is elicited as a consequence of perceptions of injustice or offence (Beck, 1991). The previously mentioned assumption of the cognitive paradigm is that the mind is a device for processing information. The information processing properties of the mind refer to "*the structures, processes, and products involved in the representation and transformation of meaning based on sensory data derived form the external and internal environment*" (Clark *et al.*, 1999). Thereby, the mind is a system that selects, transforms, encodes, stores, and retrieves information to serve the human organism's adaptation to the environment.

The structural level of cognition is represented by four concepts that are essential to the theory: 'schemas', 'modes', 'personality', and 'orienting schemes'. These are all dynamic, operative and interact with the individual's environment, which makes them central in the cognitive formulation of depression. Schemas are defined as "*relatively enduring internal structures of stored generic or prototypical features of stimuli, ideas, or experience that are used to organize new information in a meaningful way, thereby determining how phenomena are perceived and conceptualized* (Beck, 1964, 1967): schemas therefore bias all cognitive processes, favouring processing of schema-consistent information. Both the *content* and the *form* of depressive schemas are problematic, as they contain chronic misconceptions, distorted attitudes, invalid premises, and unrealistic goals that form inflexible, closed, and resistant structures. The content of schemas is the individual's beliefs or internal representations that derive from experiences and influence the cognitive processing of internal and external stimuli. In depression-prone individuals the content of the cognitive schemas is dominated by overwhelming *negativity*; they have a negative view of themselves (feeling worthless and unlovable), of the world (seeing it as overwhelming), and of the future (which seems 'dark' and hopeless). These three factors constitute a 'cognitive triad', which

influences the perception, interpretation, and memory of personal material (Gonca & Savasir, 2001). A specific stressor or situation that would be expected to lower self-esteem is therefore likely to activate the depressive schemas in vulnerable individuals. Once activated, the depressive schemas dominate the individual's cognitive processes and lead to negative automatic thoughts as well as to cognitive errors. The cognitive errors, which Beck (1963) found were evident in depression are: the *arbitrary inference,* which is the tendency to draw a conclusion in the absence of evidence, *selective abstraction,* focusing on a detail out of context while ignoring other more salient features, *overgeneralisation,* the tendency to draw a conclusion on the basis of an isolated incident, *magnification/minimisation,* exaggeration or minimisation of the significance of an event, and finally *dichotomous thinking,* a tendency to place all experience in one of two categories.

Structurally, schemas differ with respect to their *degree of interrelatedness*; schemas with more closely interrelated elements or ideas are more easily activated and thus tend to dominate cognitive processing. Further, their *degree of complexity* is essential; more complex schemas involve larger number interrelated ideas and activate a wider range of experiences, thus having a greater influence on cognitive processing. The representation of the self is a schema of high complexity consisting of an immense number of interrelated ideas that have accumulated over many years. Finally, an important structural characteristic of schemas is that they vary in "*flexibility or rigidity, permeability or impermeability, concreteness or abstraction, valence and breadth*" (Beck, 1967). From this follows that schemas that are rigid and impermeable are especially difficult to change, even when repeatedly presented with contradictory information. These negative self-schemas tend to be more rigid, absolute, and impermeable, thus leading to perseverance of the feelings of worthlessness, guilt, and self-criticism despite lack of information in support of this. Two particular aspects of negative self-referent schematic content are essential: firstly, schema content occurs at *different levels of generality*, and secondly, different schemas correspond to *diverse aspects of the personality* or psychological functioning. Three different levels of generality of the self-schemas have been identified: firstly, at the most specific level of abstraction there are some *simple schemas*, which deal with very specific ideas and single objects such as shoes, telephones, busses, and the like. These schemas have little relevance for the personal values and goals and therefore play a limited role, if any, in the pathogenesis of depression. The second, *intermediary* class of schemas is less concrete, more personal and is frequently applied to a broader array of experiences. They are often reflected in the rules that people use to evaluate themselves and others which take the form of conditional rules or 'if-then' statements (Beck *et al.*, 1987), for instance "if I am criticized, then it means that I have failed". Two classes of intermediate beliefs have been found: the *imperative beliefs*, involving 'should' and 'must' (Beck, 1976) and

compensatory beliefs; the strategies used in response to their maladaptive core or intermediary beliefs. These form a central part of the 'primary modes', the hypervalent emotional structures, and are therefore often active in psychopathological conditions. Finally, at the broadest level are the *core beliefs* that usually take the form of absolute statements concerned with the self, thus forming an important component of the self-concept and of worth. In individuals prone to depression, their predominant core beliefs are overwhelmingly negative, such as 'I am worthless', 'I am unlovable', and 'I am helpless' (Beck, 1987). These core beliefs refer to the basic aspects of human adaptation like survival and attachment and are thus more global, over-generalised, and absolute in their nature compared to intermediate beliefs. They are often characterised by a positive/negative polarity. According to Beck, individuals with proponent negative core beliefs more frequently experience strongly negative emotions and dysphoria in comparison with people possessing positive core beliefs.

The second mental structure of importance for the cognitive theory of depression is the 'mode', which compared to the schema represents a broader, more integrative, and organising construct in the representation of meaning (Beck, 1996). The mode is defined as "*a specific cluster of interrelated cognitive-conceptual, affective, physiological, behavioural, and motivational schemas organized to deal with particular demands placed on the organism*" (Clark, 1999, p.88).

This structure was added to the schema theory to explain the information processing involved in normal and abnormal emotional experiences, the cognitive basis of personality, the complexity of symptoms in affective disorders, and the broad systematic bias evident across various psychological domains that suggest a more global and complex organisation of schemas (Oatley & Johnson-Laird, 1987) At the modal level, information processing is more complex, integrative, and global and occurs automatically. The modes are hypervalent, which means that they easily dominate the information processing system once activated. The appraisals resulting from the activation of the modal structures thereby reflect the features of the modes rather than the actual situation (Clark, Beck & Alford, 1999). Three types of mode have been identified: primal, constructive, and minor modes; the two former are thought to play an important role in depression. The primal modes deal with the most basic needs of the organism such as self-preservation, procreation, and sociability. The four basic emotions listed earlier - sadness, happiness, fear, and anger- are each represented in particular primal modes: the 'loss or deprivation mode', the 'self-enhancement mode', the 'threat mode', and the 'victory mode', respectively. In depression there is a hypervalence of the 'loss or deprivation mode', which is characterised by the feeling of loss of one's crucial resources, sadness or dysphoria, fatigue, helplessness, lack of goal-directedness, loss of pleasure or interest, and withdrawal (ibid.).

The constructive modes are "*are primarily acquired or constructed through life experiences*" and are crucial for mental health in that they support productive activities that increase the essential resources of the individual (Beck, 1996). The constructive modes include the capacity for intimacy, inter-personal relations, striving for achievement, and sense of personal mastery, independence, creativity, and optimism. By playing an important role in goal attainment, as well as in productive and pleasurable activity, the constructive modes are essential in the cognitive basis of positive emotions *(*Clark *et al.*, 1999*)*. It has been suggested that in depression, extremely negative affective states may persist because of inactivity or the relative weakness of the constructive modes. Therefore the cognitive therapy of depression aims to strengthen the constructive modes of thinking to reverse negative thinking *(*Clark *et al.,* 1999).

In addition to the levels of schemas and modes, the pre-depressive personality sub-organisation is another level of conceptualisation important for understanding depression. The personality is defined as a "*relatively stable organisation of cognitive, affective, behavioral, motivational, and physiological schemas for representing adaptive or maladaptive responses to the normal demands and stresses of everyday life*" (Beck *et al.*, 1990). Personality therefore determines how we interact with other people as well as how we cope with any opportunities or demands we encounter in our lives. Schematic personality organisation thereby explains individual differences in vulnerability to depression. Two personality suborganisations have been recognised as producing depression vulnerability: 'sociotropy' and 'autonomy' (Beck, 1983). In an individual with a sociotropic personality, self-worth depends on receiving love and approval from others and maintaining close personal relationships. This individual might have the belief "I must please others in order to be loved and accepted" and therefore fears to be abandoned or rejected. This poses a danger to the self-worth of the sociotropic person, as he/she becomes more susceptible to loss of self-worth in a situation of perceived loss of social acceptance and attachment (Clark *et al.*, 1999). While the autonomous personality is oriented toward mastery and independence and bases self-worth on control, productivity, and achievement, a personality with very low autonomy, the depressogenic type, is oriented toward failure and dependence and has a relatively low self-worth. The depressogenic sociotropic beliefs may be "Nobody loves me", "I have failed", and "I am helpless".

The fourth and final structure of cognitive representation is the level of 'orienting schemes'. These support the "*preliminary, rudimentary assignment of meaning based on a matching of environmental features with the various meaning-making organizations and structures of the information processing system*" (Clark *et al.*, 1999, p.95). The orienting schemes are thus the pre-attentive preconscious stage of cognitive processing, which acts as a 'filter' or a 'screen' for

incoming information. Orienting schemes quickly allocate the information that is "relevant to me" and "irrelevant to me", of which the latter refers to the neutral objects and events that do not fit with the person's significant concerns. The schemes can demonstrate different biases, for instance towards stimuli that pose some sort of threat to the individual and therefore must receive attention. They are thus predisposed to give priority to material that is relevant to personal concerns while filtering away irrelevant information. In psychopathology, the personal category of information becomes hypervalent, and the orienting schemes therefore become primarily concerned with personal or self-referent information. In depression, the negative self-referent orienting schemas bias interpretations so that the behaviour is judged as personally relevant and negative, although it may not be directed towards the individual in reality.

3.2.3 Descriptive hypotheses: negative cognitive biases in depression

Based on the cognitive structures, content, and processing described in the preceding sections, the cognitive model of depression proposes nine descriptive hypotheses, all of which focus on aspects of cognitive functioning at a descriptive level (Clarke *et al.*, 1999). The hypotheses therefore do not inform us about any causal relationships, but describe the cognitive dysfunction characterising the disorder. This is important for understanding the interdependence of the processes and how biases in cognitive processing affect the subjective state, general mood, and behaviour, as well as drawing attention to the observable phenomenological symptoms of the disorder. Research on the descriptive aspects of cognitive functioning in depression may also warrant further studies on causal factors or agents that may change the depressive state, and as such are of crucial importance for progress in the understanding of the cognitive basis of depression.

The first hypothesis of *negativity* states that depression is characterised by absolute and persistent negative self-referent thinking about the self, the world, and the future (Beck's 'cognitive triad'); The second hypothesis of *exclusivity* refers to the exclusion of positive self-referent thinking; and the third hypothesis of *content-specificity* refers to the observation that depressive content is evident in negative cognitions and processing biases. Further, the fourth hypothesis of *primacy* asserts that negatively biased cognitive processing will profoundly influence the behavioural, affective, somatic, and motivational manifestations of depression. According to the fifth hypothesis of *universality*, heightened negative emotion, reduced positive cognition, and negative self-referent processing biases are manifest in all subtypes of depression. The sixth hypothesis of *severity/persistence* claims that characteristic negative biases in cognitive processing and reduction of positive thinking are linearly related to the severity and persistence of depression. The seventh hypothesis of *selective processing* states that depression is characterised by selective

processing bias for negative self-referent information, involving themes of loss, failure, and deprivation rooted in an automatic tendency to selectively focus on the negative features of one's personal experiences and exclude the positive elements. According to the eighth hypothesis of *schema activation,* there is increased accessibility to the negative self-referent schemas in negative emotional states like depression. The ninth and final hypothesis is that of *primal processing,* which claims that negative self-referent processing in depression is a result of primal mode processing that is involuntary, rapid, automatic, unintended and occurs at a preconscious stage. Taken together, the above hypotheses suggest that the universal characteristics of depression are the existence of universal *negative self-referent* biases in cognitive processing, which profoundly influence emotion, motivation, and behaviour. These negative biases are rapid, automatic, and unintended, and their magnitude is directly related to the severity and persistence of the depression. Because of their negative biases in self-referent emotional processing, depressed individuals are more likely to expect hostility from their surroundings, in accordance with their schemas. When this attitude naturally elicits negative responses from others, the initial expectations of hostility are confirmed and reinforced. In this way, the negative biases initiate a vicious cognitive-interpersonal circle, which both causes and maintains the depressive state (Bradley, Mogg & Williams, 1995).

3.2.4 Empirical evidence for the negativity hypotheses

The *negativity* hypothesis, which is the most fundamental hypothesis in the cognitive theory of depression, has received extensive support numerous empirical studies. Several retrospective self-report questionnaires have been developed to assess depressotypic negative cognitive content, including the Hopelessness Scale (Beck *et al.*, 1974), Cognitions Checklist (Beck *et al.*, 1987), Automatic Thoughts Questionnaire (Hollon & Kendall, 1980), and Crandell Cognitions Inventory (Crandell & Chambless, 1986). There is substantial evidence that clinically depressed and non-clinically dysphoric individuals have a significantly higher score on all of these scales than healthy controls (Hollon & Kendall, 1980; Blackburn, Jones & Lewin, 1986; Dobson & Shaw, 1986; Ingram *et al.*, 1987a; Lam *et al.*, 1987).

The *exclusivity* hypothesis does not merely refer to the relative decline in positive processing, but to the automatic *exclusion* of positive self-evaluation (Clark *et al.*, 1999). Thus the problem in depression is not restricted to excessive negative thinking, but also involves a reduction in positive thoughts. This has been confirmed in a factor analysis of the Automatic Thoughts Questionnaire Negative and Positive subscales (ATQ-N and ATQ-P, respectively), which demonstrated that a hierarchical model with correlated second-order factors of positive and negative automatic cognitions provided a significantly better fit to the data than a single underlying

factor with positive or negative cognition at opposite ends of the automatic thought dimension (Bryant & Baxter, 1997). This suggests that positive and negative thoughts are best understood as correlated distinct dimensions, supporting the exclusivity hypothesis. Various studies have established that depressed individuals have fewer self-reported positive thoughts than do non-depressed individuals, which is consistent with the prediction of the exclusivity hypothesis (Ingram, 1989, Ingram & Wisnicki, 1988; Kendall *et al.*, 1989; Ingram *et al.*, 1990).

Research on the cognitive *content-specificity* hypothesis has mostly compared cognition in depression and anxiety. Several of such studies have found that depressed individuals more frequently report personal loss and failure and lack of self-worth than do anxious individuals (Beck *et al.*, 1987; Blackburn *et al.,* 1986; *Clark et al.*, 1990; Ingram, 1984, 1989). Additionally, there is evidence that compared to anxious subjects, depressed patients demonstrate more cognitive errors, like overgeneralisation to negative events, and dichotomous thinking (Macpherson, 1989). However, other studies fail to find such differences (Butler & Mathews, 1983; Fennell & Campbell, 1984; Mitchell & Campbell, 1988). Content-specificity has also been investigated with respect to self-representation, where there is evidence of differences between depression and anxiety (Higgins, 1987). In a self-referent encoding task assessing the selective encoding and memory in depressed, anxious and healthy individuals, Greenberg and Beck (1989) demonstrated that depressed individuals consistently endorsed the trait adjectives as self-descriptive and recalled a significantly higher number of negative trait adjectives than did anxious or healthy subjects.

The hypothesis of *primacy* has been tested empirically in various ways. Mood-induction studies, which use production of negative self-referent cognition to create depressive mood shifts, have been implemented to investigate whether negative self-referent thinking can cause depressive mood states. Conversely, other studies have examined whether a reduction in negative cognition is associated with a corresponding reduction of depressive symptoms and low mood. A widely used method for mood-induction is the cognitive manipulation introduced by Velten (1968), the Velten Induction Procedure (VIP), in which subjects read a series of self-referent mood statements and try to feel the mood that is suggested by the statements. This procedure has been found to induce a number of transient depressive symptoms and transitory depressed mood (Clark, 1983). This suggests that the occurrence of negative thoughts does indeed influence the mood state and various symptoms of depression, thus supporting the primacy hypothesis. Another line of study has explored the clinical effects of decreasing the frequency of negative cognition (and the corresponding mood) during sessions of cognitive therapy. A study on the relationship between thought and mood change in patients with depressed and anxious symptoms after cognitive therapy reported preliminary evidence of significant within-session reductions of negative mood and of

belief in their negative thoughts (Persons & Burns, 1985). This correlation between the reduction of negative thoughts or their impact and depressed mood supports the primacy hypothesis.

The *universality* hypothesis asserting that negative self-referent cognition is a prominent characteristic in all subtypes of depression has received support (Haaga, Dyck & Ernst, 1991). Although most of the research has focused on unipolar depression, there is also evidence of significant elevation in negative self-referent cognitions and beliefs in bipolar (Hollon *et al.*, 1986; Rose *et al.*, 1994), psychotic, and non-psychotic (Zimmermann *et al.*, 1986) depression as well as in depression secondary to medical illness (Plumb & Holland, 1977; Clark *et al.*, 1983). There is thus substantial support for the universality hypothesis of depression.

The *severity*/*persistence* hypothesis, predicting that more severe depressive states are associated with more pervasive negativity processing biases and more frequent negative self-referent thoughts, has been validated by various studies. Research literature reviews conclude that there is evidence for a correlation between the severity of the disorder and deficits in encoding as well as psychomotor speed and short-term memory (Johnson & Magaro, 1987). Regression studies provide further support for the severity hypothesis by demonstrating a stronger relationship between mood-congruent negative cognitions and depressive symptoms than between mood-incongruent positive cognitions and symptoms (Ambrose & Rholes, 1993; Alford *et al.*, 1995; Clark *et al.*, 1989; Jolly & Dykman, 1994). There is thus considerable support for a positive relationship between negative cognitions and the severity of depression.

Research on the *selective processing* hypothesis, which predicts that negative self-referent biases are evident in all stages of cognitive processing in depression, falls into two major research lines. These have investigated biases in the *early* perceptual or encoding stages of information processing (selective attention), and in the more *elaborative* and conceptual stages of information processing, respectively. Within the first line of studies selective attention has been explored in terms of 'facilitated task performance' (also called 'priming') and 'debilitated task performance', which are reflected in the improved performance of tasks that are mood-congruent and reduced task performance caused by drawing attention to task-irrelevant mood-congruent stimuli (Clark *et al.*, 1999). Facilitated performance studies demonstrate that depressed patients when viewing rapid word representation are more accurate than non-depressed controls in identifying negative words that were previously rated as highly self-descriptive (von Hippel, Hawkins & Narayan, 1994). Consistent with this, studies comparing eye fixation differences between dysphoric and healthy individuals demonstrated that dysphoric individuals fixated more on the sad regions of the pictures (Matthews & Antes, 1992). Studies using standard lexical decision failed to find consistent support for a depression-related decision bias for negative words (Clark *et al.*, 1983; MacLeod *et al.,* 1987).

However, studies using the more refined priming version of the lexical decision task provide evidence for depression-congruent priming effects in subliminal and supraliminal (below and above threshold of conscious awareness, respectively) conditions (Bradley, Modd & Williams, 1994, 1995). Selective attentional biases in depression have also been confirmed by studies on debilitated performance, such as studies using the emotional Stroop task, in which subjects are asked to name the colours in which some rapidly presented printed words. The Stroop interference effect is reflected in a decrement in performance (longer latencies) due to interference by irrelevant stimuli (e.g. the emotional valence of the coloured word). Depressed individuals have longer latencies when naming the colour of negative depression-related words than neural words, which suggests that the attentional resources directed to encode colour are obstructed by unintended processing of the negative word itself (Williams *et al.*, 1988). There is thus substantial support for the automatic processing of negative self-referent information in depression.

In the second line of research on selective processing in depression, which focuses on the more elaborative aspects, encoding and memory has received great attention. Various studies of depressed or dysphoric individuals report substantial elevation of negative self-focused attention compared to healthy controls (e.g. Ingram *et al.*, 1987b; Pyszynczynski & Greenberg, 1987). Thus depressed individuals tend to be more negatively oriented when presented with significant self-referent information than are non-depressed people. Furthermore, it has been demonstrated that depression is associated with both *quantitative* and *qualitative* changes in explicit memory (Danion *et al.*, 1996). Quantitative changes are characterised by impairments in retrieving the information organised in semantic memory and in delayed and immediate recall (Ilsley *et al.*, 1995; Brand *et al.*, 1992). This suggests that depression reduces the number of cognitive resources allocated to a given task, impairing the elaboration of information (Danion *et al.*, 1996). In addition to these quantitative modifications, there is also evidence for *qualitative* alterations of explicit memory in depression that is caused by the presence of mood-congruent biases in cued and free recall (*ibid.*). Depressed individuals recall significantly more depression-relevant than positive words compared to control subjects, thus demonstrating biases towards depression-related information (Watkins *et al.*, 1992). Moreover, depressed patients have been found to recall significantly more negative than positive adjectives, whereas this bias is not present in non-depressed controls (Neshat-Doost *et al.*, 1998). It has furthermore been demonstrated that sub-clinically depressed individuals have a superior recall of self-esteem threat words (Hill & Dutton, 1989). These negative biases suggest that depressed people are more likely to recall negative self-referent adjectives – a central mechanism for the development and maintenance of depression according to Beck *et al.* (1979). Studies of self-referent memory confirm that depression predominantly affects the organisation of

negative self-referential material and that this trend is increased significantly in more recurrent depression compared to less recurrent depression (Dozois & Dobson, 2003). Paradigms of *implicit* memory provide no evidence for *quantitative* modifications, as depressed patients generally demonstrate the same amount of priming in implicit memory tasks as do healthy controls (Danion *et al.*, 1996). *Qualitative* alterations of implicit memory have been reported by the presence of *conceptual* but not *perceptual* priming to negative information in depressed individuals (Hill & Dutton, 1989; Bradley *et al.,* 1995). Conceptual priming has been demonstrated by greater priming of lexical decision-making for depression-relevant material both at supra- and sub-threshold levels (Bradley *et al.*, 1995; Watkins *et al.*, 1996). Taken together, the characteristic negative memory biases seem to operate both consciously and unconsciously (Watkins *et al.*, 1996), facilitating *explicit* recall of negative self-referent information as well as leading to *implicit* priming of negative information. A methodological limitation of such studies on mood-congruent memory is that they involve depressed patients exclusively. They cannot thus rule out that the reason for the 'biases' might be that the subjects have, in reality, experienced overwhelmingly negative events. Paradigms on mood-induction in *healthy* normals have, however, confirmed that emotional states do affect cognitive processing and memory, thereby providing support to the mood-congruency theories (Chastain *et al.*, 1994; Nabi, 2003). Taken together, there is substantial evidence that the negative self-referent biases operate in both early perceptual and more elaborative stages of cognitive processing (e.g. memory), which together provide support to the *selective processing* hypothesis of depression.

According to the *schema activation* hypothesis, negative self-referent processing is a result of the activation of underlying dysfunctional schemas and modes, and the prediction is that there is an increased accessibility of negative self-referent schema content in depression. Starting from the assumption that ratings of the self-relevance of descriptiveness of personality trait adjectives reflect self-schema content, various studies have investigated the endorsement of trait adjectives to explore depression-related self-schemas. The most consistent findings from these studies are that depressed and dysphoric subjects endorse significantly more negative trait adjectives than healthy controls. However, a serious limitation of interpreting trait adjective endorsement as an indicator of self-schema is that many of the traits describe sad mood rather than personality traits. The enhanced endorsement of negative words could thus be a result of the influence of mood state alone (Segal, 1988). Another problem with this method is that although depressed subjects endorse relatively more negative traits than non-depressed subjects, they still rate more positive than negative trait words as self-descriptive (Bargh & Tota, 1988: Segal & Vella, 1990). This suggests that trait adjectives may not be an accurate indicator of schema content.

Another method of assessing schema content is a sentence completion task (Teasdale *et al.*, 1995), which is construed according to the hypothesis that the depressed state lowers the activation threshold for concepts such as failure, loss, and hopelessness because these are congruent with negative self-referent schema. Sentence stems were selected so that a positive answer would reflect more depressotypic thinking (Teasdale *et al.*, 1995). Comparison between groups of clinically depressed and non-depressed individuals demonstrated that depression is associated with significantly more of such positive answers, thus demonstrating more dysfunctional self-schemas. Additionally, a second measurement three months later after significant improvement of depressed mood demonstrated reduction of the positive dysfunctional statements. Finally, studies on autobiographical memory have been employed to assess the enduring negative self-schema content in depression. These studies demonstrated that depressed or dysphoric individuals have an enhanced mood-congruent retrieval of negative and unpleasant personal memories as well as diminished recall of personal memories, compared to healthy volunteers (Fogarty & Hemsley, 1983; Lloyd & Lishman, 1975). Importantly, these effects were not a result of the depressed individual having genuinely more negative life experiences, as healthy individuals during sad mood-induction have demonstrated similarly increased accessibility of negative memories (Teasdale & Taylor, 1981). Although this could be taken as support for the existence of enduring negative self-schemas in depression, the demonstration of this effect in healthy individuals during mood-induction could suggest that the increased accessibility of negative memories is a mere mood state congruency effect.

Finally, the hypothesis of *primal processing*, asserting that negative self-referent cognition is a product of the involuntary, rapid, and automatic primal processing, has received considerable support. In an extensive literature review, Hartlage *et al.* (1993) found that while depression impedes the effortful processing of neutral material, it does not affect automatic processes such as motor performance and cognitive speed. They suggest that this pattern is a consequence of the reduction of attentional capacities in depression because of a narrowed attention to depression-relevant thoughts (which affects elaborative but not automatic processes). Further, Hartlage and colleagues state that the negative self-referent content is processed automatically in depression, which becomes evident in the biased encoding and retrieval of negative material. They suggest that a depressive episode can be triggered in depression-prone individuals who have a tendency to process negative content automatically in case of stress. When the attentional focus narrows in the stressful situation, it is mainly the negative content that is processed because its automatic nature requires minimal attentional resources (ibid.). This explanation is consistent with the primal processing hypothesis of depression. In order to confirm that the biases exist at an automatic or

primal processing level of cognition, it is important to demonstrate an occurrence of these biases outside conscious intentional control (Clark *et al.*, 1999). This has been done by implementation of the Stroop colour-naming test, in which the degree of interference of automatic unintended processing is measured. A previously discussed study on depressed individuals, where the primed Stroop colour-naming task was used, reported significantly more interference of self-descriptive negative trait adjectives primed by self-descriptive negative phrases in colour-naming than other prime-target pairing (Segal *et al.*, 1995). This indicates the existence of a rapid, unintended negative self-referent bias in depression and thus supports the primal processing hypothesis.

3.2.5 Evaluation of the cognitive theory of depression

With the conceptualisation of depression as a disorder of thought rather than a purely affective disorder, Beck's cognitive theory has profoundly influenced all theorising on affective disorders and has provided intriguing insights into the cognitive basis of depression, the relation between cognition and affect, and the influence of multiple factors including the individual's predisposition, the social environment and their interaction. By predicting the existence of pervasive processing biases in depression, affecting all stages of cognitive processing (attention, encoding, comprehension and memory) of emotionally valenced information from the proposed cognitive constructs, the theory provides a comprehensive conceptual framework for understanding and treating the disorder. More generally, another crucial value of Beck's cognitive theory is an appreciation of the phenomenology of depression, which draws the researcher into the more observable symptoms of depression and identifies the processes that may warrant further exploration.

There are, however, a number of caveats to the cognitive theory of depression. What is probably the most severe limitation of the theory is that it does not elucidate the *aetiology* of depression. The cognitive theory of depression does not explain *how* the negative self-schemas are initially formed and which factors affect the formation of negativity leading to depression. It has not been possible to prove that the negative self-referent schemas play a *causal* role in the development of depression. Thus, from the cognitive perspective, the origins of depression remain obscure (Eysenck & Keane, 2000). As a result of the lack of causal explanations, it has been argued that research on cognitive functioning at the descriptive level is uninteresting (Coyne & Gotlib, 1986). However, research at the descriptive level provides central insights into the interdependent processes of depression and into how changes in cognition are associated with concurrent alterations in subjective mood and behaviour. Thus, despite the limitation that the aetiology and the

causal relations are not accounted for, cognitive research provides much useful and valuable information about depression.

Another limitation of the cognitive theory of depression is that evidence for the existence of schemas is based on a circular argument, in which the existence of negative self-referent cognitive schemas is deduced from the behavioural evidence for negative cognitive biases in depressed individuals. The same schema is then employed to 'explain' the observed negative cognitive biases. There is thus no direct or independent empirical evidence of the existence of cognitive schemas (ibid.). Moreover, the theory lacks the dissociation of *explicit* memory (declarative conscious recollection) and *implicit* memory (the memory underlying perceptual and cognitive skills, often expressed as improvement or priming in perceptual or cognitive tasks without conscious recollection of the experiences that led to the improvement). The prediction is therefore that depressive mood-congruent biases should affect *all* aspects of processing. Empirical research on cognitive processes in depressed patients has produced data contrasting with these predictions (Watkins *et al.*, 1992); although negative memory biases in *explicit* memory tasks have consistently been found, the findings on negative memory biases in *implicit* memory have been conflicting (Hill & Dutton, 1989; Watkins *et al.* 1992; Bradley *et al.*, 1995; Ellwart *et al.,* 2003). It has been suggested that this discrepant result of implicit memory studies is due to the lack of discrimination between *perceptual* and *conceptual* processing biases, of which only the latter are present in depression, the former being present in anxiety.

3.3 The neurobiological perspective on depression

With the discovery of antidepressant drugs in the middle of the last century, the conception of affective disorders changed profoundly. Until the 1950s, depression had been conceived of as a disorder with a purely psychological aetiology and was, accordingly, treated by means of psychological therapy. However, the finding that chemical manipulation of the brain's neurotransmitter systems could lead to amelioration of the condition led to the radically new idea that depression itself could be caused by abnormalities of these neurobiological systems (Nestler *et al.*, 2002). Since the introduction of the psychopharmacological approach, there has been an enormous body of research on the disorder from a neurobiological perspective.

Today, the neurobiological understanding of depression is dominated by two major theories – the 'monoamine theory' and the 'neurotrophic theory' (Nestler, 1998; Nestler *et al.*, 2002). According to the monoamine theory, depression is caused by a disruption of the monoamine systems in the brain, upon which antidepressants act by facilitating *monoaminergic* neurotransmission. Conversely, the neurotrophic theory holds that depression is caused by a

disruption of the neurotrophic mechanisms involved in the protection and generation of neurons and the formation of appropriate neural connections, which leads to the degeneration and atrophy of neurons in various sites in the brain. Accordingly, antidepressants exert their clinical effects though increasing the *neurotrophic factors* in the brain, reversing neural degeneration and atrophy. In terms of historical perspective, the monoamine theory has long had a profound influence on the neurobiological research conducted on depression and has been the dominant paradigm since the discovery of antidepressant drugs. Recently, however, a growing body of evidence provided by brain imaging studies favours the neurotrophic theory of depression, leading to changing conceptions of the pathophysiology of depression, as well as to the strategic development of improved therapeutic agents in the future.

3.4 The monoamine paradigm

The first antidepressants to be discovered were the monoamine oxidase inhibitors (MAOIs), which exert clinical effects through manipulation of the monoamine system. This class of chemical antidepressants was found to improve depressive symptoms entirely by chance rather than on the basis of an understanding of the pathophysiology of depression that (Nestler *et al.*, 2002). However, as it was demonstrated that MAOIs act by enhancing or prolonging the actions of the monoaminergic neurotransmitters, a straightforward hypothesis of antidepressant action was proposed: facilitation of monoaminergic neurotransmission (Nestler, 1998). The discovery of the MAOIs was followed by the introduction of the tricyclic antidepressants (TCAs), which within the monoamine system act relatively selectively on serotonin and noradrenaline (e.g. Tucker & File, 1986). These major discoveries brought forth the development of tetracyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, noradrenergic, and specific serotonergic antidepressants, serotonin 2-receptor inhibitors, serotonin/noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), and selective noradrenaline reuptake inhibitors (SNRIs). These newer antidepressants exert their clinical effects through various mechanisms: by inhibiting the reuptake of noradrenaline and serotonin from the synaptic gap to the presynaptic deposits; by regulating dopaminergic neurotransmission; by stimulating the presynaptic release of monoamines; or by reversible or irreversibly inhibiting an enzyme critical for the metabolism of the monoamines.

The methodology of empirical studies on depression has long been tied to the monoamine paradigm, as it was designed to explore the monoamine systems as well as to refine the mechanisms of action of the monoaminergic antidepressants. One main reason for this focus is that the monoamine systems are distributed throughout the network of limbic, striatal, and prefrontal

cortical neural circuits and are thought to support the behavioural and physiological manifestations of depression (Manji *et al.*, 2001). Clinical studies have therefore attempted to uncover specific defects in these neurotransmitter systems by employing a variety of biochemical and neuroendocrine strategies. Studies assessing cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor binding have demonstrated a number of abnormalities of the serotonergic and noradrenergic neurotransmitter systems in depression (Manji *et al.*, 2001). As the serotonergic, noradrenergic, and dopaminergic systems exhibit complex interactions, perturbation of one system will result in activity changes in one or both of the other monoamine systems. Because of their diffuse global distribution in the entire cerebrum, the dysfunction or one or more systems will have profound consequences. Consequently, studies assessing the neurochemistry of depression have provided much useful information on the neuroendocrinological aspects of depression, which were long thought to be the primary neurobiological basis of the disorder.

Another reason for extensive research on the monoamine systems is that the early TCAs and MAOIs, despite being clinically effective agents in the treatment of depression, were found to cause considerable side effects because of their rather unspecific mechanisms of action (Nestler *et al.*, 2002). Research following the discovery of these two classes of antidepressants was therefore primarily concentrated on increasing the specificity of the antidepressants, leading to the development of newer drugs that selectively and without loss of efficiency affect the serotonin and noradrenergic systems. Consequently, the advantage of most newer antidepressants is *not* that they possess radically new mechanisms of action of higher efficiency than the TCAs, but rather that they are associated with a reduction of side effects because of the increased selectivity (ibid.; Hindmarch, 2001).

3.4.1 Limitations of the monoamine paradigm

Despite the relatively high effectiveness of monoaminergic antidepressants in the treatment of depression, there are a number of considerable limitations in the monoamine theory of depression, with respect to the methodological approaches. Firstly, the facilitation of monoaminergic neurotransmission can only be the *initial mechanism* of action, and not *per se* a mediator of the clinical effects (e.g. Nestler, 1998; Fossati *et al.,* 2005). This conclusion is based on the fact that amelioration of depressive symptoms occurs days or weeks after the commencement of therapy, whilst regulation of the monoamine neurotransmitter levels occurs within hours. It thus seems that they merely trigger a cascade of neuroendocrinological events that eventually mediate the clinical effects. From the perspective of the monoamine theory alone, the nature of long-term

antidepressant-induced adaptations, which account for symptom remission, remains poorly understood (Nestler, 1998; Hindmarch, 2001; Yamada & Higuchi, 2002). Another major limitation of the monoamine theory is that it fails to explain why *not all* agents that facilitate serotonergic or noradrenergic transmission are effective antidepressants and why some chemical agents with other mechanisms of action, such as cocaine and similar stimulants, seem to have antidepressant effects (Nestler, 1998). Likewise, the monoamine hypothesis cannot explain why some newer antidepressants that actually *enhance* serotonin reuptake can be clinically effective, or why not all depressed patients have abnormal monoamine concentrations (*ibid.*). The theory also fails to elucidate why patients with non-seasonal depression benefit from bright light as an adjunct treatment to medications (Martiny *et al.,* 2005), and why patients who do not to respond to standard antidepressants may benefit from electroconvulsive therapy (ECT) and maybe even deep brain stimulation in the metabolically overactive subgenual cingulate region (Mayberg *et al.,* 2005). Finally, there is no *a priori* reason to expect that abnormalities in monoamine pathways are the *causes* of depression, as it is well known that the site of the origin of dysfunction may be far from the site of action of an effective treatment (Reid & Stewart, 2001; Nestler *et al.*, 2002). This means that the therapeutic effects of particular drugs cannot provide satisfactory evidence on the causes of depression.

Taken together, the conception of depression as a disorder caused by a dysfunction of the monoamine systems cannot provide an account of its causes or the considerable heterogeneity of the disorder with respect to both symptom manifestations and treatment-responses. Indeed, the possibility exists that depression could represent a final common phenotype for multiple pathological states in the brain, for which the monoamine paradigm cannot account, as its methodology is limited to addressing the neurotransmitter levels. The consequent lack of an understanding of the aetiology and pathophysiology of depression within the monoamine paradigm must be considered a major obstacle in neurobiological research, as the development of improved antidepressants is still extensively reliant on the goal of exploring and refining the monoamine regulations of existing antidepressants (Nestler, 1998). The monoamine approach alone cannot thus expect to achieve any truly novel insights into the pathophysiology and aetiology of depression, which could lead to considerable improvements in the future treatments of depression.

3.5 The neurotrophic paradigm

The development of brain imaging techniques through the last two decades introduced new sophisticated methodological approaches in neuroscientific research on depression, which has given rise to novel insights into the disorder. The conception of depression as having a purely

neurochemical basis is challenged by new experimental evidence, which suggest *global structural* changes in the central nervous system (CNS) as well as *functional abnormalities* in various brain sites of depressed patients (Manji *et al.*, 2001). New structural and functional imaging techniques have proved valuable for *in vivo* localisation of brain pathology and assessment of neuromorphology and metabolic abnormalities associated with major depressive disorder. Furthermore, these neuroimaging techniques have been employed to obtain a characterisation of neurophysiological and receptor pharmacological correlates of normal versus pathological emotional states, as well as of treatment response and resistance in single-episode and recurrent illness. Understanding how these changes interrelate with the results of clinical studies, post-mortem findings, and animal studies yields insight into the neuroanatomic networks involved in affective disorders. The recent shift from the monoamine to the neurotrophic paradigm, which has gathered pace during the last few years, must be understood partly as a consequence of these major methodological developments, and partly as a result of a recognition of the need to move beyond the monoamine neurotransmitter level in order to gain insights into the complex aetiology and pathophysiology of depression.

3.5.1 Functional CNS abnormalities

Recent studies employing functional neuroimaging techniques underline the importance of functional abnormalities in various neural structures for the understanding of the aetiology and physiopathology of depression. There is some disagreement regarding the specific location and direction of these abnormalities. However, because of the interconnectedness of the neural areas affected in depression, dysfunction in one area will presumably alter the functions in other areas, thus creating more broad imbalances within these circuits.

Cortical areas, in which there is abnormally *increased* activity in depression, seem to play an important role in emotional processing, as the blood flow in these areas increases during both normal and pathological emotional states (Drevets, 2000). This suggests that dysfunction in these areas could be responsible for the emotional, behavioural, and cognitive symptoms of depression. Numerous EEG studies demonstrate that depression is associated with asymmetric pattern activation in the PFC with a relative increase in activation of the right-side PFC (Bell *et al.*, 1998; Bruder *et al.*, 1997; Debener *et al.*, 2000; Gotlib *et al.*, 1998; Pauli *et al.*, 1999; Reid *et al.*, 1998). In extension of these findings, it was demonstrated that treatment response to SSRIs was associated with reduced right-sided activation compared to non-response (Bruder *et al.*, 1997). Depression is also associated with abnormally elevated levels of rCBF in the hippocampus, amygdala, cerebellum, anterior cingulate gyrus and the basal ganglia (Videbech *et al.,* 2002). The severity of

depression correlates positively with levels of rCBF in hippocampus (Videbech *et al.,* 2002) and levels of rCBF and glucose metabolism in amygdala (Drevets *et al.,* 1992; Abercrombie *et al.*, 1998). Concordantly, the elevated amygdala activation normalises with pharmacologically induced remission from depression (Drevets, 2001; Manji *et al.*, 2001). In line with this, remitted depressed patients who demonstrated symptom relapse following serotonin depletion displayed increased amygdala activation *prior* to the depletion compared to individuals who did not relapse (Bremner *et al.*, 1997). There is therefore substantial evidence for a positive correlation between amygdaloid metabolism and severity of depression.

A metabolic *decrease* in the subgenual PFC is also believed to be central to the physiopathology of depression because of the extensive reciprocal connections between this area and the orbital cortex, hypothalamus, amygdala, accumbens, substantia nigra, raphe, and locus coeruleus (*ibid*.). Supporting this hypothesis, studies have demonstrated that metabolic reductions in the subgenual PFC cause abnormal autonomic responses to emotionally provocative stimuli, an inability to experience emotion in relation to emotion-evoking concepts, and impairment of the ability to guide social behaviour using information about the likelihood of punishment and reward (Damasio, 1990). It is thus conceivable that functional abnormalities in the subgenual PFC in depression contribute significantly to characteristic alterations in emotional and autonomic functions. Moreover, the severity of depression is negatively correlated with rCBF and regional cerebral glucose metabolism in the right cingulate cortex and bilaterally in the PFC as well as bilaterally in insula, basal ganglia, and tempo-parietal cortex (Kimbrel *et al.*, 2002), all areas that are known to play a role in emotional processing.

Studies on animal models have provided important insights for the formulation of hypotheses concerning the aetiology and pathogenesis of depression. It has been demonstrated that in rodents, certain environmental stressors produce dendritic atrophy, death, and endangerment of hippocampal neurons, apparently induced by an over-activation of the hypothalamic-pituitary-adrenal (HPA) axis by environmental stress (Manji *et al.*, 2001). An important role of the hippocampus is to provide negative feedback to the HPA-axis, and its dysfunction may therefore lead to further up-regulation, creating a vicious circle of over-activation of the HPA-axis and hippocampal atrophy (Herman *et al.,* 1989). As the hippocampus is also responsible for many aspects of spatial and declarative memory, hippocampal dysfunction could account for the memory impairment as well as the maintenance of neuroendocrine abnormalities that are found in mood disorders (Brown *et al.*, 1999; Bremner *et al.,* 2004). This is noteworthy with respect to the pathophysiology of depression, as hippocampal atrophy and hyperactivity of the HPA-axis correlate positively in many depressed patients (Brown *et al,* 1999; Sheline *et al.*, 1999; Bremner *et*

al., 2000). This agrees with the recent finding that patients remitted from recurrent depression have significantly greater HPA activity compared to patients remitted from a single depressive episode (Bos *et al.,* 2005). fMRI studies demonstrate that abnormalities of HPA-axis function prior to depression is greater in individuals with a family history of depression, indicating that HPA-dysfunction constitutes a genetic risk (Nestler, 1998). Antidepressant treatment has been found to normalise HPA axis function, which is accompanied by improvement of working memory (Zobel *et al.*, 2004). In animal models, various classes of antidepressants reverse the dendrite morphology of the pyramidal neurons in the hippocampus induced by stress (HPA-overactivity) (Kuroda & MsEwen, 1998; Norrholm & Quimet, 2001) and increase neurogenesis in the dentate gyrus (Malberg *et al.*, 2000; Duman *et al.,* 2001; Manji *et al.*, 2001). However, it is still unknown whether HPA-axis abnormalities are a primary cause of depression or, instead, secondary to some other initiating cause. The direct aetiological relationship between HPA-axis dysfunction and depression has yet to be established. However, the HPA-axis over-activation associated with excessive stress appears to play an important role of in the generation and maintenance of various symptoms of depression and its somatic consequences (Nestler *et al.*, 1998; 2002). The evidence for genetic components in depression, with some individuals being more vulnerable to stress and HPA-axis-dysfunction compared to others, highlights the complexity of the aetiological factors involved in depression (Claes, 2004). The aetiology of depression must therefore be understood as a complex interaction between environmental, neurobiological, and genetic factors (Wurtman, 2005; Levinson, 2005).

3.5.2 Structural CNS abnormalities

Recent studies employing MRI techniques demonstrate that severe depression is associated with structural abnormalities and CNS volume reductions in various sites. There is some disparity in the available findings regarding the exact anatomic structures that are affected in depression, which may reflect the heterogeneity of the disorder. Structural studies of bipolar and unipolar depression report abnormalities of the subcortical and medial temporal regions in particular. Specifically, volume reductions of the basal ganglia and amygdala have been observed in unipolar depression, while they are enlarged in bipolar disorder (Strakowski *et al.*, 2002). However, both affective disorders share in common an underdevelopment or atrophied prefrontal cortical region, which may diminish the prefrontal modulation of the subcortical structures within the anterior limbic emotional network (*ibid.*).

The available findings in unipolar depression also show some discrepancies, with different malfunctioning neuronal circuits (*ibid.*). However, the disparate findings could be explained by the

fact that not all depressed patients display the same symptoms, and represent a rather heterogeneous group (Stahl *et al.*, 2003). Generally, areas that are particularly affected by atrophy and loss of neurons and glia are the orbital and medial PFC, ventral striatum, hippocampus, and amygdala, while the third ventricle may be enlarged compared to healthy control samples (Chen *et al.*, 2000; Drevets, 2000; Duman *et al.,* 2000; Manji *et al.,* 2003; Rajkowska, 2000; Sapolsky 2000; Sheline, 2000; Bowley *et al.*, 2002, Fossati *et al.,* 2005). Additionally, depressed patients display widespread white matter lesions in various brain sites, including the frontal lobes, insula, and areas adjacent to the basal ganglia (Videbech *et al.*, 2004). Within the amygdala, glial density and the glia/neuron ration are substantially reduced in depressed individuals, predominantly on the left side (Bowley *et al.*, 2002), and considerable volume reduction of the core amygdala nuclei has been demonstrated in recurrent depression (Sheline *et al.*, 1998). PFC volume reduction has been found to be related to the severity of illness (Kumar *et al*., 1998). Conversely, no decrease in frontal cortical volume was found in patients remitted from depression when compared to healthy individuals (Bremner *et al.*, 2000). These findings suggest that decreased prefrontal volume may be related to illness state, although the precise mechanism responsible for such an association has not been identified (Strakowski *et al.*, 2002).

Currently, only one study reports an *increase* in the total regional neuron number in depression (Young *et al.*, 2004). Post-mortem analysis demonstrated an *elevated* neuron number within the anterior and mediodorsal thalamus. The reciprocal connections between these thalamic nuclei and prefrontal, orbitofrontal, cingulate, and insular cortices, suggest a crucial role for mediodorsal and anteromedial nuclei in connecting subcortical limbic structures to the limbic cortex, and emphasise the importance of these areas in the integration of emotional processing (Young *et al.*, 2004). The elevated neuron number in these regions indicates the presence of both anatomical and functional abnormalities in the limbic circuits, which may contribute to abnormal emotional processing in depression.

Neurobiological research on depression has focused mainly on the structure and function of the hippocampus. This is because there is evidence that alterations of the hippocampus play a profound role in the physiopathology and reversal of depression, and because of the involvement of this structure in contextual fear conditioning and in learning and memory (Sapolsky, 2000a & 2000b; MacQueen *et al.*, 2002). Numerous studies report the presence of structural and functional abnormalities in the hippocampus of depressed patients, which in severe cases are not fully reversed after symptom remission (Shah *et al*., 1998). Evidence of substantial volume reduction of the hippocampus in depressed subjects (Bremner, *et al.*, 2000) is complemented by studies demonstrating that patients with multiple episodes of depression have greater hippocampal volume

loss compared to single-episode patients (MacQueen *et al.*, 2002). This indicates that the morphological changes of hippocampal volume are related to the severity and recurrence of the disorder and that volume reduction could be a reason for treatment resistance.

Three mechanisms identified as potentially responsible for the reduction of hippocampal volume are (1) neurotoxicity, (2) loss of glial cells, and (3) stress-induced inhibition of neurogenesis and plasticity (Sheline, 2000). Neurotoxicity could be related to repeated hypercortisolemic episodes in depression, which give rise to the irreversible atrophy of neurons. As would be expected, studies report that 40-50% of depressed patients have abnormally high levels of cortisol (Carroll *et al.*, 1976). Secondly, loss of glial cells leads both directly and indirectly to volume loss, as glial cells also protect hippocampal neurons by sequestering glutamate, maintaining metabolic and ionic homeostasis, and by producing trophic factors, including brain-derived neurotrophic factors (BDNF). There is also evidence that stress induces inhibition of neurogenesis in the hippocampus by reducing the BDNF levels (Fossati *et al.,* 2004). The neurotrophin BDNF is known for its ability to enhance neuronal survival and plasticity and acts by suppressing neural apoptosis (a latent biochemical pathway or 'suicide' program in all cells). Lack of BDNF will therefore inhibit hippocampal plasticity and cause atrophy through activation of apoptosis and increased neural vulnerability to neurotoxicity (Duman *et al.*, 1997; Rajkowska, 2000; Sheline, 2000; Fossati *et al.,* 2004). The inhibition of hippocampal plasticity disrupts long-term potentiation (LTP), a molecular process that may underlie memory consolidation (Bliss & Lomo, 1973; Bliss & Collingridge, 1993; Malenka & Nicoll, 1993). In support of this, numerous studies on rodents have demonstrated that stress- and drug-induced LTP-inhibition cause substantial spatial learning deficits (Morris *et al.*, 1986; Morris, 1989; Davis *et al.*, 1992; Bannerman *et al.*, 1995; Saucier & Cain, 1995). In humans, there is evidence that LTP plays a role in intact verbal memory performance (Grunwald *et al.*, 1999), and a reduction of LTP in the hippocampus may therefore contribute to impairments in declarative memory associated with depression. In addition to the *decrease* of BDNF, it has been demonstrated in animal models that stress *increases* levels of glucocorticoids in the CNS and causes neural pathology, dendritic shrinkage, decreased levels of neurotrophins, and reduction of synaptic plasticity, especially in the hippocampal areas (Duman *et al.*, 1997; Santarelli, 2003; Fuchs & Flügge, 1998), correlating with behavioural deficits (Castren, 2004). As glucocorticoids impair the synaptic removal of glutamate (a neurotransmitter with neurotoxic effects at increased levels), the elevated secretion of glucocorticoids results in substantial damage to hippocampal neurons, a mechanism possibly central to the development of depression in genetically vulnerable individuals (Fuchs & Flügge, 1998; Sapolsky, 2000b; Sheline, 2000; Levinson, 2005). The role of glutamate in depression is supported by the demonstration of

disturbance to the glutamate metabolism in depressed patients, as well as sustained relief of symptoms after just a single administration of an NMDA-receptor antagonist, which decreases the levels of glutamate (Paul & Skolnick, 2003). Taken together, this evidence indicates that an increase of glucocorticoids and glutamate and a decrease of BDNF are both involved in the pathophysiology of depression. The resulting prolonged atrophy and vulnerability of the hippocampus in depressed patients could therefore explain the recurrent nature of depression, where even mild challenges such as stress could cause substantial neuronal atrophy, resulting in clinical relapse (Fujita *et al.*, 2000; Levinson, 2005).

3.5.3 The neurotrophic effects of antidepressants

Neuronal plasticity is a fundamental process by which the brain acquires information and learns to make the suitable adaptive responses. Therefore dysfunction of these fundamental plasticity processes and remodelling may play a central role in the pathophysiology of depression, and relief of depressive states may only be possible after their recuperation. In line with the neurotrophic theory of depression, the past decade has witnessed a growing interest in the neurotrophic effects of antidepressants. Recent studies on animal models, post mortem studies, and functional genomics[4] have complemented the neuroimaging approach by providing evidence that long-term administration of antidepressants stimulates the production and signalling of plasticity-related proteins[5] and results in increased expression of BDNF and neural plasticity as well as neurogenesis in the dentate gyrus of the hippocampus and areas of the cerebral cortex (Castren, 2004; Duman *et al.*, 1997; 2000; Manji *et al.*, 2000; 2003; Malberg, 2005).

The relatively new methodologies of genomics and proteomics hold great promise in that their emerging techniques and powerful tools for identifying genes and gene products may contribute significantly to our understanding of the physiopathology of depression (Yamada & Higuchi, 2002). Functional genomics have made possible extensive investigation of the underlying genetic factors involved in the up- and down-regulation of endogenous neurotrophic factors (Manji et al, 2001). Studies demonstrate that chronic antidepressant treatment up-regulates the cAMP-CREB cascade, a pathway involved in cell survival and plasticity, which has been found to correlate with remission of symptoms (D'Sa & Duman, 2002; Duman *et al.,* 2000; Malberg, 2005). Indirect human evidence from post mortem studies supports this by showing increased hippocampal BDNF expression in the brains of subjects who were being treated with antidepressants at the time of their death versus antidepressant-untreated subjects (Chen *et al.*,

[4] Functional genomics study the functions of the human genome, which is the complete set of genes in a cell or living thing (Oxford Advanced Learner's Dictionary, 2000).
[5] Such as neurotrophic factors and cAMP response element binding proteins.

2001). Moreover, behavioural models of depression demonstrate that the up-regulation of the cAMP-CREB cascade, N-methyl-D-aspartate[6] (NMDA), and BDNF seen in chronic antidepressant treatment improves the behavioural symptoms of depression (Petrie *et al.,* 2000; Malberg, 2005). These findings, together with the observation that several antidepressant treatments increase neurogenesis in the rodent hippocampus, provide support for the hypothesis that neurotrophic factors and underlying pathways play an important role in the pathophysiology and symptom remission of depression (*ibid*.; D'Sa & Duman 2002; Castren, 2004).

Another line of research which supports the neurotrophic theory has focused on the effects of lithium, a drug which has been proved efficacious in the treatment of the manic phases of bipolar depression and in other psychiatric illnesses. These studies suggest that the important mechanisms of action of lithium are its neurotrophic and neuroprotective effects. Evidence for this hypothesis comes from both *in vitro* (post mortem) and *in vivo* (neuroimaging) studies, of which the latter has demonstrated functional and volumetric normalisation over a period of weeks (Manji *et al.*, 2001). Further support for the neurotrophic theory comes from recent studies of the mechanisms of action of ECT, which are among the safest and most effective treatments for severely depressed patients who are resistant to antidepressant medication (Vaidya *et al.*, 1999; Madsen *et al.*, 2000). Interestingly, it has been demonstrated that chronic ECT-treatment induces a significant increase in BDNF as well as neurogenesis and synaptic plasticity in the rodent hippocampus (Stewart & Reid, 1993). These are believed to be the central mechanisms triggered by ECT leading to symptom remission in severely depressed patients (ibid., Vaidya *et al.*, 1999; Madsen *et al.*, 2000).

Taken together, the recent findings have raised the novel possibility that antidepressant drugs, ECT, and administration of lithium all exert their clinical effects through an *increase* in neurotrophic factors such as BDNF and a *decrease* of glutamate levels through an up-regulation of key neural pathways. Consequently, there is substantial support for the neurotrophic theory of depression.

3.5.4 Limitations within neurobiological research on depression

Despite great theoretical and methodological advances in recent neurobiological research on depression, much still remains unclear with respect to the exact aetiology and physiopathology of the disorder (Nestler, 1998). Uncertainty with respect to the precise pathogenesis and pathophysiology of depression must be regarded as a major disadvantage in the search for

[6] The NMDA receptor and NMDA play important roles in synaptic plasticity and have antidepressant effects in preclinical models (Petrie, Reid & Stewart, 2000)

appropriate treatments. This is highlighted by the fact that advances in medicine have generally occurred as a consequence of increased understanding of the underlying causes and pathophysiology of the illnesses in question (Nestler, 1998). Moreover, we still lack a fundamental understanding of cause and effect; that is, the extent to which the functional and structural abnormalities described reflect *primary* pathophysiology, which produces affective disorder, as opposed to *secondary* responses to alterations in behaviour or adaptations to chronic illness. Although current neurobiological research on depression has the advantage compared to the monoamine-paradigm of having moved beyond the neurotransmitter level, the current approach remains concerned only with the neurobiological underpinnings of the disorder. The evidence supporting the multifactorial nature of the disorder and a role for both neurobiological and psychosocial factors cannot be explained in a neurobiological conceptual framework alone, as this is limited to the neurobiological level of analysis. In order to provide a multifactorial explanation of depression which can deal with these essential aspects, we need to employ insights from cognitive psychology.

The otherwise promising line of research which focuses on developing drugs that inhibit the hyperactivity of the HPA-axis suffers from one major limitation: there are at present no available drugs that effectively and selectively reduce gluco-corticoid levels in a sustained way. Furthermore, there are a number of methodological limitations when using animal models in neurobiological depression research. Although animal models are of great value for exploring possibly therapeutic agents, they have limited value in understanding the aetiology and pathophysiology of depression (Nestler *et al.*, 2002). Firstly, because even the best animal models of depression are *theory driven*; for instance one could replicate the etiological factors that cause depression in the laboratory animal as well as many of the depressive symptoms (ibid.). In this way, the conclusions based upon animal models are rather circular and cannot provide any novel insights to the aetiology of the disorder (theory of cause → theory-driven replication of cause → depressive symptoms → confirmation of theory → theory of cause → etc.). Consequently, all available animal models of depression are based on one of two principles: either the actions of known antidepressants or different responses to stressful environmental factors (Willner, 1995; Lucki, 2001). These tests have not yet resulted in the introduction of medications with truly novel mechanisms of action (e.g. non-monoamine-based). Secondly, animal models of depression cannot grasp the complex psychological factors relevant to the understanding of the aetiology of the disorder**,** as the subjective core symptoms (e.g. depressed mood and low self-esteem) are impossible to measure in laboratory animals. This calls the validity of animal models into question. A third caveat is that the medications are active in the animal tests after acute administration, while

their efficacy is known to require chronic administration. It is therefore unclear whether the tests are sensitive to the true mood-elevating cerebral changes induced by the drugs or to some epiphenomena (Nestler *et al.*, 2002) A fourth limitation is that despite reproduction of depression-like symptoms in animal models, the question remains of whether compounds that improve these symptoms in animals will also have an antidepressant effect in humans (Nestler, 1998). An additional drawback of the available animal models of depression is that they utilise normal mice, while it is likely that depression requires genetic vulnerability in most cases (Nestler *et al.*, 2002). Despite these limitations, animal research on depression is necessary and of fundamental value as preliminary evidence for the efficacy (and unwanted effects) of a drug is needed before testing it on or applying it to human subjects. Animal models provide potentially useful means of studying the neurobiological and genetic mechanisms underlying stress and antidepressant treatment-responses. They have thus enabled the field to formulate several hypotheses by which depression may occur and antidepressants may work. When we employ animal models in *combination* with studies on humans using for example neuroimaging techniques, we have a powerful methodology for neurobiological research on depression.

A methodological impediment related to the use of structural neuroimaging to determine the size differences of particular brain regions between depressed and healthy individuals is that the identified abnormalities may have no functional correlate or, conversely, functional deficits may not require a concurrent anatomic abnormality (Strakowski *et al.*, 2002). It is important to bear in mind, firstly, that structural images are *static* and cannot provide any insights into functional *dynamic* neural changes and reorganisation. More importantly, structural (as well as functional) imaging is confined to Marr's *hardware level* and therefore cannot explain the clinical expression of the illness, which includes factors existing at different levels of description (e.g. subjective symptoms and cognitive structures and processes). Despite these inherent limitations, structural imaging has proved valuable for developing neuroanatomic models of depression through identifying the morphometric brain abnormalities associated with the disorder. These models may generate hypotheses on the neural networks involved in depression, which can be further explored through implementation of functional imaging to advance the neurobiological understanding of depression.

Functional imaging techniques also have a number of limitations. Currently, the resolution of SPECT is around 8 mm and the resolution of PET approximately 5 mm, while the resolution of fMRI is only slightly superior. Although the impact of the relatively low structural resolution of fMRI can be minimised through co-registration with high resolution structural images, it remains difficult to visualise blood flow or detect metabolic changes in very small structures. In molecular

imaging, the limiting factor is the lack of sufficiently selective tracers and probes for the different receptors and transporters involved in affective disorders. These must be individually developed and validated, and often fail after reaching the level of human application. However, advances have been made in these respects; particularly in imaging of the serotonergic system (Duman, 2002). The clinical heterogeneity of depression causes major variability in the findings of functional imaging studies, as diverse signs and symptoms may have distinct neurophysiological correlates (Drevets, 2003). Depressed patients with predominant anxiety, insomnia, and psychomotor agitation may, for instance, demonstrate different neural abnormalities from patients who are apathetic, hypersomnolent, and psychomotor slowed (Dolan *et al.*, 1993). However, it has not yet been established how each of these different symptoms contributes to the variability of image data. Finally, medication effects represent an essential source of clinical variability in functional imaging studies on depression, as metabolism and CBF in the prefrontal and limbic areas of interest can be reduced by antidepressant and antipsychotic drugs. Therefore it can be difficult to interpret the image data obtained in medicated depressives, if scans in the unmedicated-baseline condition are not available for comparison. Nonetheless, most studies on depressed patients confounded by medication effects have, however, failed to detect the areas of abnormally elevated metabolism seen in unmedicated subjects, and have instead reported regional reduction in flow and metabolism, which cannot be replicated in unmedicated samples (Drevets, 2003).

3.6 Towards a neuropsychological theory of depression

Despite progress in understanding depression, which has led to the development of new and effective antidepressants that selectively increase serotonin and noradrenaline in the brain, or attack neural degeneration and dysfunction in neural plasticity, it remains unclear how we can translate the neurochemical regulations into clinical efficiency. Because of our ignorance of how molecular and cellular events give rise to mental phenomena, we do not know how the manipulation of neurotransmitter systems leads to the improvement of mood as well as cognitive and social function that is observed when they are administered to depressed individuals (Nestler, 1998). The lack of integration between the neurobiological and psychological conceptions of depression is a great obstacle to the development of more effective treatments of the disorder.

As a result of the substantial technological and conceptual advances that have been made in the recent years, brain-based cognitive models of affective disorders have been tested with an array of techniques, including neuroimaging, experimental cognitive psychology, and neuropsychology. Today a relatively sophisticated picture is emerging that conceptualises affective disorders as *disorders of mind arising in the brain*. Within the growing multifactor conception of depression arising from these advances, neural mechanisms in affective disorders are understood as dysfunctions in specific neural circuits, and their functions and dysfunctions can be influenced or altered by various pharmacological or cognitive factors (Andreasen, 1997).

The principal goal of the neuropsychological approach to depression is therefore to bridge the gap between the established neurobiological and cognitive conceptions of the condition by uncovering the *neuropsychological* mechanisms linking these two levels of description (Andreasen, 1997). Eventually, this will lead to a *neuropsychological* account of depression, in which all conceptual levels as well as the relation between them are explained.

3.6.1 Mood induction studies

The perhaps most obvious neuropsychological strategy for investigating the functions of the different neural structures involved in the pathophysiology of depression has been to study cognitive and neurobiological (dys)functions in patients. Another line of neuropsychological research uses the alternative strategy of systematic induction of affect or mood in healthy normal volunteers to observe the resultant neural activation and behaviour. These mood-induction procedures are considered as a possible model for mild retarded depression and are associated with symptoms similar to those in clinical depression (Clark, 1983; Riskind & Rholes, 1985; Brown &

Mankowski, 1993). Mood-induction strategies therefore provide important insights into the underlying mechanisms of subjective states in health and models for various psychopathological states.

Affective processes are extremely diverse and vary in duration, frequency, quality, and intensity. In experimental research, affects have generally been sub-typed by temporal domains, with emotions the briefest, moods intermediate and temperaments the most sustained (Davidson *et al.*, 2003). As previously described, the Velten Induction Procedure (VIP) is a mood-induction method frequently used in cognitive studies of depression. Other central methods for inducing happy or sad emotions and processing of emotional information include cognitive manipulations using validated and refined cognitive tasks sensitive to depression and to the effects of antidepressant drugs. These include exposure to mood-related music and pictures of sad or happy motives, autobiographical recall, video clips of emotional scenes, visually presented emotional words, social interaction games and – feedback, and affective facial expressions. As facial expressions are crucial in social cognition and communication, providing information concerning internal emotional states and the intentions of others, the use of facial expressions to induce moods or emotional responses is a particularly fruitful procedure in affective research (e.g. Ekman, 1992).

Simultaneous implementation of neuroimaging and mood- or emotion induction procedures has made it possible to investigate the neural underpinnings of different aspects of affective processing, thereby elucidating the relation between mind and brain. In this way, the neuropsychological approach provides numerous insights into the interrelatedness of neural activation and subjective emotions, and more specifically, into which neural networks are involved in immediate and more sustained positive and negative emotional processing. Combined with the evidence of cognitive, emotional, and neuroanatomic abnormalities obtained from patient studies, this offers important clues to the complex pathophysiological mechanisms underlying disorders of emotion.

A principal advantage of mood-induction studies of neural correlates of emotional processes or mood states in healthy volunteers is that the specific moods are relatively well controlled and un-confounded compared to moods in patients. Depression is often associated with a co-morbidity of anxiety symptoms, which makes it difficult for neuroimaging studies to isolate the specific symptom effects. Given that the methodologically confounded factors in the mood-induction studies are well controlled, the demonstration that the brain regions that mediate normal emotional states (e.g. transient sadness) co-localise with the changes seen in depressed patients (e.g. depressed mood) suggests the universal involvement of these regions in the processing of negative

emotion in both health and disorder. Additional corroboration is provided by the evidence for activity changes in these identified regions during clinical remission of depression.

Although mood state may account for a large proportion of the neural activation demonstrated in neuroimaging studies using mood-induction procedures, it is also clear that more specific content effects can influence the emotional responses. To explore the more subtle neural changes occurring during brief perception or evaluation of emotional information, paradigms measuring brief neural responses to the presentation of discrete emotional stimulus presentations (i.e. emotional words or facial expressions) have proved valuable. These paradigms are made possible by recent developments in neuroimaging technology, which are utilized in high-temporal resolution methods like event-related functional magnetic resonance imaging (ER-fMRI).

3.6.2 Functional magnetic imaging

Within the last decade, cognitive neuroscience has become an important growth area combining the experimental strategies of cognitive psychology with various neuroimaging techniques, making possible a neuropsychological examination of how brain function supports cognitive processing in health and in disorder. Most studies have used the PET and fMRI to detect activity changes in specific brain regions to an emotion-related reaction. PET provides insights into neural activation with tracers that measure blood flow (e.g. oxygen-15-labeled carbon dioxide) or glucose metabolism (i.e. F-18-labeled fuorodeoxyglucose [FDG]), whereas fMRI measures the blood-oxygenation-level-dependent (BOLD) signal changes. While PET studies necessitate the injection of radioactive substances in the study subjects, which can cause some side effects, fMRI has the advantage of being a completely *non-invasive* imaging method.

The ascendancy of fMRI followed the discovery that during changes in neuronal activity there are local alterations in blood flow and amount of oxygen in the tissue, with the local increase in total oxygen delivery exceeding the oxygen utilised (Fox & Raichle, 1986; Fox *et al.*, 1998 cited in Cabeza & Kingstone, 2001). This leads to changes in the amount of oxygen in the blood vessels at the site of brain activity, with a higher level of oxygenated haemoglobin compared to the non-active parts of the brain**.** Combining this observation with the long-established knowledge that binding of oxygen to haemoglobin changes the susceptibility of protons in water molecules in the blood to magnetic fields (making them *paramagnetic*; Pauling & Coryell, 1936), Ogawa and colleagues demonstrated that *in vivo* changes in blood oxygenation could be detected with magnetic resonance imaging (MRI) (Ogawa *et al.*, 1990) and soon thereafter with fMRI (Ogawa *et al.*, 1992, Kwong *et al.,* 1992). The paramagnetic oxygenated haemoglobin is attracted to a magnetic field in contrast to *diamagnetic* deoxygenated haemoglobin which is repelled (*ibid.*). In this way, the

activity-related increase in oxygenation levels give rise to an increased signal from the protons in the water molecules in the blood, causing local distortions of the magnetic field. The resultant BOLD contrast is exploited in fMRI to detect activated brain areas. On activation, the time for the BOLD response to significantly increase from baseline is approximately 2secs and the time to reach the plateau in the 'active' state is about 6-9secs (Bandettini & Cox, 2000). In fMRI, the required imaging contrast arises as a consequence of the difference in BOLD response between oxygenated and deoxygenated haemoglobin, which causes difference in signal intensity between activated and non-activated areas. Thus, brain activation causes highly localised and time-locked changes in blood flow and oxygenation, and despite the BOLD contrast being an *indirect* measure of neuronal activity, the reliability of this signal has received support from various empirical observations. Although the signal is temporally blurred as a consequence of this latency of onset of the BOLD response, the lags of onset and the time course of signal evolution are highly reproducible (Jezzard *et al.*, 2001).

3.6.3 Event-related functional magnetic resonance imaging

Among the most influential recent developments to take place in affective research is the evolution and utilisation of ER-fMRI to visualise subtle changes in neural activity related to brief cognitive and/or emotional events. In ER-fMRI, images of transient neuronal changes, which are associated with individual cognitive tasks and with subsequent processing stages, are produced through mapping of the averaged haemodynamic changes resulting from repeated, brief (<3sec) brain activation episodes (Bandettini & Cox, 2000). The features of fMRI that made possible the development of event-related procedures are: technological advances in the speed with which fMRI data could be obtained; high consistency in the haemodynamic response summating over sequential events in a largely linear fashion; and the discovery that even brief periods of neural activity give rise to measurable signal changes despite the delayed and prolonged nature of the time-course of the haemodynamic response (Jezzard *et al.*, 2001). The latter observation allows the tracking of neural activity related to a cognitive event in the order of seconds (Buckner, 1998).

Compared to the 'block design' fMRI, which consists of presenting a series of trials in one condition during a discrete epoch of time and comparing the signal acquired during this condition to blocks of different task conditions, the 'event-related design' has two principal advantages; firstly it allows for detection of the transient signal changes that are not sustained across multiple trials; secondly, because the transient signals are determined by *individual* trials (e.g. individual words presented), different *types* of trials (e.g. positive versus negative words) can be randomly intermixed for comparison, which allows the subtle transient response to a specific event of interest

to be defined (Jezzard *et al.*, 2001). With ER-fMRI, the haemodynamic responses related to certain *types* of stimuli can be revealed through measurement of the haemodynamic changes time-locked to the presentation of each stimulus. These are then averaged together to provide a representative average signal of particular event types. As each signal contains noise (random neural activity), averaged signals extract that part of the haemodynamic response that is systematically related to the cognitive event of interest.

Although powerful in extracting the transient signals of interest, a considerable limitation is that ER-fMRI experiments are difficult to analyse by techniques that require implementation of a single predicted time course. This is because the brief presence of the elevated signal in a small number of time points can lead to errors in the shape of the modelled time course. In this way, there is a risk that genuine activations will be missed (Clare *et al.*, 1999). It has, furthermore, been argued that the averaged signal is not a direct measure of the response that occurs in individual trials, but an averaged response to the type of trial. The averaged response could thus potentially show little relation to those of individual trials, thereby producing a distortion which leads to uncertainty in interpretation. This caveat, however, is only of importance in studies examining single trial data or distributions from many individual trials and thus has less relevance to experiments which investigate the general response to *types* of trials.

3.6.4 Neural areas involved in emotional processing

Although many brain regions have been implicated in regulating emotions, we still have a rudimentary understanding of the neural circuitry underlying normal mood and the abnormalities in mood that are central in depression. This is underscored by the fact that there is no clear consensus in the field as to the site of the pathology (Nestler *et al.*, 2002). Recent brain imaging studies suggest that processing of emotional information is associated with activity in a broad neural network including: limbic and paralimbic structures (amygdala, insula, medial temporal, and anterior cingulate cortex), prefrontal cortices (PFC; medial, dorsolateral, and orbitofrontal regions), posterior cingulate and visual cortices; and other subcortical structures (thalamus, hypothalamus, and caudate) (Baker *et al.*, 1997; Davidson & Irwin, 1999; Schupp *et al.*, 2003; Fossati *et al.,* 2003; Geday *et al.,* 2003; Teasdale *et al.*, 1999). The question remains, however, whether positive and negative emotions are mediated by the *same* neural structures or whether there is a *differentiation* within the neural structures subserving different aspects of emotional processing.

Various neuropsychological studies support differentiation, suggesting that sadness and happiness are not merely associated with opposing activity in identical brain regions, but rather that these emotions affect different brain regions (in divergent directions) (Williams *et al.*, 1988; George

et al., 1995). In a PET study, George and colleagues (1995) demonstrated that transient sadness significantly activates bilateral limbic and paralimbic structures (cingulate, medial prefrontal, and mesial temporal cortex), as well as the brainstem, thalamus, and caudate/putamen. In contrast, transient happiness was found to *reduce* cortical rCBF, particularly in the right prefrontal and bilateral temporal-parietal regions. Consistent with this finding, it has been suggested that processing of negative emotions (e.g. fear, sadness and disgust) is associated with *increased* activity in the right prefrontal cortex (Davidson & Irwin, 1999). Studies of cerebral blood flow in depression provide support to this notion of lateralisation, by demonstrating that depressed subjects display reduced activity in the left anterior and the right posterior cortical regions (Heller & Nitschke, 1997). A CT study on stroke patients with either left or right hemisphere lesions and depression found that severity of depression was considerably increased in patients with lesions in the left anterior cortex. Additionally, patients with right posterior lesions were more depressed than patients with right anterior lesions, who appeared indifferent and disproportionately cheerful (Robinson *et al*., 1984). Concordant with this, an EEG study demonstrated that depressed individuals had less left-sided frontal activation than did normal control subjects, which suggests a deficit in mechanisms mediating positive affect in depressed subjects. Despite some evidence of cortical lateralisation of emotional processing, studies of anterior brain function are inconclusive on the question of whether depressed and negative emotion are associated with a reduction in left or right anterior functioning, or both. Various studies suggest that the activation patterns associated with negative and positive emotion in the prefrontal regions are non-lateralised, and that differentiation instead occurs within ventral and dorsal areas (Schneider *et al.*, 1995; Teasdale *et al.*, 1999). By use of PET, Schneider and colleagues (1995) found that lateralisation occurred at a subcortical limbic level, with increased rCBF in the left amygdala and decreased rCBF in right amygdala during sad mood.

Neuropsychological research provides crucial insights into which neural areas are involved in emotional processing in health and disorder. Human lesion studies as well as functional imaging studies of healthy volunteers during mood induction and of depressed patients indicate a central involvement of the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, and amygdala.

3.6.4.1 Prefrontal cortex

The PFC is not only the region of higher cognitive control, strategy, and planning, but also plays a fundamental role in various aspects of affective processing. Miller and Cohen (2001) have outlined a comprehensive model of prefrontal function based on nonhuman primate anatomical and neurophysiological studies, human neuroimaging findings, and computational modelling. This

model suggests that the main role of the PFC is to maintain the representation of goals and the means to achieve them. In ambiguous situations where there is a competition between different alternative responses, the PFC sends bias signals to other brain sites to facilitate awareness of the most task-appropriate or adaptive response, thus ensuring the individual's affect-guided anticipation (Miller & Cohen, 2001). A typical situation is when one's emotional arousal is inconsistent with an overall goal that has already been initiated, such as in the presence of an immediate reward that may not serve or even oppose the person's general goal. In this case, the PFC is indispensable for producing a bias signal to other brain areas guiding behaviour toward the acquisition of a more adaptive goal that would in this case delay reinforcement. Consistent with this model, studies report that patients with lesions of ventromedial PFC demonstrate impairments in affect-guided planning and anticipation (Damasio, 1994).

Abnormality in affect-guided anticipation is an important factor in depression, contributing to the maintenance of maladaptive behaviour and depressed mood (Davidson & Irwin, 1999; Davidson *et al.*, 2000). Initiation of appetitive goals requires left-sided PFC activation as well as hypoactivation of the circuits that are linked to depression, while maintenance of goals requiring behavioural inhibition and withdrawal is linked to right-side PFC activation (Davidson *et al.,* 1999, 2000). This is supported by an ER-fMRI study investigating the neural networks subserving response and response-inhibition by use of variants of 'go/no-go' tasks (Konishi *et al.*, 1999), in which subjects are instructed to either respond (go trial) or not respond (no-go trial), depending on the cue stimulus presented. Konishi and colleagues (1999) found transient dominant activity within the right inferior prefrontal area during no-go trials, suggesting that this area is involved in response inhibition. Concordantly, an ER-fMRI study found that go-responses elicited signal change in left frontal areas, whereas working memory-dependent no-go responses activated the right dorsolateral PFC (Mostofsky *et al.*, 2003). A recent ER-fMRI study exploring the association between regional cerebral activation during no–go trials and impulsiveness in humans (Asahi *et al.*, 2004) found a negative correlation between no–go related activation in the right dorsolateral PFC (RDLPFC) and motor impulsiveness. This suggests that RDLPFC activity is an indicator of the individual capacity or tendency for response inhibition. Asymmetry of PFC activity in depression could explain deficiency in the initiation of positively anticipated goal-directed and the predominant behavioural inhibition, core features of depression.

Neuroimaging and electrophysiological studies have found that orbital and ventral frontal cortices are involved in the representation of reward and punishment. One fMRI study found that distinct areas of the orbitofrontal cortex (OFC) were activated by abstract rewards and punishments (O'Doherty *et al.*, 2001). While the left-side medial OFC was particularly responsive to rewards,

the right side was primarily responsive to punishment. Another study, using single-neuron recordings of responses to emotional stimuli within the right ventral PFC, found that neurons in healthy tissue exhibit short-latency responses only to aversive visual stimuli (reflecting selective responsiveness) (Kawasaki *et al.*, 2001). This supports a differentiation of the representation of reward and punishment within the ventral PFC, with the right-side preferentially processing punishment.

These findings suggest that hypoactivity in the left OFC and left ventral PFC and the increased relative right-side PFC and OFC activity in depression, may be partly responsible for characteristic impairments in positive anticipation and dominating thoughts of negative outcomes and guilt.

3.6.4.2 Anterior cingulate cortex

Another structure involved in emotional processing is the anterior cingulate cortex (ACC), which is thought to serve as a bridge between attention and emotion by integrating the visceral, physical, attentional, and affective information which is essential for self-regulation and adaptability (Thayer & Lane, 2000). The ACC thereby plays a central role in selective attention processes, emotional processing and social behaviours. Functional neuroimaging studies provide emerging evidence of a functional differentiation between an affective and a cognitive subdivision within the ACC (Bush *et al.*, 1998; 2000; Whalen *et al.*, 1998). The affective subdivision encompasses the rostral and ventral areas of the ACC and possesses extensive connections with limbic and paralimbic regions such as the lateral hypothalamus, subgenual ACC amygdala, nucleus accumbens, OFC, and anterior insula. The cognitive subdivision includes dorsal ACC regions and is closely connected with the dorsolateral PFC (DLPFC), posterior cingulate cortex, parietal cortex, and spinal cord. While the function of the affective division is to regulate visceral and autonomic responses to stressful emotional events, emotion expression, and social events, the cognitive subdivision is involved in response selection and processing of cognitively demanding information such as during interference between competing information (Pardo *et al.*, 1990), or in the monitoring of cognitive and reward related conflicts (Carter *et al.*, 2000; Rogers *et al.*, 1999). Various studies report activation of the affective subdivision of the ACC during various emotional states and manipulations, suggesting that this subdivision is crucial for assessing the presence of possible conflicts between the current functional state of the individual and incoming information with potentially relevant motivational and emotional consequences (Reiman, 1997; Bush *et al.*, 2000). Although the precise interaction between the affective and cognitive subdivisions of the ACC remains uncertain, it has been suggested that the affective subdivision may serve to integrate salient

affective and cognitive environmental information, and that the cognitive subdivision subsequently modulates appropriate attentional processes (Mega *et al.*, 1997; Mayberg, 1997; Mayberg *et al.*, 1999; Pizzagalli *et al.*, 2001). This hypothesis is supported by evidence that both the amygdalar pathways involved in emotional processing and the dorsal anterior and posterior cingulate pathways responsible for attentional processes all converge in the rostral area of the ACC (Mega *et al.*, 1997). These mechanisms may help to explain the observation that depressed patients displaying an *elevated* glucose metabolism in the rostral ACC respond significantly better to antidepressant treatment, than do depressed patients without elevated rostral ACC activity (Mayberg *et al.,* 1997). Hyperactivation of the 'affective' rostral ACC may reflect an increased sensitivity to affective conflict, which issues a call for further processing. In turn, the cognitive division modulates the increased attentional processing activity that is appropriate for solving the emotional conflict. It is this increased conflict-solving activity that is hypothesised to aid the treatment response (Pizzagali *et al.*, 2001). The theory is thus that individuals with elevated rostral ACC activity may thus be more motivated to resolve discrepancies between their current mood state and appropriate behaviour in a given situation and are therefore less likely to give in to immediate maladaptive urges.

3.6.4.3 Hippocampus

Hippocampal and parahippocampal regions have long been known to play a crucial role in episodic, declarative, contextual, and spatial memory, as well as in the formation, storage, and consolidation of fear conditioning (Squire & Knowlton, 2000; Fanselow, 2000). This suggests a central role for the hippocampus in contextual learning and memory, and therefore also in affective function. Functional neuroimaging studies demonstrate that hippocampal and parahippocampal activation is present during the perception of *negative* emotional stimuli and experience of negative affective states (Büchel *et al.*, 1999), perception of aversive complex stimuli (Lane *et al.*, 1997), vocal expressions of fear (Phillips *et al.*, 1998), and threat-related words (Isenberg *et al.*, 1999), but also during *positive* affect, such as the perception of a loved person (Bartels & Zeki, 2000), pleasant affective autobiographical memories (Fink *et al.*, 1996), increases in winning in a game-like task (Zalla *et al.*, 2000), and recognition memory for pleasant films (Hamann *et al.*, 1999). These findings suggest that hippocampal activation is *not* a result of emotional valence, but rather of the availability of contextual cues, which was the common factor in the experiments (Fanselow, 2000). The hypothesis is that the hippocampus plays a critical role in forming contextual memory through its involvement in the formation, storage, and consolidation of an integrated representation of a particular context (ibid.). This is supported by a recent fMRI study, which found evidence of a

critical role for the anterior hippocampus in relational memory (Giovanello *et al.*, 2004). Another ER-fMRI study on the distinct neural bases of memory involving a re-experience of the original event and memory accompanied only by a feeling of familiarity found that hippocampal activity increased only in the former case (Eldridge *et al.*, 2000), thus supporting the role of the hippocampus in retrieval of contextual and episodic memories.

Although the precise mechanisms underlying contextual conditioning in humans remain to be elucidated, emerging evidence points towards the importance of plasticity in the functional connectivity between the hippocampus and regions that are involved in decoding the emotional and behavioural significance of incoming information, such as the amygdala and the pulvinar (Morris *et al.*, 1997; 1999; Richter- Levin & Akirav, 2000; Richardson *et al.,* 2004; Phelps, 2004). While the amygdala and hippocampal complex are linked to two independent memory systems, each with unique characteristic functions, there is evidence of a subtle but important synergic interaction between these two systems in emotional encoding and memory (Richter-Levin & Akirav, 2000; Phels, 2004). The amygdala appears to modulate both the encoding and the storage of hippocampal-dependent memories, whereas the hippocampal complex, by forming episodic representations of the emotional significance and interpretation of events, influences the amygdala response when emotional stimuli are encountered (Phels, 2004). A recent fMRI study of patients with variable degrees of left hippocampal and amygdala pathology showed a reciprocal dependence between amygdala and hippocampus during the encoding of emotional memories (Richardson, Strange & Dolan, 2004). Hippocampal and amygdaloid pathology generally decreased memory performance. However in those cases where emotional words were successfully recalled, encoding-related hippocampal activity correlated with the degree of left amygdala pathology. Conversely, with respect to subsequently remembered emotional words, amygdala-evoked activity correlated with the degree of left hippocampal pathology. The two structures thus engaged in a dynamic relationship in which they complemented each other, which has led the authors to suggest that the two structures are functionally dependent in both the encoding and memory of emotional information. However, such conclusion should only be seen as tentative as these changes may reflect posttraumatic reorganisation rather than an interaction present in the normal brain.

The evidence that the hippocampus plays a key role in both encoding and memory of contextual and emotional information has led to the suggestion that depression could be regarded as a disorder in context-regulation of affect linked to hippocampal dysfunction (Davidson *et al.*, 2000). Although depressed individuals do display normative affective responses (such as sadness or guilt), this is often in an *inappropriate* context. Sadness or guilt may be appropriate in the acute period following a loss or having done something wrong, but when these feelings persist for years

following the event, they must be regarded as inappropriate emotional responding. The hippocampal dysfunction in depressed individuals may thus contribute essentially to the disorder through an abnormal context-regulation of affect.

3.6.4.4 Amygdala

The amygdala has been consistently identified as being implicated in the perception of emotional cues and the production of emotional responses. The central involvement of the amygdala in aversive conditioning and negative emotion (e.g. fear and disgust) is well established (Ledoux, 2000). Electrical stimulation of the human amygdala can produce anxiety, dysphoria, and recollection of negative events, as well as increased cortisol secretion; findings that are complemented by evidence that excessive amygdaloid activity can contribute to depressive symptoms like inactivity, panic attacks, reduced pain sensitivity, and social withdrawal (Drevets, 1999; Nestler *et al.*, 2002).

Emerging evidence suggests a broader function of the amygdala in emotional processing, in which its involvement in negative affect is just a special case of its more general role in directing attention to affectively salient stimuli and issuing a call for further processing of them. According to this view the amygdala is crucial for recruiting and coordinating cortical arousal and vigilant attention for optimising the perceptual processing of novel, surprising or ambiguous stimuli (Davis & Whalen, 2001; Holland & Gallagher, 1999). A study of patients with amygdala lesions, which employed an attentional-blink paradigm, found that patients with left amygdala lesions lack the enhanced perception for aversive stimulus events that is present in healthy individuals (Anderson & Phelps, 2001). A PET study found evidence of differential neural response in the human amygdala to facial expressions of fear and happiness with larger left amygdala activation to fearful compared to happy expressions, and significant interaction between amygdala response and the intensity of emotion (increasing with increasing fearfulness, decreasing with increasing happiness) (Morris *et al.*, 1996). The role of the amygdala in the processing of negative facial expressions is supported by an ER-fMRI study of depressed patients, which found depression-associated hyperarousal in the left amygdala to fearful faces, and reversal of this following antidepressant treatment (Sheline *et al.*, 2001). A recent ER-fMRI study found that the amygdala response to positive and negative emotional pictures was not uniform, but changes considerably with age (Mather *et al.*, 2004). Although both older and younger subjects in this study showed larger amygdala activation while processing emotionally charged relative to neutral pictures, older adults had greater amygdala activation to positive pictures compared to negative pictures. Thus it seems that the amygdala may show decreased reactivity to negative information with age while maintaining or increasing its

reactivity to positive information. The role of the amygdala in the processing of emotional facial expressions is also supported by the observation that damage to the amygdala causes selective deficits in the recognition of fearful facial expression and impaired fear conditioning (Adolphs *et al.*, 2002; Weniger *et al.,* 2004), and that unilateral and bilateral amygdala damage cause impairment in recognition of social emotions (Adolphs *et al.*, 2002), thus suggesting that the human amygdala is relatively specialised to process emotional and social perceptual stimuli.

In addition to having a central role in emotional processing of *perceptual* information, the amygdala also engages in *conceptual* emotional processing. An fMRI study examining neural response to emotionally positive, negative, and neutral words reported that relative to neutral words, both positive and negative emotional words elicited greater activity in the left amygdala (Hamann & Mao, 2002). Another fMRI study using a similar protocol demonstrated that depressed individuals displayed sustained amygdala responses to negative words compared to healthy volunteers, thus indicating more extensive processing of negative conceptual information in depression (Siegle *et al.* 2002). Finally, the role of the amygdala in recall of emotionally arousing memories, particularly those of negative valence, is well established (Adolphs *et al.,* 1997; Hamann *et al.*, 1999). A study of declarative memory in patients with bilateral amygdala damage found evidence of substantial impairment in long-term declarative memory for emotionally arousing material (Adolphs *et al.,* 1997). This underlines the importance of the human amygdala in the acquisition of declarative knowledge regarding emotionally arousing stimuli. Supporting these findings, a PET study found that bilateral amygdala activity during memory encoding was correlated with enhanced episodic recognition memory for emotional (both pleasant and aversive) visual stimuli relative to neutral stimuli (Hamann *et al.*, 1999).

In summary, the available evidence indicates that the amygdala plays a crucial role in the encoding of both perceptual and conceptual emotional information irrespective of valence, as well as in the consolidation and expression of emotional memories. The elevated metabolism and structural enlargement of the amygdala and the sustained amygdala processing of negative information in depression may therefore contribute profoundly to the key symptoms in depression (Drevets, 2001).

3.6.5 A novel approach to research on depression

A new approach in neuropsychological research on depression explores the mechanisms by which manipulation of neurotransmitter systems leads to changes in psychological processing, with the aim of forming an account of the neuropsychological mechanisms of antidepressant drug action. Such an account would provide an understanding of how neurobiological mechanisms influence

psychological and subjective phenomena, and would provide insights into the relation between mind and brain and more specifically how antidepressant drug treatment ameliorates subjective symptoms of depression.

In the treatment of depression, cognitive psychological theories emphasise the importance of correcting the negative biases of emotional processing and improving dysfunctional social functioning, whereas neurobiological theories stress the fact that antidepressant medication inhibiting the reuptake of serotonin or noradrenaline is effective in the treatment of the disorder. The new neuropsychological approach to depression attempts to integrate these accounts of the mechanisms underlying treatment response by addressing the questions of whether antidepressants can directly modulate the neural processing of emotional information, and whether they can induce direct changes in those components of social behaviour that are particularly affected by depression.

The diversity of the pharmacological actions of different antidepressants suggests that they may exert their clinical effects in the treatment of depression by diverse functional means. Selective serotonin reuptake inhibiting antidepressants (SSRIs) have been found to be effective for the treatment of nervous conditions other than depression, such as obsessive-compulsive disorder, post-traumatic stress disorder, and social phobia (Tranter *et al.*, 2002). However, they seem less effective for melancholic or severe depression than are antidepressants, which target the catecholamine or specifically the noradrenergic systems. It has been demonstrated that compared to SSRIs, selective noradrenaline reuptake inhibitors (SNRIs) have superior efficacy in patients with severe depression (Massana *et al.*, 1999; Fava *et al.*, 2003) and are more effective in improving the social adaptation of depressed patients (Dubini *et al.,* 1997). Both types of antidepressants have been found to improve various aspects of human social behaviour, such as speech, eye contact, and communication (Weismann, 2000). Arising from these observations, a number of clinical trials have been conducted to test the effects of antidepressants on emotional processing and social functioning.

The acute effects of antidepressants are not associated with improvement in mood per se, as the therapeutic actions occur after weeks of continuous drug administration. Nevertheless, a number of the following studies explore the acute effects of antidepressants, consistent with the assumption that these might be the *early* mechanisms of action. This assumption will be discussed later.

Studies of depressed individuals, which compared the effects of the SSRI fluoxetine with the SNRI reboxetine, found that the two drugs had different effects on the individuals' evaluation of their social functioning (Dubini *et al.*, 1997; Massana *et al.*, 1999). This finding was also confirmed in a healthy volunteer study, where clinical doses of SNRI reboxetine or the SSRI

sertraline had differential effects on social adaptation, with reboxetine being more energy enhancing (Tranter *et al.*, 2002).

Acute administration of a single dose of the SSRI citalopram, the SNRI reboxetine or placebo in healthy volunteers revealed that reboxetine reduced hand fiddling during aversive social interaction with a confederate of the experimenter and gave more cooperative communication during a mixed-motive game, compared to the citalopram and control groups. This suggests that noradrenaline reduces self-focus and increases social engagement and cooperation. Citalopram had less effect on cooperative behaviour, but caused less energy variation after aversive social interaction. Thus, serotonin appears to be associated with protection of the self from the negative consequences of social interaction. Although acute administration of antidepressants altered social interaction in the mixed-motive game and stranger-dyadic social interaction procedure, it is possible that longer-term administration of antidepressants has different effects on social behaviour. A placebo-controlled study of the effects of longer-term SNRI intervention on social behaviour in healthy volunteers was therefore conducted (Tse & Bond, 2003). Subjects treated with reboxetine were considered to be more agreeable and cooperative and less submissive by their flat mates, which may reflect promoted friendship building and increased independence. In the social interaction paradigm, however, they showed less eye contact and gave fewer helplessness messages in avoiding social contact with the stranger (study confederate). They also spoke faster and more fluently on the reading task after social interaction, thus reflecting increased social energy and motivation. A study with a similar methodology investigating the effects of the SSRI citalopram (Tse & Bond, 2002b) found no effects on general cooperation as rated by their flat mates, dominant pattern of eye gaze in the stranger interaction, increased cooperativeness in the mixed-motive game, and no variation in speech fluency. In conclusion, the antidepressants in both studies decreased submissiveness rated by flat mates, which may therefore be a general effect of antidepressants, where their primary action on different neurotransmitters overlap and promote self-efficacy. The distinct behavioural effects of the two different antidepressants may relate to their neurochemistry; drugs acting on noradrenaline are more likely to promote social bonding within the individual's own social circle and enhance energy, whereas drugs affecting the serotonin may enhance social status and affiliative behaviour with strangers. These insights may be crucial for an understanding of the mechanisms behind the clinical effects of antidepressant treatment on social perception and behaviour in depressed patients.

A different focus in neuropsychological research is how cognitive functions such as memory in healthy volunteers are affected by antidepressants. Such an understanding is of central importance in the light of the observation of memory impairments in depressed patients, which are

reversed with antidepressant treatment (Cassano *et al.*, 2002; Levkovitz *et al.*, 2002). The memory improving effect of antidepressants in depressed patients may be confounded by symptom improvement. A placebo-controlled study testing the effects of one dose of the SSRI citalopram in healthy volunteers (Harmer *et al*., 2002) showed improved memory performance in terms of delayed recall and recognition, which indicates that a *direct* effect of antidepressant drugs on memory consolidation may be responsible for the improvement of memory function in depression.

Another line of research aims to illuminate the effects of antidepressants on the early perceptual and conceptual processing of emotional information. The actions of repeated administration of SSRI citalopram, the SNRI reboxetine, or placebo administration on perception and memory for positive and negative emotional information were investigated in healthy volunteers (Harmer *et al.*, 2004). The study revealed that citalopram and reboxetine modulate emotional processing in both the perceptual (faces and pictures) and conceptual (words) tasks in the absence of significant differences in ratings of mood, and further that the two drugs had a differential profile of effects. Both drugs reduced the identification of negative facial expressions of anger and fear, and increased the relative recall of positive (versus negative) emotional words. However, only citalopram was found to eliminate the increased startle response found in reaction to negative emotional images. This indicates that short-term administration of SSRIs and SNRIs reduces the processing of negative information in a direct fashion not confounded by changes in mood.

In line with this, acute manipulation of the serotonin system significantly influences the emotional processing of facial expressions in healthy individuals (Harmer *et al.*, 2003a). Intravenous citalopram selectively increased sensitivity to facial expressions of fear and happiness and reduced response times to these expressions, suggesting that acute administration of SSRIs affects neural processes involved in the processing of emotional facial expressions. These findings are consistent with a study on the effects of citalopram on electrophysiological responses to pleasant and unpleasant visual emotional stimuli in healthy volunteers (Kemp *et al.*, 2004). The central finding was that citalopram attenuated electrophysiological activation to unpleasant valence within the frontal and occipital cortices, but potentiated activation to pleasant valence within the parietooccipital areas. Augmentation of serotonin thus appears to enhance cortical electrophysiological responses to pleasant and suppress responses to unpleasant visual emotional stimuli in humans. Antidepressant-induced reductions in clinical symptoms of depression may therefore be related to neuropsychological and neurophysiological changes in the processing of emotional information, so that processing of positive information is enhanced, while processing of negative emotions is suppressed (Harmer *et al.*, 2003a; Kemp *et al.,* 2004). This is consistent with

the finding that *reduced* cerebral serotonin availability in healthy volunteers during tryptophan depletion produces deficits in the emotional processing of positive information, while intellectual ability such as planning was intact (Murphy *et al.*, 2002). As the deficits were specific and not due to global sedative effects, the results suggest that serotonin reduction may be involved in the disrupted emotional processing seen in depression.

Acute administration of the SNRI reboxetine in healthy subjects has been found to increase positive biases (significantly greater recognition of happy facial expressions and greater priming towards positive words) and reverse the negative memory biases that were present in the control group (Harmer *et al.,* 2003b). There were no significant differences between groups in the processing and memory of non-emotional information, suggesting that a single dose of a SNRI enhances both perception and memory of emotional information by specific action on emotional processing.

In summary, recent neuropsychological research suggests that antidepressants may have essentially the same mechanisms of action as cognitive-behavioural therapy; they directly redress negative biases in emotional processing, facilitate the processing of positive information, and promote self-efficacy and sociable behaviour. If these are the *early* mechanisms of action of antidepressants, then continuous antidepressant drug administration may induce gradual behavioural adjustments to the more positively perceived environment as well as greater self-efficacy and more rewarding social interaction. According to this interpretation, it may thus be these *secondary* drug-induced behavioural and cognitive changes that relieve depressive states. From this it could follow that it is the prolonged drug-induced psychological processes that underlie symptom remission, rather than a time-consuming neurobiological process, as otherwise assumed. However, the rather rigid timeframe of the therapeutic effects of antidepressants suggests an involvement of some important lengthy neurobiological components in the process. To avoid the hazard of taking an *either* psychological *or* neurobiological stand, one could argue that *both* psychological and neurobiological processes could be responsible for the therapeutic effects. According to this neuropsychological view, symptom remission may occur as a consequence of a mutual interaction between the drug-induced psychological and neurobiological processes, which influence one another through reciprocal upward and downward causations.

The possibility of integrating the two approaches is further supported by the finding that effective antidepressant and psychological treatments of depression are associated with metabolic changes within various cortical and limbic areas known to subserve emotional processing (Mayor, 2004; Goldapple *et al.,* 2004). Interestingly, a recent review of studies on the neuroanatomy of psychotherapy and pharmacotherapy found an only partial overlap between changes associated with

these two treatment modalities. One limitation of literature on psychotherapy and neuroimaging (versus pharmacotherapy and imaging) is the heterogeneity across these studies, which limits our ability to compare them directly (Roffman *et al.,* 2005). This is due to disparities in rationale, technique, and efficacy of the different psychotherapies and to individual differences between therapists, such as skills and adherence to a given framework (*ibid.*). Despite this caveat, studies that directly compare the neural effects of CBT and antidepressant treatment support the notion of discrepancy in the neural modulation of treatment-response to the two treatment types (Goldapple *et al*., 2004). There is thus evidence that *different* mechanisms underlie the (*similar*) clinical improvement in response to psychotherapy and antidepressant treatment. This stresses the lack of "identity" between psychological symptoms and neurobiological dysfunctions and therefore the importance of a distinction between different levels of analysis in the understanding of depression.

The emerging neuropsychological evidence suggests that bridging the gap between the neurobiological and psychological approaches to depression may be a fruitful avenue for future research. However, even with impressive progress in elucidating the relation between the neurobiology and psychology of the brain, various questions remain unanswered. Questions that call for further investigation are: What are the precise brain areas involved in the encoding and memory of positive and negative emotional information? Do antidepressant drugs produce a *simultaneous* change in neural activation patterns and cognitive events associated with emotional processing? Currently, no published study has yet employed a *simultaneous* investigation of the effects of antidepressants on the neural activation patterns *and* the cognitive psychological aspects of emotional processing in healthy volunteers. Such an investigation would increase our understanding of the interaction between neurobiological and psychological mechanisms in emotional processing and provide new insights into the neuropsychological understanding of depression. A study investigating these issues by Miskowiak and colleagues (submitted) is presented in the following section.

4 Acute antidepressant administration modulates the neural processing of positive versus negative self-referent personality characteristics

4.1 Introduction

There is still something of a conceptual gap between the psychological and neurobiological approaches to the understanding and treatment of depression. While cognitive psychological theories suggest that negative biases in the cognitive processing and memory of self-referent information are key features in the development and maintenance of depression (Beck *et al.,* 1979), current neurobiological views of depression hypothesise abnormalities in cellular pathology involving, for example, such basic processes as synaptogenesis and neurogenesis in key brain regions involved in emotional regulation (Nestler, 1998).

Despite this traditional division between psychological and pharmacological theories, recent evidence suggests that antidepressant drugs may modify emotional processing in a similar manner to the changes believed to underlie successful cognitive psychological therapies. In particular, we have reported increased positive vs. negative emotional processing in healthy volunteers following antidepressant drug administration across a range of tasks including facial expression recognition and emotional memory (Harmer *et al.*, 2003b). These effects of antidepressant drugs can be seen from the beginning of treatment. For example, a single dose of the selective noradrenaline reuptake inhibitor (SNRI) reboxetine significantly facilitated speed to categorise positive compared to negative self-relevant emotional information and facilitated memory for these positively valenced personality descriptions in healthy volunteers (Harmer *et al.*, 2003b). These effects were also found after 7 days of reboxetine treatment in a separate study (Harmer *et al.*, 2004) and in both studies, effects occurred in the absence of effects on subjective mood. Given the importance of negative biases of information processing in depression, these kinds of changes in the relative processing of positive vs. negative emotional information could be an important factor in the therapeutic actions of antidepressant drugs in depression. How psychological and neurochemical effects may be related remains uncertain, because, while antidepressant and cognitive-behavioural treatments (CBT) of depression are both associated with metabolic changes within various cortical and limbic areas subserving emotional processing, these changes are not necessarily overlapping (Mayor, 2004; Goldapple *et al.*, 2004).

The effects of reboxetine on emotional memory and categorisation were seen in a task demanding self-referent processing of positive vs. negative personality characteristics (e.g.

'honest', 'ugly', 'poised' (Harmer *et al.,* 2003b; Harmer *et al.,* 2004). Emotional words encoded in reference to the self are generally better remembered than emotional words processed in semantic terms (Rogers *et al.,* 1977), a phenomenon named the Self Reference Effect (SRE) (Symons & Johnson, 1997). Recent work demonstrates that encoding of emotional self-referent personality characteristics engages the medial prefrontal cortex (MPFC), while subsequent successful memory reactivates the right MPFC as well as lateral prefrontal regions, premotor cortex, parietal and occipital cortex, and subcortical areas (Fossati *et al.,* 2004). Increased neural response in the visual cortex has been demonstrated during attention to presentation of emotional compared to neutral information (Junghoefer *et al.,* 2001; Taylor *et al.,* 2000) irrespective of the visual complexity of the stimuli (Taylor *et al.,* 2000). This suggests that the visual cortical response may be a component of the distributed neural system engaged in the response to visually presented emotional information. The finding of significantly greater occipital activation during retrieval of negative compared to positive self-referent characteristics in healthy volunteers suggests that negative self-descriptors command greater early visual processing (Fossati *et al.,* 2004) presumably through efferent connections from limbic areas such as the amygdala which signal the biological importance of emotionally salient information.

A greater understanding of the neural basis of the effects of reboxetine on emotional processing may help the integration of the pharmacological effects of antidepressant drugs with their effects on emotional neuropsychological functioning. The current study therefore investigated the effects of a single dose of reboxetine compared to placebo on the neural responses during self-referent emotional categorisation and memory in healthy volunteers using event-related fMRI.

4.2 Method

4.2.1 Subjects

Ethical approval of the study's methods was obtained from the Oxford Psychiatry Research Ethics Practice (OPREC). Healthy volunteers between the ages of 23 and 38 years were screened using the Structured Clinical Interview for DSM-Clinical Version (SCID-CV) (Frances *et al.*, 1995) to exclude current or previous history of psychiatric disorder and/or substance or alcohol abuse, and/or serious neurological or physical problems. Subjects were also screened to be free of medication other than contraceptives. fMRI scanning also required the following exclusion criteria: spectacles, heart pacemaker, mechanical heart valve or any mechanical implants, potential

pregnancy, and claustrophobia. After complete description of the study to the subjects, written informed consent was obtained.

4.2.2 Experimental design

Twenty four healthy volunteers were randomly allocated to receive either reboxetine (4mg) or placebo in a double-blind between-groups design. The two groups were matched for: gender (7 males and 5 females in each group), age (mean=28.1 years, SD=3.0, and mean=26.6 years, SD=4.5) and IQ measured with the National Adult Reading Test (Nelson, 1982) (test score: mean=118, SD=9, and mean=114, SD=8). Subjects fasted for three hours prior to and during study participation to ensure similar rates and levels of reboxetine absorption. As previous work indicates that levels of salivary cortisol (indicative of central noradrenaline levels) peak approximately two hours after the administration of reboxetine and remain elevated for at least two hours (Hill *et al.,* 2003), fMRI and psychological testing were initiated two hours after drug/placebo administration.

4.2.3 Psychological tasks

Psychological tasks were projected from a MR-compatible computer using e-prime software onto a white screen at the foot end of the scanner bed, which the subjects viewed through mirror glasses and responded to by pressing the keys of a response pad with their right hand.

4.2.4 Emotional categorisation

60 personality characteristics, selected to be extremely dislikeable or likable, were presented in a randomised order on the screen for 500msec (words were matched on length, frequency, and meaningfulness). Subjects were instructed to as quickly and accurately as possible categorise these personality characteristics as likable or dislikeable in a self-referential fashion. Subjects indicated their decision on the response pad by pressing either a left or right key for 'likeable' or 'dislikeable'. Neutral control words (n=10) ('left' and 'right') were presented randomly in between the personality characteristics to provide a neutral condition, to which responders pressed the left or right key. Response keys (left vs. right) were counterbalanced across the two experimental groups.

Incidental emotional memory: 120 personality characteristics were presented on the screen; of these 60 had been presented in the previous task and 60 were novel. The subjects were asked to indicate whether or not they remembered having seen the particular words in the preceding task, again by pressing either a right or left key on the response pad according to the version administered. Words were matched in length, imaginability, and frequency.

4.2.5 Mood scales

Mood and subjective state were assessed at three intervals; at baseline before drug administration (time -15mins), before the scan (+90mins), and at the end of the study (+300mins). This was achieved by administering the visual analogue scales (VAS), the Befindlinchkeits Scale (BFS), and the State and Trait Anxiety Questionnaires (STAI). Monitoring mood and subjective state allowed for the control of any effects related to major shifts of mood during the experiment. The Beck Depression Inventory (BDI) and the Trait Anxiety Questionnaire were used to control for significant differences in mood between groups.

4.2.6 fMRI data acquisition

All imaging data were collected using a Siemens Sonata scanner at the Oxford Centre for Clinical Magnetic Resonance Research operating at 1.5 T. Functional imaging consisted of 35 T2*-weighted echo-planar image slices [repetition time (TR)=3000ms, echo time (TE)=50 ms, matrix=64x64], $3mm^3$ isotropic voxels. To facilitate later co-registration of the fMRI data into standard space, we also acquired a Turbo FLASH sequence [TR = 12ms, TE = 5.65ms] voxel size = $1mm^3$. The first two EPI images in each session were subsequently discarded to avoid T1 equilibration effects.

4.2.7 fMRI data analysis

fMRI data were pre-processed and analysed using FEAT (FMRIB Expert Analysis Tool) version 5.00, part of FSL (FMRIB Software Library) (www.fmrib.ox.ac.uk/fsl). This included within-subject image realignment, spatial normalisation to a standard template using an affine procedure and spatial smoothing using a Gaussian kernel (5mm full-width-half-maximum). The time series in each session was high pass-filtered (40s cut-off) to remove large-scale non-stationary components and low frequency noise. FSL was used to compute individual subject analyses in which the time series were pre-whitened to remove temporal autocorrelation (Jezzard *et al.,* 2001).

Each of the conditions (e.g. negative, positive, and neutral) was modelled separately by convolving trials with a canonical haemodynamic response function (*ibid.*) Temporal derivatives were included as covariates of no interest to increase statistical sensitivity. All analyses were done at the group level using random effects analyses, and differences considered significant at $Z>2.0$ ($P<0.05$, corrected).

Event-related fMRI was employed to explore the rapid neural activity changes triggered by categorisation and recognition of the randomly presented emotional words in the two experimental

tasks. In the first-level analysis of the emotional categorisation task, individual activation maps were produced comparing responses to 1) negative minus neutral words and 2) positive words minus neutral words. In the emotional memory task, individual activation maps were produced comparing the response to 1) negative target words minus negative distractor words and 2) positive target words minus positive distractor words. For all tasks only the responses during correct trials were included. A mixed-effects group cluster analysis (a second-level analysis) was carried to establish group effects for these same contrasts (higher-level GLM analysis; corrected for multiple comparisons, Z=2.0, p=0.05). Brain sites with significant activation were localised using Talairach co-ordinates (Stereotaxic Atlas of the Human Brain) (Talairach & Tournoux, 1988).

4.2.8 Statistical analysis of behavioural data

Behavioural data were analysed using repeated-measures analysis of variance (ANOVA) with group and valence as factors for the categorisation and recognition memory tasks. To obtain a further measure of memory accuracy corrected for the subject's response tendency, signal detection theory was applied. The proportion of correctly recognised words (cr) and of falsely recognised words (fr) constitute the non-parametric sensitivity measure: d'= 0.5 ((cr-fr) (1+cr-fr) / 4 cr (1-fr)), with a higher d-value reflecting greater accuracy of memory (Grier, 1971). Subjective state ratings were also analysed using repeated measures ANOVA with group as the between-subjects factor and times of rating (3 levels: -15mins, +90mins, and +300mins) as the within-subjects factors.

4.3 Results

4.3.1 Subjective state

The two groups were well matched in terms of general mood, indicated by no significant differences in BDI and STAI scores (all p>0.05). Control of the relevant transient mood changes revealed that there were in no significant differences between the two groups overall (all p>0.05). However, volunteers receiving reboxetine reported feeling subjectively more alert (F=5.59, df= 1, 22, p=0.03).

4.3.2 Performance

Accuracy in both categorization and memory tasks was high in both groups (average accuracy in categorization: 92%, emotional recognition: 75%). Reboxetine did not affect speed or accuracy of emotional categorization (Table1: all p>0.05). Accuracy of recognition was also not affected by reboxetine (all p>0.05). Reboxetine-treated subjects were, however, significantly faster at

recognising positive compared to negative characteristics than those receiving placebo (Table 2 and Figure1: valence x group (F=4.73, df=1, 22, p=0.041).

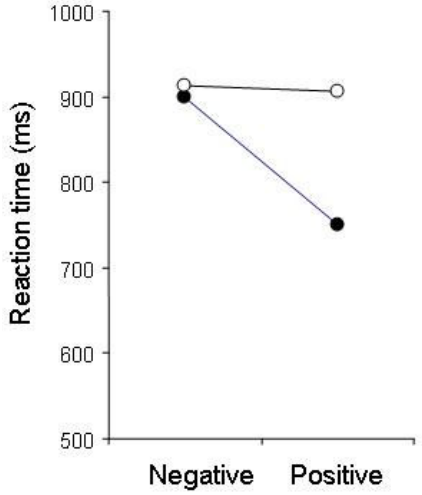
TABLE 1. Reaction Times (msec) during Emotional Categorisation for the Reboxetine and Placebo Groups.

	Reboxetine (N=12)		Placebo (N=12)							
					Main effect of valence		Interaction		Main effect of group	
	Mean	SD	Mean	SD	F	P	F	P	F	P
Positive words	583.9	241.9	705.3	282.1	F(2,42) =15.1	<0.001	F(2,42) = 0.04	0.96	F(1,21)= 1.87	0.19
Negative words	690.8	290.5	807.7	286.2						
Neutral words	435.3	175.9	575.5	226.0						

TABLE 2. Performance During the Incidental Memory Task the Reboxetine and Placebo Groups

Performance Measure	Reboxetine (N=12)		Placebo (N=12)		Analysis			
					Main effect of valence		Interaction	
	Mean	SD	Mean	SD	F	P	F	P
Accuracy (number of correct responses)								
Negative recognised target words	22.6	4.5	20	5.3				
Positive recognised target words	23.9	3.6	22.4	7.8	F(1,22) =4.4	0.048	F(1,22) = 0.33	0.57
Negative rejected distracter words	23.5	6.3	22.8	5.3				
Positive rejected distracter words	23.2	4.3	20.4	5.4	F(1,22) =2.9	0.10	F(1,22) =1.69	0.21
Accuracy corrected for response bias								
d-values positive words	0.777	0.049	0.075	0.070				
d-values negative words	0.661	0.060	0.071	0.062	F(1,22) =0.649	0.43	F(1,22) =0.173	0.68

FIGURE 1. Speed to recognise Positive vs. Negative Target Words for the Reboxetine (n=12) and Placebo (n=12) Groups in MS. Values represent Means; Dark Bars following Reboxetine and Light Bars following Placebo.



4.3.3 Task- and group-related BOLD change

4.3.3.1 Emotional categorisation

Main effect of task: Correct categorisation of positive (compared to neutral) self-referent personality characteristics produced significant activation within the left superior frontal gyrus Brodmann's area (BA 9), left inferior frontal gyrus (BA 47), left posterior cingulate (BA 23), and right precentral gyrus (BA 18), Table 3. Correct categorisation of negative (compared to neutral) characteristics significantly activated the left inferior (BA 47), left superior (BA 9), left frontal gyrus, and the left orbital gyrus (BA 11), Table 3.

Effects of reboxetine: Reboxetine differentially affected the neural response to the positive vs. negative words in the categorisation task. Reboxetine reduced activation to both positive and negative personality characteristics in an overlapping area encompassing the right superior temporal gyrus and inferior parietal cortex, Table 3, Figure 2. However, reboxetine additionally increased neural activation to positive characteristics within the right precuneus, Table 3, Figure 3.

TABLE 3. Cluster Maxima of BOLD fMRI Signal Change during Correct Categorisation of Emotional Self-referent Personality Characteristics.

Task and Region	Estimated Brodmann's Area (BA)	Z Score	Coordinates c)		
			X	Y	Z
Categorisation of positive words					
Task related activation					
L. Superior Frontal Gyrus		5.35	-8	58	26
L. Inferior Frontal Gyrus	47	5.89	-46	24	-12
L. Posterior Cingulate		4.3	-2	-58	4
R. Precentral Gyrus		5.01	10	-24	74
Reboxetine > Placebo					
R. Parietal Lobe, Precuneus		3.96	26	-60	34
Placebo > Reboxetine					
R. Superior Temporal Gyrus		5.39	58	-52	12
Categorisation of negative words					
Task related activation					
L. Inferior Frontal Gyrus	47	5.9	-46	24	-12
L. Superior Frontal Gyrus	9	3.98	-8	58	32
L. Orbital Gyrus	11	5.06	0	50	-22
Placebo > Reboxetine					
R. Inferior Parietal Lobule	40	5.28	54	-34	48

c) Standard space coordinates for the peak activation in each cluster identified thresholded at Z=2.0 and $p<0.05$ corrected.

FIGURE 2. Reboxetine reduced activation to the negative words in the right inferior parietal cortex (BA 40) compared to placebo.

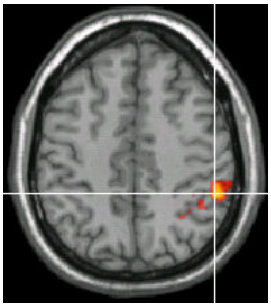
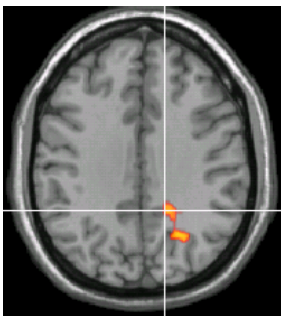


FIGURE 3. Reboxetine increased the neural response during the correct categorisation of positive self-referent personality characteristics within the right parietal lobe, right precuneus (BA 31) compared to placebo (right precuneus activation shown).



4.3.3.2 Emotional memory

Main effect of task: Correctly recognising target negative personality characteristics produced significant activation within the left inferior parietal lobule (BA 40 and 39), and the left inferior temporal gyrus (BA 20); Table 4. Correctly recognising target positive characteristics activated the left precuneus significantly; Table 4.

Effects of reboxetine: Between-group contrasts revealed that reboxetine significantly reduced neural activation during correct discrimination of positive self-referent personality targets compared to matched distractors within left and right medial frontal gyrus, Table 4, Figure 4. Furthermore, reboxetine significantly increased activation in recognition of negative self-referent personality characteristics within the right medial frontal gyrus, the left precuneus (BA 7), and subcortically in the pons; Table 4, Figure 5.

TABLE 4. Cluster Maxima of BOLD fMRI Signal Change during Correct Recognition of Emotional Self-referent Personality Characteristics.

Task and Region	Estimated Brodmann's Area (BA)	Z Score	Coordinates c)		
			X	Y	Z
Recognition of negative words					
Task related activation					
L. Inferior Parietal Lobule	39, 40	4.63	-52	-54	54
L. Inferior Temporal Gyrus	20	4.6	-54	-34	-22
Reboxetine > Placebo					
L. Precuneus		4.98	-2	-74	52
Brainstem, Pons		4.14	0	-16	-28
R. Medial Frontal Gyrus		3.15	10	34	-12
Recognition of positive words					
Task related activation					
L. Precuneus	7	4.52	-24	-82	48
Placebo > Reboxetine					
R. Medial Frontal Gyrus	6	5.09	20	-12	62
L. Medial Frontal Gyrus		4.12	-6	20	50

c) Standard space coordinates for the peak activation in each cluster identified thresholded at $Z=2.0$ and $p<0.05$ corrected.

FIGURE 4. Reboxetine reduced activation in frontal (BA 6) and parietal areas (BA 3, BA 7) during the correct recognition of positive characteristics (frontal activation shown).

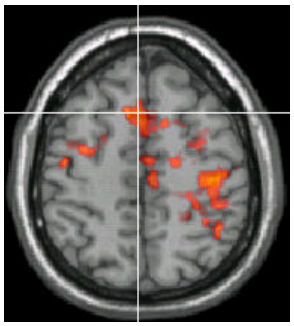
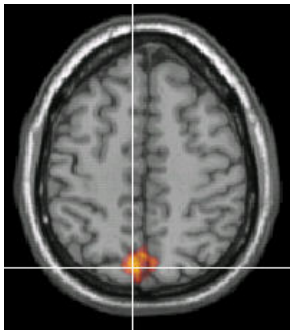


FIGURE 5. Reboxetine increased activation during correct recognition of negative haracteristics in parietal cortex, bilateral precunei (BA 7) (left parietal activation shown).



4.4 Discussion

The current study suggests that a single dose of the antidepressant reboxetine affects the neural processing of emotional self-referent information in healthy volunteers. In particular, reboxetine reduced the response during the presentation of both positive and negative personality characteristics in the right superior temporal- inferior parietal boundary and additionally enhanced the response during the presentation of positive personality descriptors within the right precuneus. In a subsequent recognition memory task, reboxetine was found to enhance activation within the medial frontal and parietal cortex and pons when correctly discriminating previously presented negative words from matched distractors, but to decrease bilateral medial frontal activation when recognizing the positive words. These results complement the behavioral effects of reboxetine previously reported in healthy volunteers (Harmer *et al.*, 2003b) and highlight key neural areas, which may be involved in these effects.

4.4.1.1 Neural systems subserving emotional categorisation

Categorisation of both positive and negative self-referent personality characteristics activated a similar network of areas to those previously reported including the superior frontal gyrus (BA 9) and inferior frontal gyrus (Kuchinke *et al.*, 2005; Goldin *et al.*, 2005; Fossati *et al,* 2003). In addition, we found significant brain activation to categorisation of positive words in the left posterior cingulate cortex (PCC) (BA 23) consistent with an involvement of this limbic area in emotional processing (Goldin *et al.*, 2005; Maddock *et al.,* 2003; Aalto *et al.,* 2002; Vogt *et al.,* 1992). Categorisation of negative characteristics additionally activated the left orbital gyrus, suggesting that this task taps into similar areas to those previously identified during negative emotion (Wayne & Drevets, 1998; Paradiso *et al.,* 1997).

4.4.1.2 Emotional categorisation: effects of reboxetine

In the current study, reboxetine reduced activation during categorisation of both positive and negative characteristics in an overlapping area encompassing the right superior temporal gyrus and inferior parietal cortex (BA 40). Additionally, reboxetine increased right precuneus (BA 31) activation during categorisation of positive characteristics. Right-side precuneus-activation in processing of both positive and negative but not neutral stimuli (Paradiso *et al.,* 1999) has been suggested to reflect increased attention to all aspects of emotional compared to neutral stimuli in healthy subjects. The increased precuneus activation to positive words found here could thus reflect increased attention to positively valenced information after reboxetine administration. This effect of reboxetine is consistent with results from our previous study which showed a behavioural bias towards positive emotional information following acute reboxetine in healthy volunteers (Harmer *et al.*, 2003b). In the previous study, reboxetine increased speed to categorise positive vs. negative personality characteristics, enhanced positive emotional memory and facilitated the recognition of happy facial expressions. Taken together with the current changes in activation, these results suggest that antidepressants may have surprisingly early effects on the neural processing of emotional information in a manner predicted to enhance the processing of positive vs. negative material. While it should be noted that the reaction time data was not affected by reboxetine in this task in the current study, this may reflect the difficulty of indexing cognitive performance during fMRI scanning. In particular, the noise of the scanner and the supine response position may interfere with the ability to detect small differences in reaction time.

4.4.1.3 Neural systems subserving emotional recognition memory

Successful recognition of negative self-referent personality characteristics activated a network of areas including the left inferior parietal cortex and left inferior temporal gyrus (BA 20). These areas

have also been highlighted in previous studies exploring the neural correlates of self-referent processing (Kircher *et al.,* 2000), and emotional processing (Bremner *et al.,* 2003; Ruby & Decety, 2004). Successful recognition of positive self-referent personality characteristics activated the left precuneus, which is consistent with the involvement of this structure in emotion (Teasdale *et al.,* 1999; Ochsner *et al.,*2004) and recognition memory (von Zerssen *et al.,* 2001).

4.4.1.4 Emotional memory: effects of reboxetine

An emotional recognition task was used in the place of the free recall approach used in the previous behavioural studies because of its compatibility with the fMRI procedure. This task revealed increased efficiency (in this case speeded reaction times) to recognise positive words following reboxetine, consistent with the positive bias in free recall previously reported (Harmer *et al.*, 2003b). In line with these behavioural differences, there was a differential effect of reboxetine on BOLD responses during the successful recognition of positive and negative personality characteristics. This comparison examined the difference in response during the correct discrimination of the emotional target words relative to matched distractors, therefore assessing the systems involved in memory processes rather than presentation of negative and positive information per se. Reboxetine was observed to reduce activation in a network of areas involving the medial frontal gyrus bilaterally during the recognition of positive emotional words. By contrast, reboxetine increased activation during the successful recognition of negative words in left precuneus, right medial frontal gyrus, and pons. Taken together with the behavioural data, this pattern of increased activation during the recognition of negative words and decreased activation during the recognition of positive words following reboxetine may imply differences in ease of memory processes. For example, increased activation during the recognition of negative words may reflect greater recruitment of resources required to recognise these words successfully. It is generally accepted that increased difficulty or impaired memory function can be associated with increased activation in fMRI studies. For example, neuroimaging studies on cognitive function in schizophrenia (Callicott *et al.,* 2003b) and depression (Harvey *et al.*, 2005) suggest that patients whose working memory performance is similar to that of healthy control subjects use greater prefrontal resources, while patients without such exaggerated prefrontal activity achieve lower memory accuracy (Callicott *et al.,* 2003b). This interpretation is supported by the behavioural data collected during the scan suggesting that volunteers receiving reboxetine were able to recognize the positive compared to negative personality targets more quickly compared to those receiving placebo. Indeed, if reboxetine treated volunteers automatically attend more to positive words during

categorisation it is perhaps unsurprising that the subsequent recognition of these words may be accomplished with greater ease and with reduced recruitment of neural resources.

4.4.1.5 Emotional processing and limbic areas

It is noteworthy that the effects of reboxetine were largely constrained to areas of parietal and medial prefrontal cortex in this study. Previous investigations have highlighted the importance of other areas such as the amygdala, hippocampus, and anterior cingulate in emotional processing and emotional memory, which we did not see here using self-referent personality characteristics. This is consistent with previous work investigating the neural substrates of positive and negative self-referent categorisation and memory (Fossati *et al.,* 2004). The involvement of parietal cortex is indicative of relatively early changes in processing of emotional information, and an early locus of effect of reboxetine on attention to emotional stimuli. However, it is unlikely that these areas of the parietal cortex process much information about the emotional valence and salience of stimuli but rather respond to information from limbic areas concerning events of importance to be attended to. Indeed, differences in visual processing to salient emotional information have been associated with amygdala response (Norris *et al.,* 2004).

Further studies are required to assess the involvement of limbic areas in the effects of reboxetine on emotional processing using a higher number of volunteers powered to allow functional connectivity analysis.

4.4.1.6 Pharmacological fMRI

It is important when examining the effects of a drug manipulation on BOLD responses with fMRI to assess whether the observed effects could be the result of more global effects of the drug on blood flow or neural coupling. Previous studies have found a close correspondence between event-related potential (ERP) data and BOLD responses following drug challenges such as sulpiride (Bullmore *et al.,* 2003). The current study did not assess ERP responses following reboxetine. However, the finding that reboxetine had opposite effects on BOLD responses during positive and negative words suggests that these results are unlikely to occur through these non-specific processes.

4.4.1.7 Conclusions

In summary, we demonstrated that a single dose of reboxetine affects neural and cognitive processing of positive versus negative emotional information. Reboxetine reduced activation during visual presentation of both positive and negative self-referent personality characteristics in an overlapping area encompassing the temporal-parietal boundary (peak within BA40), but

additionally increased neural responses in the precuneus area of the parietal cortex during presentation of positive characteristics. By contrast, reboxetine decreased activation during the recognition of positive personality characteristics, while increasing activation with recognition of negative characteristics. Our data provide support for the hypothesis that antidepressants may bias processing towards positive emotional information and may therefore work via the elaboration of these biases into memory and learning very soon after the start of antidepressant treatment. Such a mechanism would be compatible with cognitive-behavioural theories of depression, which emphasise the importance of negative biases in the maintenance of depressive illness. Future studies are required to assess the effects of longer term administration of reboxetine in healthy and depressed subjects and to assess whether these early effects of antidepressants on emotional processing are predictive of the therapeutic response to these drugs.

5 The neuropsychological approach: methodological and theoretical perspectives

5.1 The contributions of the present study

The present ER-fMRI study is the first to employ a parallel investigation of the effects of antidepressants on the neural activation patterns and cognitive aspects of emotional processing in healthy volunteers. This investigation of the acute effects of the SNRI reboxetine on neural and cognitive processing of emotionally self-referent personality characteristics in healthy volunteers contributes to our understanding of the link between mind and brain in the affective sciences. Firstly, it provides insights into which neural networks engage in the processing of positive and negative emotional information, which can supplement previous findings. Secondly, and more importantly, the study provides novel insights into the neuropsychological mechanisms by which alterations in *neural* activation induced by antidepressants lead to *cognitive* changes in the processing of emotional self-referent information. The present findings suggest that at both the neural and psychological levels, reboxetine impedes the processing of negative self-referent information and facilitates the processing of positive self-referent information. The study thus provides support for the neuropsychological argument that antidepressants and cognitive-behavioural therapy have a similar mechanism of action.

With respect to the treatment of depression, the present findings contribute to further integration of the psychological and pharmacological interventions and to the development of innovative strategies, which combine the key therapeutic elements of the two approaches. From a theoretical perspective, the study promotes the neuropsychological understanding of depression, in which both the neural and cognitive levels of description as well as the *relation* between the two are encountered. The manipulation of neurotransmitter systems leads to changes in global neural information processing in the brain. In turn, these changes in neural activation patterns favour the processing of positive and redress the processing of negative emotional information. These bidirectional mechanisms lead to subtle biases in emotional processing at the cognitive level, which in the longer term may positively affect the conscious subjective experiences of oneself and the world. The interdependence of the different levels that comprise emotional processing suggests that a complete scientific understanding of affective disorders must involve both levels of analysis as well as the mechanisms by which they interact. The long-standing separation and disagreement between the psychological and neurobiological accounts of depression must now be overcome and synthesised into a comprehensive account of the disorder.

5.2 The relation between neural activation and cognitive function

In the present study, the SNRI reboxetine reduced neural activation to positive and negative emotional words in the parietal-temporal boundary but additionally increased activation to positive words in the precuneus, suggesting amplified attention to positive relative to negative material. Although it is well established that fMRI BOLD response reflects increased neural activity, it has been argued that increased activation does not necessarily reflect *better* and more efficient processing. As previously described, greater prefrontal resources (increased BOLD response) are needed in patients suffering from schizophrenia (Callicott *et al.,* 2003b) and depression (Harvey *et al.,* 2005) in order to obtain a working memory performance similar to that of healthy comparison subjects. These findings clearly demonstrate the possibility that *more extensive* neural processing particularly in frontal areas can reflect *less efficient* cognitive processing, while *relatively reduced* activity may reflect *more efficient* processing. On the basis of these observations one could ask what basis we have for suggesting that the relative increase in neural activity during encoding of positive words in precuneus associated with reboxetine reflected facilitated processing. Comparing the evidence supporting the conclusions by Callicott *et al.* (2003b) and Harvey *et al.* (2005), it is worth noting that unlike their working memory task, our 'emotional categorisation task' *did not* pose any significant demand on the attentional or working-memory resources. Our subjects merely indicated whether they would like or dislike, if somebody referred to them as selfish or charming, to which the answers were fairly self-evident. Their (high) accuracy on the task was therefore unaffected by the drug, and it is very unlikely that the relative increased neural activation to positive words reflected greater difficulty with processing of positive characteristics.

The second major finding of the present study was that in a subsequent memory test, reboxetine increased neural activity within prefrontal and parietal areas during the recognition of negative words and reduced activation in these areas during the recognition of positive words. The nature of the 'incidental memory task' differs considerably from the 'emotional categorisation task' as it necessitates memory and more attentional resources. Consistent with the view presented by Callicott *et al.* (2003b) and Harvey *et al.* (2005), we assumed that superior memory efficiency would be reflected by reduced activity due to the need of less extensive neural processing (provided that behavioural measures did not differ), while impaired efficiency would necessitate recruitment of more neural resources. This assumption was the basis for our suggestion that reboxetine enhances memory efficiency for the positive words (as reflected in the reduced neural activity) and impedes memory for negative words (which necessitate the mobilisation of more neural resources and more attention for their recognition). This suggestion found further support in the behavioural

evidence that reboxetine-treated subjects were faster at recognising positive versus negative words compared to control subjects.

5.3 The role of the neuropsychological approach

The principal objective of the neuropsychological approach to affective disorders is to promote an interdisciplinary framework, in which insights from the cognitive and neurobiological perspectives are united in a multilevel understanding of affective disorder, encompassing psychological, psychosocial, and neurobiological factors as well as their interdependence. According to the neuropsychological view, the cognitive and neurobiological accounts of depression must be integrated into a complete account of affective disorder. This is because the numerous factors involved in the etiology, maintenance and remission of depression cannot be explained with reference to only 'mind facts' or 'brain facts', but require different conceptual vocabularies (e.g. feelings of worthlessness versus monoamine dysfunction), which belong to different levels of analysis. The neuropsychological approach therefore aims to dissolve the long-lasting polarisation of the two conceptions of depression, which have the common inherent characteristic that they leave out some factors of crucial importance to the understanding of depression: while the cognitive approach cannot explain the neural fundament from which cognitive phenomena rise, the neurobiological perspective is incapable of elucidating the cognitive subjective symptoms characterizing the disorder.

Relating this polarisation to Marr's meta-theoretical model (1982), the crucial relevance of the neuropsychological approach in the quest for a complete understanding of depression becomes clear. Indeed, the model emphasises that a full explanation of the human brain requires a consideration of three levels of analysis; the hardware, the representational level, and the computational level. With the aim of explaining the neuropsychological mechanisms by which the neurobiological and psychological levels are related, the neuropsychological approach can be regarded as more comprehensive than any of the former approaches. The importance of including both the psychological and neurobiological perspectives on depression is highlighted by the fact that *diverse* syndromes of affective dysregulation may in fact involve the *same* structures (Davidson *et al.*, 2003, p.901). This highlights the necessity of elucidating *more* than merely the biological level of affective disorders in order to be truly able to understand the nature of the disorder. We cannot merely reduce depression to dysfunction in prefrontal and limbic areas and suppose that the disorder is then fully explained. The possibility remains that exactly the same neurobiological dysfunctions may lead to rather different symptoms in different individuals, which

demonstrates that there is no direct 'identity' between psychological and biological dysfunctions. Thus the neurobiological framework is on its own inherently incapable of providing a full understanding of affective disorder; we need a contemplation of the psychological perspectives as well to reach a complete understanding. An important issue in continuation of this is the enormous plasticity of the brain, which makes it impossible to ascribe any specific pathological affective syndrome to a particular neurochemical or anatomical system. Emotional engrams are coded in various places and are mediated by changing and evolving neuroanatomic and neurochemical substrates that reflect various psychological phenomena like appraisal, anticipation, readiness for future action, and planning. It is therefore crucial to appreciate the cognitive, experiential, and contextual elements of affective function and disorder. In a given situation, the cognitive and contextual components play a role in determining the individual's affective reaction; at the same time, internal affective experiences may colour the cognitive interpretation and have an impact on the neurochemical and physiological underpinnings of such experiences. The cognitive, affective, and neurobiological components of affective processing are intimately linked and engage in mutual interactions. Because of this interrelatedness, it is crucial to identify which of the abnormalities are related to the primary pathology of a given affective syndrome versus those that are secondary compensatory and adaptive mechanisms. In the light of this, perhaps the most effective strategies for dealing with affective disorders are treatments that address and target elements at all levels of analysis: interpersonal social support for better coping and stress reduction, cognitive therapy for the reduction of thought distortions, behavioural approaches for emotion modulation, and antidepressant medication for the neurobiological abnormalities. The neuropsychological approach to depression, which begins to elucidate the mechanisms, by which these different levels of description are related, may contribute extensively to such integration and advance the understanding and treatment of depression.

5.4 Theoretical and practical implications

5.4.1 Monotherapies or combination treatments?

There is substantial evidence for the effectiveness of both cognitive and pharmacological treatments of depression (e.g. Kieve *et al.*, 2001; Thompson *et al.*, 2001; Thase *et al.*, 1997; March *et al.*, 2004; Pampallona *et al.,* 2004; deRubeis *et al.,* 2005; Hollon *et al.,* 2005; de Mello *et al.,* 2005). However, with respect to the relative superiority of the two types of treatment, the findings vary. One study comparing the effects of the pharmacological and cognitive-behavioural therapy of

elderly depressed patients found that there were no significant treatment-response differences between patients receiving pharmacological treatment (desipramine, TCA) and patients receiving cognitive behavioural therapy (CBT) (Thompson *et al.*, 2001). This is consistent with a review of multiple-cell randomized, controlled, double-blind studies on mild to moderate depression comparing response rates to medications, psychotherapy, and control conditions (Casacalenda *et al.,* 2002). Here it was demonstrated that while antidepressants (TCAs and phenelzine) and psychotherapy (primarily cognitive behaviour and interpersonal therapies) were both more efficacious than control conditions, there were no significant differences in efficacy between the two treatments – a finding supported by a more recent review (de Mello *et al.,* 2004). This indicates that both antidepressant medication and psychotherapy are effective in the treatment of patients with mild to moderate depression. Additionally, new evidence suggests that cognitive therapy can be as effective as medications even among more severely depressed patients (DeRubeis *et al.,* 2005). Consistent with this, a review comparing the acute outcomes of antidepressant and CBT in severely depressed outpatient subgroups found no significant advantage for either treatment modality. A recent study demonstrated that patients withdrawn from successful cognitive therapy were less likely to relapse during continuation than patients withdrawn from medications (30.8% vs. 76.2%), and no more likely to relapse than patients who kept taking continuation medication (30.8% vs. 47.2%) (Hollon *et al.,* 2005). Other studies have, however, demonstrated the superiority of pharmacological to psychological treatment of depression; a large randomized controlled trial of adolescent patients with depression found that the SSRI fluoxetine was significantly more effective than CBT (March *et al.*, 2004). Thus although both psychological and medical treatments are effective in the treatment of depression, findings on their relative efficiency are inconsistent.

A vast majority of individuals with depression suffer from multiple episodes over a lifetime and are especially prone to relapses shortly after an index episode (Vos *et al.,* 2005). Maintenance treatment is therefore required to reduce the burden of depression. Relying on maintenance pharmacotherapy alone to ensure sustained recovery from depression has a number of drawbacks. The use of maintenance pharmacotherapy relies on the assumption that patients will continue to take their medication for extended periods. However, adherence to antidepressant medication use is a problem in clinical practice, in which the rate of noncompliance is estimated to be around 40% (Basco & Rush, 1995). For instance, it was demonstrated that in a study on 155 patients in primary care, 28% of the patients stopped taking their medication during the first month of treatment, while 44% had stopped by the third month (Lin, *et al.,* 1995). According to one cost-effectiveness study, however, providing acute-phase structured psychotherapy to all patients may be unrealistic, as this is significantly more costly than medical maintenance treatments (Segal *et al.*,

2002). Another, more recent, cost-effectiveness study concludes the opposite; maintenance treatment with CBT, if provided by publicly funded psychologists, is more cost-effective than maintenance drug treatment (Vos *et al.,* 2005). Finally, there is a growing recognition that although antidepressant monotherapy may be effective for many patients there is still a need for other strategies for patients resistant to antidepressants (Shelton, 2003, Mayberg *et al.,* 2005). In the light of the limitations of monotherapy, there has been substantial research on the possibility of combining pharmacotherapy with psychotherapy to capitalize their respective benefits. A systematic review on compliance and treatment-response to the combined pharmacotherapy and psychotherapy of depression reported that psychological treatment combined with antidepressant therapy leads to a significantly higher improvement rate than drug treatment alone (Pampallona *et al.*, 2004). Further, in longer-term therapies, the addition of psychotherapy reduces the number of dropouts significantly (*ibid.*). This demonstrates that combined treatment is more acceptable for the patients, who are less likely to drop out and therefore, ultimately, more likely to recover. The benefit of combining pharmacotherapy and psychotherapy is further supported by March *et al.* (2004), who found that the combination treatment with fluoxetine and CBT in adolescents had a substantially higher success rate than either treatment alone. Moreover, clinically significant suicidal thinking, which was present in 29% of patients at baseline, was reduced the most by the combination treatment (*ibid.*). Combination treatment therefore appears to offer the most favourable trade-off between benefit and risk in the treatment of adolescents. As depression in adolescence is common (prevalence of 1 in 20) and is associated with significant morbidity and family burden, public health would be positively influenced by improvements in the treatment of depression in adolescents, such as the combination treatment (*ibid*.).

Thompson and colleagues (2001) found that in elderly patients with more severe forms of depression, the combined CBT-antidepressant treatment was of greater effectiveness than either the psychological or pharmacological treatment alone. This is compatible with a meta-analysis of several studies comparing psychotherapy and combined psychological/pharmacological treatment of depressed individuals (Thase *et al.*, 1997), which found that the combined condition was notably superior to either psychotherapy or pharmacotherapy alone in the more severely depressed patients. Patients with less severe depression, by contrast, did not benefit significantly from the combined treatment, when compared with psychotherapy alone. A meta-analytical review of recent publications on the comparative efficacy of the combination of pharmaco- and psychotherapy versus either monotherapy found that certain subgroups of patients benefit substantially from combination compared to either psychotherapy and pharmacotherapy alone: the acute and long-term treatment of more severe forms of chronic depression, and the long-term treatment of older

depressed patients (Hegerl *et al.,* 2004). There is thus substantial evidence for the benefit of combining pharmacological and psychological treatment in more severe recurrent depression and depression in elderly patients, while patients with milder forms of depression profit equally from psychological intervention alone.

Relapse and recurrence after successful treatment of depression is a common regrettable outcome that has massive social costs. Although many depressed patients obtain sustained recovery though maintenance pharmacotherapy, the long-term outcome is still poor in a considerable number of 'difficult to treat' patients (Segal *et al.,* 2002). A recent review evaluating the role of combined psycho- and pharmacotherapy in minimizing relapse and recurrence rates in depression demonstrated that 'consecutive sequencing' of medical and psychological treatment is beneficial both for the conversion of partial to full response and for prevention of relapse and recurrence. The review further reported that 'crossover treatments', in which patients are switched from one treatment to another after an adequate response to the first, is advantageous in the prevention of relapse and recurrence. Various studies by Fava and colleagues (1996; 1998; 2004) provide support for the idea of a superior prophylaxis for patients receiving various types of combined psychological/ pharmacological treatment. In a four-year follow-up study they found evidence that cognitive behavioural therapy (CBT) of residual symptoms after successful pharmacotherapy significantly reduces the relapse rate (Fava *et al.,* 1996). Consistently, their most recent follow-up study demonstrated that CBT after successful pharmacological treatment of difficult-to-treat patients not only displayed fewer residual symptoms after the discontinuation of the drug therapy, but also had a significantly lower relapse rate (40%) at a six-year follow-up after drug discontinuation compared to the patients who only received clinical management (90%) (Fava *et al.*, 2004). These findings are further confirmed by substantial evidence that cognitive therapy decreases relapse rates (Paykel *et al.*, 1999; Hollon *et al.,* 2005). Taken together, these results suggest that the sequential use of cognitive behaviour treatment after pharmacotherapy improves the long-term outcome in recurrent depression. This challenges the assumption that long-term drug treatment is the only way to prevent relapse in patients with recurrent depression. A significant proportion of depressed patients may be able to withdraw from medication successfully and stay well with a focused course of CBT, which gives them means to "do the therapy for themselves" (Hollon *et al.,* 2005).

Overall, there is growing evidence for an advantage of combining cognitive and pharmacological treatments of depression. By increasing our knowledge of the neuropsychological mechanisms underlying symptom remission, neuropsychological research may contribute

importantly to the development of novel treatments that combine the key mechanisms of action of the cognitive and pharmacological treatments.

5.4.2 A holistic understanding of depression and therapeutic implications

Current neuropsychological research on depression has important implications both for the theoretical conceptualisation of the disorder and for future treatment strategies. Some new insights into the neuropsychological mechanisms of antidepressant drugs have been suggested in accordance with the theory put forward by Popper and Eccles (1977), which argued that all natural phenomena exist at hierarchical emergent levels in the nature and interact with one another through upwards as well as downwards causations. That is, phenomena at lower levels can influence higher-level phenomena, and vice versa. The idea of 'downwards causation' is confirmed by the mood-induction studies and evidence that CBT can lead to transient or sustained metabolic changes the brain. These studies demonstrate persuasively that conscious emotional cognitions produce specific neurophysiological patterns of activity in the brain. This direct influence of mental phenomena on the physical brain challenges the epiphenomenalist view of the mind-brain relation. The notion of *upwards causation* is supported by the recent findings that manipulation of neurotransmitters cause changes in both emotional processing and social interaction. The novel finding in our study involves an additional intermediate level: The manipulation of noradrenergic neurotransmitters affected the higher emergent level of more *global* patterns of neural activation during emotional processing. In turn, this influenced the still higher emergent level of cognitive processing of emotional information. Finally, this may affect the highest emergent level of consciousness experience, so that the environment is perceived more positively and more happy life experiences are recalled. The present study therefore provides experimental support to the conjectures by Eccles and Popper (1977), questioning the validity of the strict demarcations between traditional objectivity and subjectivity in science.

However, there is a severe limitation of the present study, which applies to neuropsychological research in general. The precise relation between *cognitive* processing and *conscious* experience of emotional information remains perplexing. The fundamental question of how increased neural and cognitive processing of positively valenced information leads to *any* conscious experience at all remains just as hard to answer. This is because of an 'explanatory gap' between accounts of cognition and consciousness itself. While cognitive functions can be fully explained by the functions they perform (e.g. positive biases lead to increased attention to positive stimuli), phenomenal experiential states (e.g. feeling of improvement of mood) are *not* defined by the causal roles they play: "*Even if the appropriate functional organization always gives rise to*

consciousness in practice, the question of why *it gives rise to consciousness remains unanswered.*" (Chalmers, 1996, p.47). Despite this limitation, the present study may be an important step forward towards the goal of creating a complete all-encompassing theory of affective disorder, in which all relevant factors involved in the development and remission of the disorder are integrated. Although much still remains to be elucidated, we can today, on the basis of the neuropsychological findings, conclude that there is an intimate relation between neurobiology and cognition, so we must now resist engaging in the traditional rivalry between the cognitive and neurobiological approaches. In order to be able to progress towards an understanding and towards effective treatment of depression, we must formulate an integrated approach, which acknowledges the existence of objective 'brain facts' as well as cognitive and subjective 'mind facts'. Such a neuropsychological account may contribute to research and lead to advances in the treatment of depression by providing the optimal possibilities for a *holistic* understanding and treatment of depression.

It is increasingly recognized that there may be a conflict between the objective medical conceptions of mental disorder within the professional health sector and the individual's understanding of his/her disorder. Elsass (1993) argues that this can be conceptualized as an opposition between the 'illness model' and the 'disease model' of mental disorder. The illness model refers to the individual's holistic folk psychological notion of symptoms, which is formed by his/her culture and particular life biography and serves to make the illness meaningful. Contrastingly, the 'disease model' is the conception represented by the professional medical world and thus originates from the perspective of the doctor. Disease is the objective conceptual framework, in which the disorder is expressed in biological terms and described as a set of abnormalities in biological function (ibid.). These two rather disparate conceptions of mental disorder may collide in the meeting between the doctor and the patient, which is rather unfortunate with respect to their understanding and collaboration and for the likelihood of subsequent compliance by the patient. In the case of depression, the disease model reduces the subjective symptoms to neurochemical imbalances or functional abnormalities in brain metabolism. This understanding has little in common with the perceptions of the depressed patient who is engaged in depressing thoughts, sadness, and personal loss, feelings of giving up and need for being understood and taken care of. A treatment of the disorder which focuses on the disease process and mainly employs neurobiological concepts foreign to the patient, can therefore meet resistance in the patient who wishes a treatment based on illness experiences. It is thus a central responsibility of the clinician to bring together and balance the two perspectives on the disorder, such that there is not assigned too much priority to either the reductionistic disease model or the subjective disease experiences of the patient, so that competent professional treatment can be undertaken. Our

growing understanding of the neuropsychological mechanisms of effective cognitive and pharmacological therapies of depression and thus our development of novel effective combinational treatments may facilitate integration between the disease and illness perspectives. In this way, neuropsychological research contributes to an improved understanding between the clinician and the patient and will increase compliance and thus success rates of treatment.

6. Conclusion and future directions

The existing literature on depression reveals a major gap between the psychological and neurobiological understandings of the disorder. Cognitive theories explain the genesis and maintenance of depression through negative biases in cognitive processing and memory of self-referential information. Today Beck's Cognitive Theory (CT) is a leading theory of depression, having profoundly influenced psychological research and treatment of depression throughout the last four decades. The theory was based on Beck's own observation of depressed individuals and was brought forth by the cognitive revolution in the 1960s, when the behavioural paradigm was replaced by cognitive psychology and the mind was again subjected to scientific study. Beck observed that the central features in depression were universal negative self-referent biases in cognitive processing, which were particularly salient when making judgements about the self, the world, and the future, thus comprising a 'negative cognitive triad'. According to Beck all cognitive processing is organised within cognitive schemes that are relatively enduring and rigid internal structures, through which new information is 'filtered'. In depression, the presence of negative self-referent schemas bias all information processing such that information is judged as negative and referring to the self, although this may not be the case, in reality. The CT provides a framework for understanding the various cognitive dysfunctions and their influence on emotion and behaviour in depression, and is supported by substantial empirical evidence as well as by its effectiveness in the treatment of depression. Although the CT was considered a breakthrough in the psychological conceptualisation of depression, it suffers from a number of limitations of which the most important ones are its inability to elucidate the aetiology of the disorder or to explain the role of the neurobiological dysfunctions associated with depression.

In contrast with the cognitive conception of depression, neurobiological theories regard depression as a *biological* disorder caused by imbalance in key neurotransmitter systems and by structural and functional CNS abnormalities. The discovery of antidepressant drugs in the 1950s changed the conception of depression profoundly; the amelioration of symptoms of depression through manipulation of the neurochemistry of the brain suggested that depression itself could be understood as a neurobiological disorder. Subsequent neurobiological research on depression has been dominated by two major theories: the 'monoamine theory' and the 'neurotrophic theory'. While the monoamine theory states that depression is due to disruption of monoamine systems in the brain, upon which antidepressants act by facilitating *monoaminergic* neurotransmission, the neurotrophic theory holds that the disorder is caused by disruption of neurotrophic mechanisms, which leads to neural degeneration and atrophy in various brain sites. Accordingly, antidepressants act by increasing the *neurotrophic factors* in the brain to reverse neural degeneration and atrophy.

The major limitation of the monoamine approach is that it is confined to the level of neurotransmitters and cannot therefore elucidate the complex physiopathology and aetiology of depression. In this respect the neurotrophic paradigm represents an advantage, as by using of sophisticated brain imaging techniques it has provided insights into the global *structural* and *functional* changes in various brain sites in depressed patients. Insights from clinical, post-mortem, and animal studies have increased our understanding of the neuroanatomic networks involved in affective disorders. The neurotrophic paradigm offers an explanation of depression beyond the monoamine neurotransmitter level by accounting for the complex functional and structural neurobiological abnormalities associated with depression. Despite the disparities between the two neurobiological theories of depression, they share the fundamental assumption that depression can be fully explained in a biological pharmacological framework and treatments of the disorder should be designed to target the neurobiological abnormalities in depression.

These conflicting conceptualisations of depression proposed by the cognitive and neurobiological approaches originate from conflicting views on the more fundamental question of how the mind and brain relate. The mind-brain problem is the fundamental conceptual gap between the subjective phenomenal mind and the objective physical brain. We know that mind and brain are closely linked; however physical observation of the brain reveals nothing about the nature of conscious thoughts and feelings. The question of how the mind and brain relate has been a central theme throughout centuries of philosophical debate, and has recently also become the subject of scientific enquiry. This is a result of major conceptual developments allowing scientific investigation of subjective phenomena, and of great technological advances, which provide sophisticated neuroimaging techniques for examining the conscious brain. The mind-brain-debate has long been dominated by two main positions: dualism and monism, which represent a dichotomy offering opposing answers to the mind-brain-problem. Whereas dualists claim that the mind and brain are two fundamentally different metaphysical entities, the view proposed by the majority of monists is that mind can be explained within the framework of the physical world. These conflicting standpoints in the mind-brain-debate affect the main approaches to scientific research on depression and lead to conflicting accounts of the disorder.

The assumption of cognitive psychology is that people are autonomous intentional individuals who have a symbol-processing mind, through which they interact with the world. Although it is recognised that the mind arises from a neurobiological substrate, the neurobiology is not thought to play any significant causal role in the disorder. This reflects a conception of depression as a disorder of the mind, which must be explained by use of 'mind facts' only. Although 'brain facts' are not refuted altogether, they (and their relation to the mind) are assigned

no importance whatsoever. Thereby the underlying philosophical position of the cognitive approach to the mind-brain debate is *dualist*, although attention is given to the mind. In contrast, the neurobiological approach focuses entirely on the neurobiology of depression, which is consistent with the dominating view that depression is a neurobiological brain disorder caused by brain abnormalities that can be reversed by means of antidepressant drug therapy. Although the existence of the mind is recognised by some neurobiologists, mind facts are not given any attention due to the assumption of the closedness of the physical systems, according to which something 'non-physical' cannot influence the physical brain. The underlying assumptions of the mind-brain-relation in the neurobiological approach are therefore either *reductionistic materialist* or *epiphenomenalist*. It is thus clear that the contrasting conceptualisations and treatments of depression within the two approaches are a result of a profound disagreement on the question of how mind and brain relate. Although both approaches contribute with central insights to the disorder, neither can fully account for depression, as they leave out either the mind facts or the brain facts. The neurobiological perspective fails to explain how structural and functional CNS alternations summate to depressive symptoms, or how the actions of antidepressant medication can be translated into the clinical relief of subjective symptoms of the disorder. On the other hand, cognitive psychology does not elucidate the roles played by genetics and the neurobiology of the brain or how they influence cognitive processing in depression. This fundamental paradigmatic gap between the cognitive and neurobiological conceptions of depression is thus a considerable obstacle to progress in research on depression.

The apparent conflict between the two approaches to depression can, however, be resolved in the light of Marr's meta-theoretical framework of different theoretical levels of description. According to Marr (1982), a complete scientific understanding of information processing systems like the brain requires explanation at three different levels of description, which are linked into a cohesive whole; the computational, representational, and hardware levels. These three levels specify, respectively, the *function* or *purpose* of the computation, the *representation* of the computation, and how the representation is realised *physically.* While the cognitive approach focuses on the effects of processing of negative emotional information and how this negative processing is performed, the neurobiological approach investigates how depression is realised physically. The two approaches thereby belong to different levels of description: the cognitive approach addresses the two top levels in Marr's model (the representational and computational levels), while the neurobiological approach is concerned with the lowest, hardware level. Through the distinction between different levels of analysis in research on depression we can place the neurobiological and cognitive approaches on their respective levels, which together constitute a

more complete picture of the disorder. The two approaches are therefore not each another's antithesis, but can be synthesised to form a multifactor or multilevel understanding of depression. However, what the cognitive and neurobiological approaches separately do not elucidate is the *relation* between these levels of analysis.

The conceptual and explanatory complexity of depression has recently led to the recognition that an understanding of the neurobiological, the psychological and the social aspects of the disorder as well as their mutual interactions is required. The more recent neuropsychological approach to depression, in which both mind and brain facts are acknowledged, aims to integrate all three levels of description by elucidating the *neuropsychological* mechanisms by which the neurobiological and cognitive processes are related. The principal goal is thus to create a unified non-reductionistic understanding of the disorder that encompasses both mind and brain facts as well as their interaction. Through studies of the neural and cognitive components of affective processing in depressed patients and in healthy individuals, in whom certain moods and emotions were induced, the neuropsychological approach has produced many intriguing findings on the relation between the neurobiology and psychology of depression. Brain areas that have been identified as particularly crucial in the processing of emotional information both in health and in disorder are the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, and amygdala; all specialised in different aspects of affective processing. Neuropsychological research has demonstrated that the mind can indeed affect the brain: mood-induction and cognitive therapy can change the transient neural activation patterns and prolonged metabolism in various brain sites. On the other hand, the brain can also affect the mind: manipulation of neurotransmitters can alter social behaviour and the cognitive processing of emotional information. The neuropsychological approach is thus compatible with the philosophical view that mind and brain can be regarded as levels of emergence that interact with one another through both upwards and downwards causation (Popper & Eccles, 1977). The precise causal relations between the two levels of emergence remain uncertain, but converging neuropsychological evidence is beginning to disclose this relation to form a more complete and integrated account of the disorder.

A recent line of neuropsychological research investigating how antidepressants influence the cognitive processing of emotional information in healthy volunteers suggests that clinically efficacious antidepressants have a very similar mechanism of action to cognitive-behavioural therapy: they directly reduce negative and enhance positive biases in emotional processing. This novel interpretation is supported by recent findings, including the ER-fMRI study, which is part of the present dissertation. This study is the first to employ a simultaneous investigation of the effects of antidepressants on the neural activation patterns and cognitive aspects of emotional processing in

healthy subjects. By clarifying how an antidepressant affects both the neural and cognitive processing of self-referent emotional information in healthy volunteers, the study contributes to an understanding of the *neuropsychological* mechanisms linking mind and brain.

Our finding that the SNRI reboxetine reduced neural activation to both positive and negative (compared to neutral) emotional words in the parietal-temporal boundary but additionally increased precuneus activation to positive words suggests a relatively facilitated processing of positive over negative information. In emotional memory, reboxetine increased prefrontal and parietal activation during the recognition of negative words and reduced activation in overlapping areas during the recognition of positive words. Levels of activation in frontal areas are correlated with task difficulty, which suggests that reboxetine may cause difficulties in remembering negative words and facilitate memory for positive words. In agreement with this interpretation, reboxetine-treated subjects were significantly faster to recognise positive versus negative words compared to control subjects. The findings thereby suggest that the early action of reboxetine may be a reduced neural and cognitive processing of negative and increased processing of positive information, which results in 'positive biases' in cognition and memory. This supports the neuropsychological argument that the mechanism of action of antidepressants may be similar to cognitive-behavioural therapy. Antidepressants may thus relieve depressive states over weeks by leading to gradual behavioural adjustments to the more positively perceived environment, greater self-efficacy and more rewarding social interaction.

From a theoretical perspective, the present study promotes a neuropsychological understanding of depression, in which both the neural and cognitive levels of description as well as the relation between the two are encountered. The evidence of interdependence of the different levels of description comprising emotional processing indicates that a complete scientific understanding of affective disorders must address all levels. The long-existing separation and disagreement between the psychological and neurobiological accounts of depression must therefore be synthesised into a more complete multifactor account of the disorder.

The present and earlier research findings on the effects of antidepressants on emotional processing suggest that the development of innovative combination strategies, which bring together the key therapeutic elements of pharmacological and psychological approaches, is a fruitful way forward in the treatment of depression. The need for integration of the cognitive and neurobiological treatments of depression is further supported by evidence that although both treatments are clinically efficient, combination treatments involving elements from both have superior efficacy in some patient groups, both with respect to acute symptom reduction and decrease in relapse rates. The relative superiority of the combination treatments may partly result

from greater compatibility between the understanding of the disorder of the professional sector and the individual (the 'disease' and 'illness' models; Elsass, 1993). Adding psychological elements to the antidepressant treatment of depression may be beneficial in several ways, by improving the 'therapeutic relation' between the therapist and patient. This may increase patient compliance, which is known to be a major problem in pharmacotherapy, and give the patient some conscious strategies and resources for preventing relapse. Further insights into the neuropsychological mechanisms linking the mind and brain in depression will be of crucial value for designing holistic multilevel-treatments that address all levels of the disorder, and for providing a foundation for adapting treatment to individual patients, according to their particular symptom manifestations, physiopathology, and needs. We may thus conclude that the new neuropsychological approach is important for creating an integrated understanding of depression that assigns equal importance to the physical and mental aspects. The importance of this holism was highlighted by the Greek philosopher Plato around 400 BC in the following statement:

> *For you will do me much greater good by putting an end to ignorance of my psyche than if you put an end to an affliction of my body.*
>
> Plato, Hippias Minor (Graham, 1993)

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