The Neuropsychological Effects of Antidepressant Reboxetine in Autobiographical Memory

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Abstract

Backround: The pharmacological treatment of depression has been long established, but the neuropsychological underpinnings of antidepressant drug action remain far from being understood. Autobiographical memory retrieval to a given cue word is one of the information processes that have been associated with depression, as it has been suggested that depressed mood leads to overgeneral autobiographical remembering, but its neuropsychological interaction with antidepressant drug action has not been formally assessed.

Method: A single oral dose of the antidepressant reboxetine or placebo was administered to 24 healthy volunteers. Effects on the neural response to emotional autobiographical remembering were assessed using functional magnetic resonance imaging (fMRI). The specificity of the memories was assessed after the scan using the Autobiographical Memory Test (AMT, Williams & Broadbent, 1986), a cue-word paradigm.

Results: The functional imaging data revealed significant differences in the recall of negative autobiographical memories under acute antidepressant action that involved activations in the right insula and various areas of the frontal gyrus. Additionally, brain areas that are implicated differentially in the processing of negative versus positive autobiographical memories were identified. These activations involved the cerebral cortex and were largely confined to limbic or paralimbic regions. The behavioural measures were not affected by the administration of a single dose of reboxetine.

Conclusion: This study was the first fMRI study to investigate the neural circuity of emotional autobiographical memory by using the AMT in healthy

volunteers and to examine how this circuity is modified by the administration of a single oral dose of the antidepressant reboxetine. The findings support the involvement of a widely distributed set of brain regions in the processing of autobiographical remembering, which are distinct for the re-activation of positively and negatively viewed autobiographical episodes. Moreover, they provide a basis for a better understanding of the neurobiological mechanisms involved in emotional processing under acute antidepressant administration.

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Abbreviations

ACC	Anterior Cingulate Cortex
A□T	Autobiographical Memory Test
ASD	Acute Stress Disorder
BDI	Beck Depression Inventory
BET	Brain Extraction Tool
BFS	Befindlichkeits Scale
BOLD	Blood Oxygenation Level Dependent
BPD	Borderline Personality Disorder
DSMV-IV	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electoengephalogram
ERPs	Event Related Potentials
EVs	Explanatory Variables
FEAT	FMRI Expert Analysis Tool
FILM	FMRIB's Improved Linear Model
FLAME	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's Linear Image Registration Tool
FMRI	Functional Magnetic Resonance Imaging
FMRIB	FMRI of the Brain
FSL	FMRIB's Software Library
FWHM	Full-Width-Half-Maximum
GML	General Linear Model
ICD-10	International Classification of Mental and Behavioural Disorders
MAOIs	Monoamine Oxidase Inhibitors
MBCT	Mindfulnes-Based Cognitive Therapy
MCFLIRT	Motion Correction FLIRT
MRI	Magnetic Resonance Imaging

NART	National Adult Reading Scale
OCMR	University of Oxford Centre for Clinical Magnetic Resonance Research
PET	Positron Emossion Tomography
PTSD	Post Traumatic Stress Disorder
RT	Recall Time
SNRIs	Selective Norepinephrine Reuptake Inhibitors
SPSS	Statistical Package for the Social Sciences
SSRIs	Selective Serotonine Reuptake Inhibitors
STAI	Stait-Trait Anxiety Inventory
TCA	Tricyclic Antidepressants
TE	Echo Time
TR	Repetition Time
VAS	Visual Analogue Scale

Chapter 1
Introduction

The pharmacological treatment of depression has been long established and it has proven to be effective for a large number of patients (Kent, Coplan & Gorman, 1998). Yet, the neuropsychological underpinnings of antidepressant drug action remain far from being understood. It has been argued in that respect that antidepressants "may work in a similar manner to that of psychological treatments that aim to redress negative biases in information processing" (Harmer, Hill, Taylor, Cowen & Goodwin, 2003). Autobiographical memory (AM) retrieval to a given cue word is one of those information processes that have been associated with depression and are considered to play a key role to its maintenance and resolution, but its interaction with antidepressant drug action has still not been formally assessed.

1.1 Depression –a brief overview

Depression is a widely-occurring recurrent illness, with estimated life prevalence rates as high as 17%, while the recurrence of depression after recovery from an episode appears to be between 75%-80% (Angst, 1992; Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen & Kandler, 1994).

According to the ICD-10 (World Health Organization, 1993), in typical depressive episodes the individual suffers from depressed mood, loss of interest and enjoyment and reduced energy leading to increased fatigue and diminished activity. Other common symptoms are reduced self esteem and confidence, ideas of guilt and unworthiness, disturbed

sleep, reduced concentration and attention, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide and diminished appetite (also see the Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV) classification, compiled by the American Psychiatric Association (1994), for a similar definition).

1.2 Depression from the cognitive perspective

Cognitive theories of depression attempt to explain the information processing strategies that could play a role in its aetiology, maintenance and recovery. They predict that in all levels of processing (perception, attention and memory) mood congruent biases are manifested by depressed patients.

In his schema based "Cognitive Distortion" model of depression, Beck (1976) proposes that the way we process information is governed by structures called *schemata*. Beck defined schemata as "relatively stable cognitive patterns which form the basis for the regularity of interpretations of a particular set of situations". When the schemata focus on beliefs about the self, the world and the future (the cognitive triad) in a negative way, this causes and maintains depression. Schemata filter stimuli in such a way that schema-congruent interpretations are imposed on ambiguous information and that the access to schema-consistent memories is facilitated. Treatment consists of correcting faulty or illogical thinking by repeatedly confronting cognitive schemata and therefore levelling out negative bias in information processing (Cook, 1996).

A related theory is Teasdale's Differential Activation Hypothesis (1988), which is a review of Bower's network theory (1987). According to this theory, emotion nodes are activated in memory by environmental

stimuli, resulting in increased activation of associated nodes. Entering any particular emotional state (e.g. depression) will enhance the salience of information congruent with that emotion through the spreading activation phenomenon. Again, therapy consists in trying to eliminate this cognitive bias.

Memory biases are therefore of particular importance for the generation and maintenance of psychological disorders such as depression. It has even been stated that, "in principle, one could cure psychological disorders if the memories giving rise to them could be replaced with more pleasant and/or self-assured ones" (Loftus, cited in Tryon, 1999).

1.3 Depression from the neurological perspective

Although the precise neurobiological underpinnings of depression remain unclear, evidence suggest that the activities of the monoamine systems and their modulators in the brain and the central nervous system play an important part in the pathogenesis and resolution of depression. The leading hypothesis on depression aetiology is therefore the *monoamine hypothesis*, first put forward 30 years ago, which states that depression results from a central nervous system deficiency of monoamine function (Hirschfeld, 2000; Leonard, 2000; Möller, 2000). There are three key monoamine neurotransmitters: norepinephrine, serotonin and dopamine. Dysfunction in one or more of these neurotransmitter systems is thought to result in depression, but the specific nature of this dysfunction is unclear and it is likely to vary among patients. The monoamine hypothesis has led to another form of treatment for depression, apart from cognitive therapy: the pharmacological treatment via antidepressant drugs.

The majority of currently available antidepressants are thought to exert their therapeutic effects through altering the synaptic concentrations of monoamines. The mechanisms of their action are still not clear, but they involve increased levels of norepinephrine and serotonin or both at postsynaptic neurons by blocking their re-uptake or metabolism at pre-synaptic terminals (for a review on depression aetiology and antidepressant drug action see Möller, 2000 and Reid, 2001).

A newly developed selective norepinephrine reuptake inhibitor is *reboxetine*. Reboxetine appears to have almost no pharmacological activity other than patently blocking the reuptake of norepinephrine (Delgado & Michaels, 1999). Clinical studies have shown that reboxetine is highly effective for the treatment of major depression (Moller, 2000; Scates & Doraiswamy, 2000; Schatzberg, 2000), both in the short (4-8 weeks) and long term (up to 12 months) treatment and that the therapeutic effect is maintained for at least up to one year (Montgomery, 1997). Additionally, reboxetine is effective in all grades of depression, as well as in elderly patients (Montgomery, 1997; Versiani, Mehilane, Gaszner & Arnaud-Castiglioni, 1999; Venditti, Arcelus, Birnbaum, Greenberg, Barr, Rowland & Williamson, 2000; Montgomery, Ferguson & Swartz, 2003). Reboxetine is well tolerated, having few side effects, with insomnia, sweating, constipation and dry mouth being the most commonly reported (Versiani et al., 1999; Scates & Doraiswamy, 2000). It is not cardiotoxic and it is not associated with an increased risk of seizures or of orthostatic hypotension, it has a low potential for drug interactions and causes no significant impairment of cognitive or psychomotor functioning as well as no increase in suicidal ideation (Hindmarch, 1997; Montgomery, 1998; Tanum, 2000). Further, it appears to improve social functioning (Venditti et al., 2000). Therefore, "the level of efficacy and apparently favourable tolerability

profile makes reboxetine an important alternative in the medical treatment of depressive illness" (Tanum, 2000).

1.4 Autobiographical memory and depression

A wide variety of terms and definitions are used when describing autobiographical memory (AM). While some authors focus on the temporal-spatial aspect of AM (Fitzgerald, 1981), others emphasize on the association with the "self" (Barclay, 1986, 1996; Brewer, 1986, 1996, 1998; de Renzi, Liotti & Nichelli, 1987; Conway, 1996; Swales, 1997). The definition proposed by de Decker, Hermans, Raes & Eelen (2003) is very similar to the one used by Nelson (1993) and Swales, Williams & Wood (2001) and combines both aspects. According to them, "Autobiographical memory is defined as the memory for personally experienced events that (a) can be retrieved within temporal and spatial relation toward other events and (b) are relevant for the self-concept because they form the individuals' history of life". Tulving (1983) has given the following definition: "Autobiographical memory consists of the recall of events related to one's life and belongs to the episodic memory category", whereas Greenberg & Rubin (2003) define AM as "a memory of a personally experienced event that comes with a sense of recollection or reliving"

AM has been proposed to be organized in a three-level hierocracy: (a) the first level contains memories of periods of life measured in years or decades; (b) the second level corresponds to general memories, such as repeated events distributed in time, measured in days, weeks or years and (c) the third level comprises rare and specific events measured in minutes or hours (Kolodner 1983; Conway & Bekerian, 1987). Such an organization

lends itself to the distinction between general and specific memories on the basis of the frequency of events.

A well-known aspect of AM function in depression is overgeneral memory. In the case of AM, overgenerality was first observed by Williams and Broadbent (1986), when they asked controls and suicide attempters to retrieve specific memories related to a given word. In this study, as well as in the work that followed and will be presented further, memory specificity was tested by a cue word paradigm, known as the Autobiographical Memory Test (AMT; Williams & Broadbent, 1986). For each word in a set of cue words (positive, negative and, in some studies, neutral) participants are asked to retrieve a specific memory that this word reminds them of. A specific memory, as defined by Williams and Broadbent (1986), refers to an event that has happened at a particular place and time and has lasted no longer than a day ("When I turned 18 my father bought me a car" would be an example of a specific memory in response to the cue word "happy".). If subjects respond with a memory that is not specific, they are prompted to do so. The authors found a remarkable difference in the memory retrieval style between the two groups: more than the control group, the suicide attempters responded with overgeneral memories that referred to events that happened repeatedly (categoric memories, e.g. "every time my grandmother used to take me to the park") or events which lasted longer than a day (extended memories, e.g. "the time I lived in Paris"). Subsequent research showed that overgeneral memories were more often categoric than extended memories (Williams, 1996).

Further studies using the AMT showed that the overgenerality of autobiographical memories is not a unique characteristic of suicidal patients. Overgeneral autobiographical memories have been found in

patients with depression, (Kuyken & Dalgleish, 1995; Goddard, Dritschel & Burton, 1996; Brewin, Watson McCarthy, Hyman & Dayson, 1998; Moore, Watts & Williams, 1988; Williams & Scott, 1988; Scott, Stanton, Garland & Ferrier, 2000; Wessel, Meeren, Peeters, Arntz & Merkelbach, 2001; Nandrino, Pezard, Posté, Réveillére & Beaune, 2002 and Williams, 1996 for a review), in Post Traumatic Stress Disorder (PTSD) (McNally, Litz, Prassas, Shin & Weathers, 1994; McNally, Lasko, Macklin & Pitman, 1995) and in individuals with a history of trauma (Kuyken & Brewin, 1995; de Decker et al., 2003; Hermans, den Broeck, Belis, Raes, Pieters & Eelen, 2004). Subsequent research found that overgeneral AM can be also found in a wide range of clinical problems, such as Acute Stress Disorder (ASD) (Harvey, Bryant & Dang, 1998), Borderline Personality Disorder (BPD) (Jones, Heard, Startup, Swales, Williams & Jones, 1999) and paranoid delusions (Kaney, Bower-Jones & Bentall, 1999).

In the light of the above findings, one could jump to the conclusion that overgeneral autobiographical memory is a common characteristic of the people that suffer from any kind of psychiatric disorder. However, this conclusion would not be a valid one. As de Decker et al. (2003) suggest, "most of the results that were observed in studies with other patient groups can be explained by the comorbidity of an underlying depressive disorder or a history of trauma". In fact, a clear relation between overgeneral AM and depression has been observed in many studies (Wilhelm, McNally, Baer & Florin, 1997; Wessel et al., 2001). Moreover, overgeneral AM has not been found in patients who suffer from anxiety disorder (Richards & Whittaker, 1990; Burke & Mathews, 1992; Wilhelm et al., 1997; Levy & Mineka, 1998; Wessel et al., 2001) -an exception to the pattern of overgeneral autobiographical memories in psychiatric disorders. Further, the findings of a meta-analysis of 14 studies contacted by van

Vreeswijk and de Wilde (2004) confirm that depressed mood moderates the recall of overgeneral memories.

This cognitive characteristic of overgenerality in depression has been shown to be open to modification. In the study by Williams, Teasdale, Segal and Soulsby (2000), formerly depressed patients were treated either by standard psychological relapse prevention treatment or by Mindfulness-Based Cognitive Therapy (MBCT). The patients that were treated with MBCT showed a significant reduction in overgeneral memories, compared to those treated by standard psychological treatment. Moreover, another study by Watkins, Teasdale and Williams (2000) that used decentering instructions (Socratic questions designed to facilitate viewing moods within a wider perspective) in contrast to ruminating instructions, observed that decentering instructions produced momentary decreases in the proportion of categoric memories.

Apart from the overgenerality issue, some studies also addressed the issue of the latency of recall. Williams and Broadbent (1986) in their previously mentioned study with the suicide attempters found that the latter took longer than controls to retrieve a memory when given a positive cue word, but were comparable to controls in latency when responding to negative cue words. Williams and Dritschel (1988) and Kuyken and Brewin (1995) however failed to replicate this result and found no overall difference in the speed of response in a parasuicide group and in a group of depressed women respectively when compared to controls, but Evans, Williams, O'Loughlin and Howells (1992) did reproduce the result with another sample of parasuiciders.

Thus, there is a clear relationship between overgeneral recall of AM and depressed mood, whereas the latency in recall of autobiographical memories is still an issue that needs to be further investigated.

1.5 The neural basis of autobiographical memory

The basic neural mechanism of autobiographical memory (AM) includes the parallel storage of information in a set of independent neural systems, the selective retrieval and reaggregation of this dispersed information within an appropriate spatiotemporal context and the organization of this aggregate by a narrative (Jacobs & Nadel, 2000). Therefore, there is no single brain system specialized for the purpose of storing complete autobiographical memories, but instead these systems are distributed throughout the brain (Lashley,1950; Luria 1966; Fuster, 1995; Toth & Hunt,1999; Conway, 2001; Greenberg & Rubin, 2003).

Most theories of memory claim that memory requires an interaction between medial temporal lobes, frontal lobes and the rest of the cortex (Conway & Pleydell-Pearce, 2000; Damasio, 1989; Fuster, 1995; Kopelman, 2000; Kopelman & N.Kapur, 2001; Mayes & Roberts, 2001; Markowitsch, 2000; McClelland, McNaughton & O'Reilly, 1995; McDonald, Ergis & Winocur, 1999; Murre, 1999; Murre, Graham & Hodges, 2001; Shastri, 2002; Squire, 1992). In the case of AM in particular, its neural correlates are known to primarily comprise areas of the prefrontal cortex, the medial and lateral temporal cortex, as well as the posterior cingulate and retrosplenial cortex (Cabeza & Nyberg, 2000; Conway & Pleydell-Pearce, 2001; Piefke, Weiss, Ziles, Markowitsch & Fink, 2003; Graham, Lee & Patterson, 2003; Greenberg, Cooper, Rice, Cabeza, Rubin & LaBar, 2003). Moreover, closely linked to AM recall are the retrieval activations in the cuneus and precuneus regions which have been attributed to memory related imagery (Fletcher, Frith, Baker, Shallice, Frackowiak & Dolan, 1995; Fletcher, Frith, Grasby, Shallice, Frankowiak & Dolan, 1995; Fletcher, Shallice, Frith, Frackowiak & Dolan, 1996) and retrieval success (Kapur, Craik, Jones, Brown, Houle & Tulving, 1995) and the retrieval activations in

the cerebellum which have been attributed to self-initiated retrieval operations (Bäckman, Almkvis, Andersson, Nordbrg, Winblad, Reineck & Långstrom, 1997; Cabeza, Kapur, Craik, McIntosh, Houle & Tulving, 1997) There is also a substantial literature on case studies of impairments of AM that demonstrates that lesions in frontal, temporal and occipital lobes, as well as in midbrain structures in hippocampus, amygdale, fornix and the thalamus disrupt AM (for a review see Conway & Fthenaki, 2000 and Greenberg & Rubin, 2003).

AM is typically emotionally valenced (Markowitsch, 1998, 2000; Dolan, Lane, Chua & Fletcher, 2000) and both the encoding and the retrieval processes have been found to be influenced by its emotional content (Holmes, 1970; Brewer, 1988; Bower, 1992). However, the experimental investigation of the neural basis of emotional AM remains a challenge to neuroscientists, due to the highly complex interaction of cognitive and emotional processes. There have been some interesting findings, though, that point to the importance of the frontal cortex for affect-laden autobiographical memories (Lane, Reiman, Ahern, Swatz & Davidson, 1997; Lane, Fink, Chau & Dolan, 1997; Lane, Reiman, Bradley, Lang, Ahern, Davidson & Scwartz, 1997; Reiman, Lane, Ahern, Swarch, Davidson, Friston, Yun & Chen, 1997; Phan, Wager, Taylor & Liberzon, 2002, Markowitsch, Vandekerchove, Lanfermann & Russ, 2003) as well as to the existence of distinct neural nets for the re-activation of positive and negative autobiographical episodes (Markowitsch et al., 2003). In that respect, a meta-analysis by Phan et al., (2002) concluded that "no specific brain region was consistenly activated for the majority of studies, across individual emotions and induction methods, suggesting that no single brain region is commonly activated by all emotional tasks".

1.6 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a technique based on magnetic resonance imaging (MRI). The latter provides images of the distribution of hydrogen atoms in tissue water. The technique relies on the use of magnetic fields to distort the behaviour of atoms, and the information gained on how long the atoms take to recover from this distortion is used to create an anatomical image of the brain. An opening for MRI in the area of functional brain imaging emerged when it was discovered by Fox and colleagues that during changes in neural activity there are local changes in the amount of oxygen in the tissue (Fox & Raiche, 1986; Fox, Raiche, Mintum & Dence 1988). More specifically, as neurons become active, they increase their use of oxygen which causes a temporary dip in the amount of oxygen in the blood. At the same time, the neurons signal the blood vessels to dilate to increase blood flow. The resulting increase in blood flow brings more oxygen to the area than the neurons can actually use and thus produces a relative increase in local oxygen. Now, the amount of oxyhemoglobin is higher than the amount of deoxyhemoglobin, whereas before the neural activation they were about equal. These changes in the oxygen content of the blood alter the magnetic properties of the blood's water, affecting the MRI signal. By combination of this observation with a much earlier observation made by Pauling and Coryell that changing the amount of oxygen carried by hemoglobin changes the degree to which hemoglobin disturbs a magnetic field, Ogawa et al. were able to demonstrate that in vivo changes of blood oxygenation could be detected by MRI, introducing us to functional MRI (Pauling & Coryell, 1936; Ogawa et al., 1990). The fMRI method is therefore based on the blood-oxygen-level-dependent (BOLD) signal (for

further details about the underlying basis of the fMRI and references, see http://www.fmrib.ox.ac.uk).

Several caveats of this ground breaking methodology should not be ignored. Although fMRI offers greater spatial resolution than techniques such as those employing event-related potentials (ERPs), it does not share the same temporal resolution as a haemodynamic response will always be slower than a neural one. Moreover, as it measures haemodynamic rather than neural response it does not allow for precise characterization of the neuronal activity taking palace. Despite these disadvantages, fMRI is now one of the most widely used methods for investigating which brain regions are activated by the performance of various cognitive tasks and it is the method of choice for the current study.

1.7 Aims and objectives

Previous work suggests that a single dose of the antidepressant reboxetine increases emotional processing in tasks measuring perception and memory in healthy volunteers (Harmer et al., 2003). These effects suggest a mechanism by which antidepressant drugs may work that is compatible with cognitive theories of depression, which claim that negative biases of information processing play an important role in maintaining the symptoms of depression, as mentioned previously. Namely, it is suggested that antidepressant drugs directly modulate the neural processing of emotional and social information to enhance positive processing and therefore remediate the negative biases in depression.

The present study aims to explore these effects further by using functional MRI and by focusing in biases previously observed in AM by the AMT. AM has been shown to be characterized by an overgeneral

retrieval style in depressed mood and this specificity has been found to be modifiable by cognitive interventions. This study aims to investigate whether reboxetine acts in the same manner as cognitive therapies and manages to reduce AM overgenerality. Moreover, it has been suggested by some studies that there might also be a difference in recall times of positive and negative autobiographical memories and this will be investigated as well.

Furthermore, the study aims at exploring the neural basis that is distinct in the recall of positive and negative autobiographical memories under antidepressant action and specifically under a single dose of the antidepressant reboxetine. The latter is the primary purpose of the study. An additional goal is to contribute towards the indentification of the brain areas that are implicated differentially in the processing of negative versus positive autobiographical memories by using the AMT paradigm.

The present study is an exploratory study as it aims to investigate for the first time the neural basis of the AMT and its modulation by antidepressant drug administration. It is hypothesised that positive and negative emotional recall will involve different components within the limbic system and that these components will be differentially affected by antidepressant administration.

Chapter 2
Method

2.1 Participants

Twenty-four healthy volunteers participated in the study (14 males, 10 females). All subjects underwent medical and psychological screening before proceeding with the study. Exclusion criteria included a current or previous history of psychiatric disorder, substance abuse and serious physical and neurological problems. Exclusion criteria specific to the fMRI scanning also included a heart pacemaker, mechanical heart valve, other metal implants such as an aneurysm clip, hip replacement and possibility of pregnancy. Participant's eyesight needed to be normal or corrected, since it is not possible to wear normal glasses in the scanner. All participants were free of medication apart from contraceptive pills. For the participants who passed the screening procedure, a letter was send to their GP two weeks prior to their participation in the study to ask for his/her permission. Only volunteers whose English was sufficient to understand the task and instructions were included in the study. The participants were reimbursed for their time and traveling expenses.

The study was undertaken with ethical approval granted by the Oxfordshire Psychiatric Research Ethics Committee (OPREC: O03.045)

2.2 Drug

Reboxetine is a selective norepinephirine inhibitor licensed for the treatment of disorders such as depression and is given in a daily dose of 8-15mg over a period of weeks or months. The dose that was given for the

purposes of the present study was a single oral dose (4mg) on one day. Some side effects such as nausea, sleep problems, dry mouth, and temporary sexual difficulties are known to possibly occur with this drug.

Volunteers were given either reboxetine or a matched placebo in a double-blind between groups design.

2.3 Task –Autobiographical Memory Test

A version of the Autobiographical Memory Test (AMT, Williams & Broadbent, 1986) was used. It consisted of eight emotional words (four positive and four negative) and four neutral words. The cues were presented visually on the screen in a fixed order with alternative positive, negative and neutral words (namely *nice, alone, agility, tender, insult, carry, kindness, dismal, client, sweet, nasty, ginger*). Participants were asked to recall a specific memory, i.e. a memory for an event that lasted less than a day and occurred at a particular time and place, in response to each cue word and were allowed 20 seconds for each response, even though they were unaware of this time limitation. They were asked to press a button as soon as they had come up with a specific memory and dwell on that memory until the word disappeared from the screen. After each of the words, a nonsense-word (e.g. *Hwvbxaqda, Aopexma, Iuopwvaq*) appeared on the screen and the participants were asked to press a button as soon as they had silently counted the number of letters in the non-word. This was a way of displacing the memory so that the participants would discontinue thinking about the same memory. A training session took place outside the scanner and the participants practiced with three neutral words (namely *newspaper, rain*, and *milk*) and were encouraged to keep searching for a memory until they reported a specific one.

2.4 Physiological measures

Saliva samples were taken to check for cortisol levels in the saliva. Previous work has shown that a single oral dose of reboxetine significantly increases salivary cortisol (Hill, Taylor, Harmer & Cowen, 2003). Therefore, cortisol levels were used as a simple and relatively non-invasive indicator of reboxetine absorption.

2.5 Instruments

The following questionnaires were used to assess IQ, mood and subjective state of the participants (see Appendix):

National Adult Reading Test, second Edition (NART; Nelson, 1982). The NART is a simple reading test that involves pronouncing 50 unusual English words which do not follow normal speech patterns, such as "ache" and "thyme". People who pronounce most of the words correctly tend to have intact mental functioning and verbal intelligence skills. Therefore, this test was administered as a measure of the participants' IQ, to ensure that the two groups were well matched.

Visual Analogue Scale (VAS; Bond & Lader, 1974). The VAS is a self-report device which consists of horizontal lines, 117mm in length anchored by "not at all" and "extremely" in the left and right pole respectively. Participants are asked to mark on the line the point that they felt represented best their perception of their current state. The following emotional states are used: *happiness, sadness, fear, disgust, alertness, anxiety.*

Beck Depression Inventory (BDI; Beck & Steer, 1993). Depressed mood was assessed by means of the Beck Depression Inventory, which consists of 21 four-choice statements. Participants are asked to mark the statements that describe best how they felt during the previous week.

State-Trait Anxiety Inventory (STAI; Spielberg, Gorusch & Lushene, 1970). The State-Trait Anxiety Inventory is a validated generic measure of anxiety. The two parts of this inventory consist of 20 items each and assess state and trait anxiety, respectively. State anxiety refers to situational feelings such as apprehension, tension, nervousness and worry, whereas trait anxiety refers to general feelings of anxiety -proneness.

Befindlichkeits Scale (BFS; Von Zerrsen, Strian & Scwarz, 1974). The Befindlichkeits Scale is a 28-item self-reporting inventory, which was used to provide additional measures of variations in normal mood and energy. It gives two scores: the *total* score includes the general score while the *energy* score is a measure of the items relating to motivation and alertness. Participants are asked to select between two contesting adjectives that describe their current emotional state.

2.6 Procedure

The study took place using between groups, double-blind, randomised design with two groups: (a) reboxetine (b) matched placebo capsule. The randomisation code was drawn up by a researcher who was not involved in this study and the information was kept in a sealed envelope. Since reboxetine did not cause subjective state changes or significant side effects it is unlikely that the researcher guessed allocation. These groups were matched on age (mean=28 years, SD= 3 for the reboxetine group and mean =26.5 years, SD= 4.5 for the placebo group), gender, IQ (NART score mean=118.2, SD= 9.2 for the reboxetine group and mean= 113.7, SD=8.2 for the placebo group) and emotional state (Trait Anxiety Inventory score mean=30.5, SD=3.8 for the reboxetine group and mean=31.91, SD=5.6 for the placebo group and BDI score mean= 1.25,

SD=1.8 for the reboxetine group and mean=3.42, SD=4.5 for the placebo group).

The participants attended the hospital having fasted from breakfast to ensure the absorption of the drug. They were briefed on scanner safety and gave written consent before the study began to take place. The NART, the BDI and the Trait Anxiety Inventory were administered at baseline, i.e. before the administration of the drug. Mood and subjective state were monitored at baseline, 90 minutes (before entering the scanner) and 300 minutes (at the end of the study) and saliva samples were also taken at the same times. Psychological testing begun 2 hours after the administration of the drug, in line with the pharmacokinetics of the reboxetine, for which peak drug levels are attained within 2 hours (Dostert, Benedetti & Poggesi, 1997). The scan lasted approximately 1.15 hours, involving tasks other than the autobiographical memory task as well.

For the testing phase the participants were placed inside the scanner and made as comfortable as possible. They were given time to acclimatize to the scanning environment and they were given a panic button to press should they had felt unwell during the scan. All were given prism glasses that allowed them to see a screen placed at the end of the scanner on which the task stimuli were presented and their right hand was placed on the button box. Foam pads were placed around the participants' heads in order to hinder head movements and earplugs to minimise the noise in the scanner in order to protect their hearing and avoid distraction, as well as MR-compatible headphones for communication via inter-com. The participants were reminded of what each task demanded before it was launched. The light was turned off in the scanner room during the experimenter to minimise distraction. Participants were asked to maintain visual fixation in the centre of the screen at all times.

After exiting the scanner, the participants were asked to report the memories that they had recalled for each cue word during the scan and their responses were recorded.

Participants were debriefed about the aims of the study after its completion.

2.7 MRI acquisition

Imaging was performed at the OCMR (University of Oxford Centre for Clinical Magnetic Resonance Research) Unit at the John Radcliff Hospital in Oxford by using a whole body 1.5 Tesla scanner (Siemens Sonata Medical Systems) with a standard quadrature birdcage head coil. The structural scans were acquired with a 3D T1-weighted FLASH sequence for each subject (scan parameters: repetition time (TR) of 12ms, repetition time (TE) of 5.6ms, flip angle = 19o, 1mm isotropic voxels, matrix = 256*160*208; elliptical sampling, orientation = coronal, acquisition time = 5m14s). Functional images were acquired in the form of T2*-weighted echo-planar imaging (EPI) slices (parameters: TE of 50ms, TR of 3s, 30 slices at 3.0x3.0x3.0mm). The first 4 images of each task session were discarded to allow T1 equilibrium to be reached.

2.8 Statistical analysis

2.8.1 Physiological data analysis

Salivary cortisol was measured with an in-house double antibody radioimmunoassay. The intra and inter assay coefficients of variation were 3% and 10%, respectively, and the lower limit of detection was 0.5 nmol/l.

2.8.2 Behavioural data analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS) software program (version 12.0).

The recall times of the autobiographical memories, as shown by the pressing of the button in the scanner by the participants as soon as they had come up with a memory, were analysed using a two-way analysis of variance (ANOVA) with group (reboxetine and placebo) and mean recall time for each of the valence of the cue words (positive, neutral and negative) as factors.

Mood scales were analysed using repeated measures analysis of variance with group (reboxetine and placebo) and time of rating as factors.

The specificity of the recalled memories that were reported after the scanner was encoded as follows:

1= Specific memories: memories of events that had occurred in a specific time and place and had lasted less than a day, e.g. "When I was with my son, long time ago, drawing a drawing in his kindergarten", was considered to be a specific memory.

2= (Specific) Extended memories: memories that described a time period rather than lasting less than a day, e.g. "When I visited France with my boyfriend".

3= General memories: repeated events distributed in time, e.g. "When I am sad I picture in my mind a surrealistic picture of an angel who cries alone".

4= Missing data: a. No memory for the cue word.

b. No understanding of the meaning of the word.

c. Inability to retrieve the memory that was recalled in the scanner.

The number of specific responses, i.e. the number of those coded with 1, was the dependent variable (Raes, Hermans, de Decker, Eelen & Williams, 2003). A two-way analysis of variance was used to assess differences between groups in respect to the specificity of the recalled memories.

2.8.3 Imaging data analysis

A block-design fMRI paradigm design was used. Block designs involve "on" and "off" periods. The experimental manipulation takes place during "on" periods and the "off" periods resemble the "on" periods in all aspects apart from the experimental manipulation. More specifically, the "on" periods included the memories for positive, negative and neutral words and the "off" periods were the periods when the participants saw the nonsense-words or where fixating in the centre of the screen. The functional activation images obtained on trials in which the cue words were neutral words were substracted from those aquired when the cue words were positive or negative. In addition, the images of the reboxetine group were compared to the images of the placebo group. The explanatory variables (EVs) were the valence of the cue words (positive, negative and neutral) and the group (reboxetine or placebo) and the dependent variable was the neural activation.

A general linear model (GML) of haemodynamic responses was used. Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.00, part of FSL (FMRIB's Software Library, available at www.fmrib.ox.ac.uk/fsl).

The following pre-statistics processing was applied: motion correction using MCFLIRT (Motion Correction FMRIB's Linear Imaging Tool; Jenkinson, Bannister, Brady & Smith, 2002), non-brain removal using

BET (Brain Extraction Tool; Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM (full-width-half-maximum) 5mm; mean-based intensity normalisation of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma=50.0s). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brayd & Smith, 2001). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05 (Worsley, Evans, Marrett & Neelin, 1992, Friston, Worsley, Frankowiak, Mazziotta & Evans, 1994, Forman, Cohen, Fitzgerald, Eddy, Mintun & Noll, 1995). Registration to high resolution and/or standard images was carried out using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002).

Higher-level analysis, i.e. the group analysis, was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.0 and a (corrected) cluster significance threshold of P=0.05.

Chapter 3

Results

3.1 Physiological measures

The analysis of the saliva samples gave the following results: the main effect of cortisol as well as the interaction between cortisol and the two groups (placebo and reboxetine) were found not to be significant ($F=2.95$, $p=0.06$ and $F=2.18$, $p=0.125$ respectively). Moreover, no significant differences in cortisol levels between the two groups were detected in baseline i.e. before the administration of the drug ($F=0.25$, $p=0.81$). However, a significant difference in saliva cortisol between groups was detected ($F=319.8$, $p<0.0001$). A repeated measures analysis of variance of cortisol differences from baseline with difference in cortisol levels over time (two levels: cortisol levels at 90 minutes after the administration of the drug minus cortisol levels at baseline and cortisol levels at 300 minutes after the administration of the drug minus cortisol levels at baseline) and group as factors was carried out which showed a significant main effect of group ($F=4.37$, $p=0.050$). The results demonstrate clearly that cortisol levels were elevated after the administration of reboxetine when compared to the administration of the placebo

The means and standard deviations of the cortisol levels for the two groups and the three times of measurement are given in *Table 1*.

Group	N	Cortisol Levels Time 1 (nmol/l)		Cortisol Levels Time 2 (nmol/l)		Cortisol Levels Time 3 (nmol/l)	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Reboxetine	12	15.69	6.22	17.48	6.67	14.85	5.29
Placebo	12	15.07	6.05	11.57	4.72	9.29	3.76

Table 1. Means and standard deviations of the cortisol levels for the reboxetine and placebo groups for the three times of measurement. It should be noted that Time 1 refers to baseline, i.e. before the administration of the drug, Time 2 refers to the measure taken 90 min after the administration of the pill and before the participants had entered the scanner and Time 3 refers to the measurement at 300 min after the administration, i.e. after the participants had exited that scanner, as it will in the consecutive tables.

3.2 Behavioral data

3.2.1 Mood assessment

Repeated measures analyses of variance in the State Anxiety Inventory, BFS and VAS (for each emotional state) with group (reboxetine or placebo) and time of assessment as factors revealed no effect of reboxetine on mood or subjective state (for all comparisons $p>0.05$), with the exception of a significant interaction between groups for VAS alertness ($F=6.86$, $p=0.003$). This interaction was significant for time 3, i.e. at 300 minutes ($F= 5.59$, $p=0.027$). Further, a significant effect of time (but not group) for the BFS scores for total and energy was detected ($F=4.3$, $p=0.05$ and $F=6.8$, $p= 0.016$ respectively) *(see Table 2).*

3.2.2 Specificity of recall

Analysis of variance for the specificity of the recalled memories failed to reach a significant level for the differences between the reboxetine and the placebo groups ($F=2.28$, $p=0.14$) (see *Table 3*).

3.2.3 Recall times

One participant from the placebo group was excluded from the recall times (RT) analysis, because her mean response time was 110ms, SD=41ms, which had presumably been so quick due to her pressing the button in error. The RT analysis revealed a main effect of group, though marginal, with the reboxetine group being quicker in its responses ($F= 4.34$, $p=0.05$) (see *Table 4* and *Figure 2*). The main effect of the valence of the cue words as well as the interaction between the valence of the cue words

and the group were found not to be significant though (F=1.765, p=0.197 and F=0.303, p= 0.742 respectively).

Inventory	Time	N	Reboxetine		Placebo	
			Mean	Standard Deviation	Mean	Standard Deviation
State Anxiety	Time 1	12	30.91	6.35	30.41	6.30
	Time 2	12	30.41	7.34	29.66	6.84
	Time 3	12	32.33	9.66	31.41	10.23
BFS Total Score	Time 1	12	17.75	18.65	15.00	8.06
	Time 2	12	11.83	10.88	11.75	6.85
	Time 3	12	18.91	21.54	23.08	11.38
BFS Energy Score	Time 1	12	4.08	3.05	3.50	2.57
	Time 2	12	3.66	2.8	4.08	2.87
	Time 3	12	4.66	3.39	6.41	3.05
VAS Happy	Time 1	12	6.91	1.38	7.05	1.45
	Time 2	12	7.36	2.32	7.37	1.67
	Time 3	12	5.78	2.54	6.52	3.30
VAS Sad	Time 1	12	1.39	1.82	1.09	1.54
	Time 2	12	0.79	1.27	0.35	0.55
	Time 3	12	1.20	1.86	0.94	1.90
VAS Disgusted	Time1	12	0.30	0.50	0.15	0.24
	Time 2	12	0.77	2.03	0.13	0.27
	Time 3	12	0.86	1.57	0.45	1.14
VAS Angry	Time 1	12	0.23	0.47	0.25	0.43
	Time 2	12	0.90	2.07	0.14	0.27
	Time 3	12	0.75	1.27	0.50	1.22
VAS Fear	Time 1	12	1.25	1.99	0.65	0.82
	Time 2	12	0.97	1.72	0.78	1.31
	Time 3	12	0.64	1.02	0.26	0.44
VAS Anxious	Time 1	12	2.02	2.43	1.63	1.87
	Time 2	12	2.03	2.80	1.55	1.50
	Time 3	12	1.32	1.38	0.20	0.33
VAS Alert	Time 1	12	5.97	3.35	4.88	1.93
	Time 2	12	6.51	2.96	5.66	2.11
	Time 3	12	6.20	3.26	1.76	2.07

Table 2. Means and standard deviations of the scores of the reboxetine and placebo groups on the mood scales for the three times of assessment.

Group	N	Total		Positive Cue Words		Negative Cue Words		Neutral Cue Words	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Reboxetine	12	10.25	0.33	3.58	0.66	3.08	0.99	3.66	0.48
Placebo	12	9.16	0.64	3.08	0.99	3.00	0.73	3.25	0.75

Table 3. Mean number and standard deviations of specific memories for the reboxetine and placebo groups in total and for the different valences of the cue words.

Group	N	Recall Time(ms)		Recall Time to Positive Words (ms)		Recall Time to Negative Words (ms)		Recall Time to Neutral Words (ms)	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Reboxetine	12	547	46	586	215	542	182	512	182
Placebo	11	724	73	750	296	763	263	658	281

Table 4. Mean recall times and standard deviations for the reboxetine and placebo group.

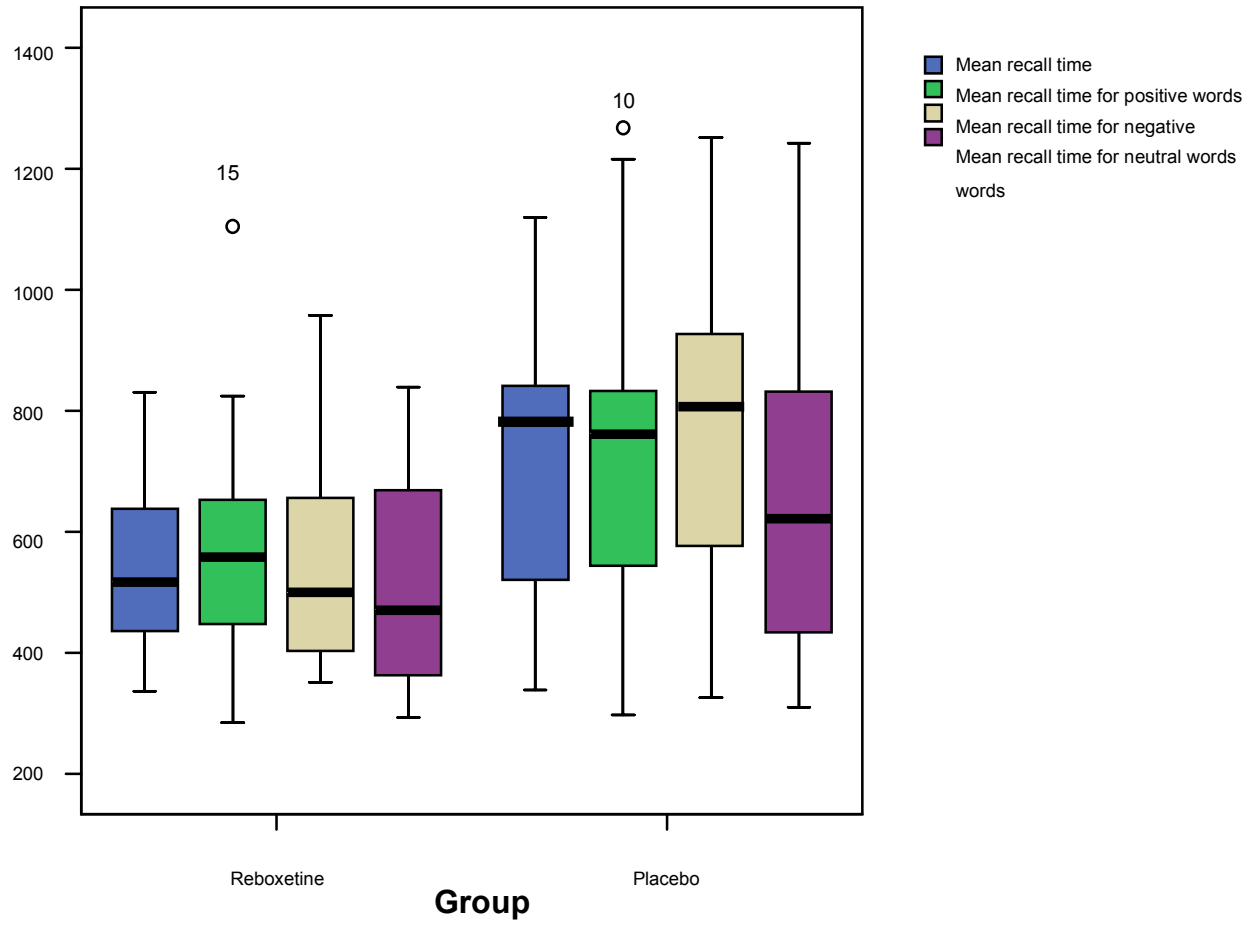

Figure 2. Box plot illustrating the mean response time for each valence condition and mean response time for each group. On the x axis is the group and on the y axis time in milliseconds.

3.3 Imaging data

3.3.1 Main effects of negative autobiographical recall

Activation that represents the effect of the task (autobiographical remembering to a cue word) irrespective of the reboxetine and placebo groups was detected. Activation for negative minus neutral memories was found to be significant in the areas shown in *Table 5* and illustrated in *Figure 3*. These areas consist of the bilateral medial prefrontal cortex.

Estimated Area of Activation	Coordinates			Max Z Peak
	X	Y	Z	
L Medial Prefrontal Cortex	-2	36	56	4.82
Medial Prefrontal Cortex	0	54	32	4.47
R Medial Prefrontal Cortex	6	52	44	4.12
L Medial Prefrontal Cortex	-8	26	58	4.09
L Medial Prefrontal Cortex	-8	30	58	4.06
L Medial Prefrontal Cortex	-12	26	58	3.96

Table 5. Clusters of activation recorded for the group as a whole which were elicited from negative minus neutral autobiographical memory recall. L and R are used to indicate the side of the brain in which these clusters are found. Voxels are 3.0x3.0x3.0mm. Coordinates given are those of the peak voxel within the cluster (in Talairach space).

The following images highlight a number of the clusters of voxels, which were found to be significant for negative minus neutral autobiographical recalling. The images follow normal radiological convention, i.e. the left side of the brain is represented by the right side of an image and vice versa, as it will be represented in every succeeding figure.

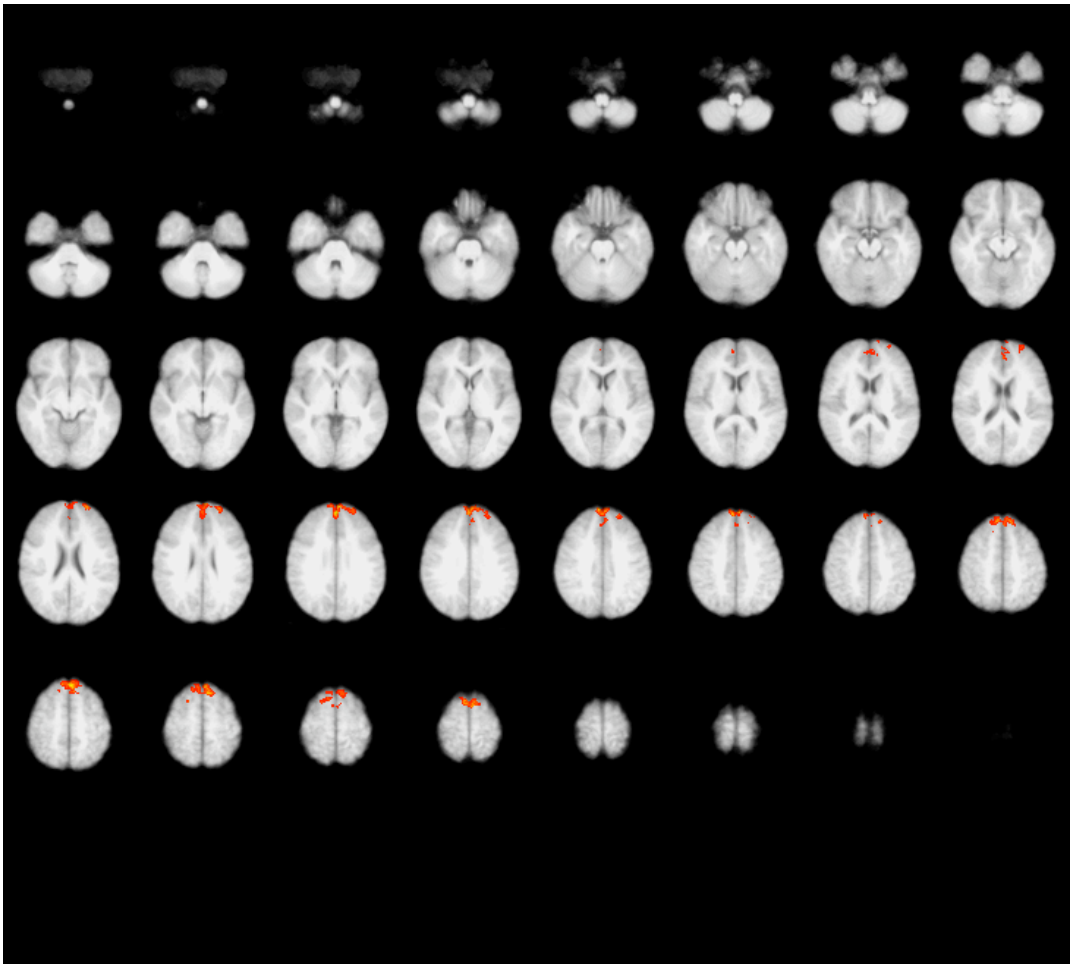

Figure 3. Consecutive axial slices which show group activation for the recall of negative minus neutral autobiographical memories.

3.3.2 Main effects of positive autobiographical recall

Activation for positive minus neutral memories was found to be significant in the areas shown in *Table 6* and illustrated in *Figure 4*. They include bilateral anterior cingulate, the right medial frontal cortex, the left declive, bilateral precuneus, the left cuneus and the right insula.

Estimated Area of Activation	Coordinates			Max Z Peak
	X	Y	Z	
R Anterior Cingulate	4	44	12	5.07
L Anterior Cingulate	-12	28	-6	4.42
R Medial Frontal Cortex	4	54	-4	4.46
L Declive	-28	-64	-18	3.64
L Declive	-28	-68	-16	3.44
L Declive	-34	-62	-18	3.34
L Lingual Gyrus	-22	-62	4	3.35
L Precuneus	-12	-52	32	3.59
L Precuneus	-6	-62	30	3.18
L Precuneus	-16	-46	30	4.05
R Precuneus	2	-58	38	3.09
R Precuneus	12	-60	30	3.19
L Cuneus	-6	-66	32	2.89
R Insula	40	-22	4	3.30

Table 6. Clusters of activation recorded for the group as a whole which were elicited from positive minus neutal autobiographical memory recall. L and R are used to indicate the side of the brain in which these clusters are found. Voxels are 3.0x3.0x3.0mm. Coordinates given are those of the peak voxel within the cluster (in Talairach space).

3.3.3 Main effects of reboxetine in negative and positive autobiographical recall

Activation for memories on trials in which the cue words were negative (minus neutral) in the reboxetine group compared to the placebo group produced significant activation clusters. The location and significance of these areas are given in *Table 7* and are illustrated in *Figure 5*. They include the right insula, the right inferior frontal cortex, bilateral medial frontal cortex and the left superior frontal cortex.

The regions that represent activation for positive memories (minus neutral) in the reboxetine group compared to the placebo group did not survive the strict statistical correction for the whole-brain that was used in this study.

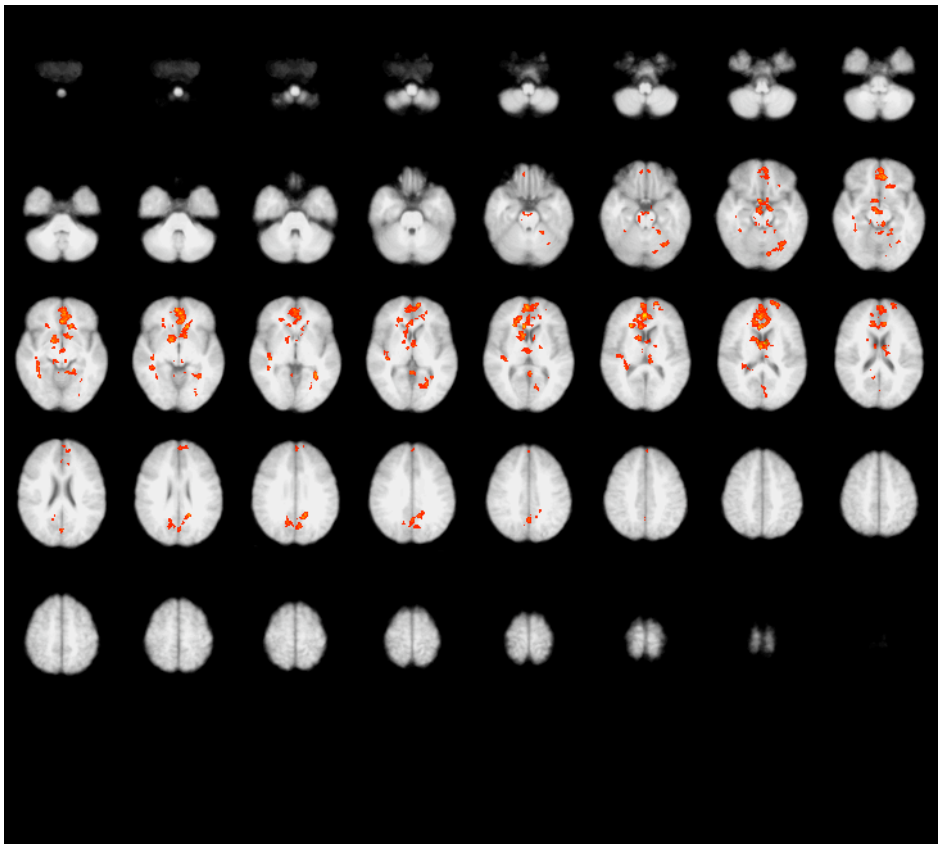

Figure 4. Consecutive axial slices which show group activation for the recall of positive minus neutral autobiographical memories.

Estimated Area of Activation	Coordinates			Max Z Peak
	x	Y	Z	
R Insula	44	10	0	4.29
R Insula	42	-28	14	3.96
R Insula	42	-4	-4	3.84
R Inferior Frontal Cortex	38	20	-8	3.73
R Inferior Frontal Cortex	42	20	-8	3.66
L Medial Frontal Cortex	-28	44	12	4.14
R Medial Frontal Cortex	18	48	-6	3.34
L Superior Frontal Cortex	-20	66	12	3.27
L Superior Frontal Cortex	-26	60	14	4.24

Table 7. Clusters of activation which were elicited from negative minus neutral autobiographical memory recall in the reboxetine group compared to the placebo group. L and R are used to indicate the side of the brain in which these clusters were found. Voxels are 3.0x3.0x3.0mm. Coordinates given are those of the peak voxel within the cluster (in Talairach space).

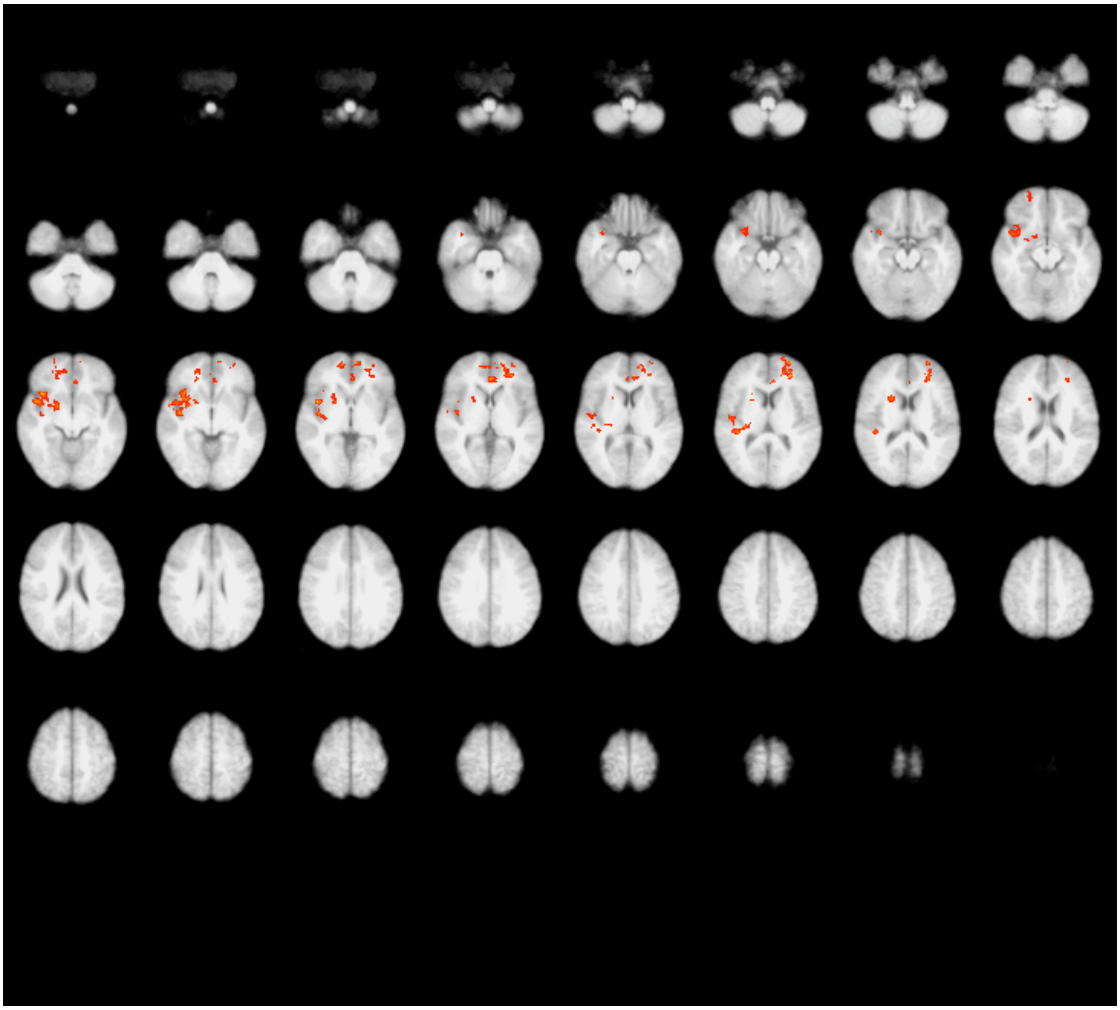

Figure 5. Consecutive axial slices which show group activation for the recall of negative minus neutral autobiographical memories in the reboxetine group compared to the placebo group.

Chapter 4
Discussion

The purpose of the current investigation was twofold. Namely, on the behavioural level the aim was to investigate whether reboxetine acts in the same manner as cognitive therapies and manages to reduce autobiographical memory (AM) overgenerality as well as to explore its effects in recall times of positive versus negative autobiographical memories. On the neural level, the present study aimed at exploring the neural basis that is distinct in the recall of the positive and negative autobiographical memories under acute antidepressant action. An additional goal was to contribute towards the indentification of the brain areas that are implicated differentially in the processing of negative versus positive autobiographical memories by using the Autobiographical Memory Test (AMT) paradigm for the first time.

The analysis of the physiological measure i.e. the salivary cortisol confirmed both that the drug was successfully absorbed by the reboxetine group as well as that the neuropsychological testing was performed at the right time, the latter being two hours after the administration of the drug (Hill et al., 2003). Moreover, the mood assessement analysis revealed no significant mood changes throughout the study for both groups, replicating previous findings that acute administration of antidepressants does not affect mood (Harmer et al., 2003). The significant changes in alertness for the reboxetine group in the mood assessment that took place at 300 minutes after the administration of reboxetine and after the participants had exited the scanner were to be expected, due to the fact that one of the central functions of norepinephrine is in fact improving alertness (Jouvat, Alberede, Lubin & Meyrignac, 1991). Further, a

significant effect of time (but not group) for the BFS scores for total and energy was found, illustrating the fatigue of the participants of both groups at the end of a rather long study.

4.1 Modulating effects of antidepressant drug administration in autobiographical memory

A number of neural regions were identified when comparing the activation on trials in which the cue words were negative (minus neutral) in the reboxetine group compared to the placebo group. These regions included the right insula, the right inferior frontal cortex, bilateral medial frontal cortex and the left superior frontal cortex.

All the above areas, except for the insula, are located in the frontal lobes which are the anterior portion of the cerebral cortex. Indeed, autobiographical remembering has been demonstrated by previous studies as including networks in the frontal lobes, especially during the period that the retrieval starts and even in the pre-retrieval phase, when the cue to begin memory search is being awaited (Conway, 2001; Conway, Pleydell-Pearce & Witcross, 2001; Graham et al., 2003; Piefke et al., 2003). The functional role of the frontal lobes has therefore been claimed to be the search for relevant information and the inhibition of irrelevant ones –it is putatively involved in the selection of one particular association from multiple associations that have been stored at many different times via its interaction with the medial temporal lobes. Yet, the frontal lobes and the medial temporal regions do not themselves provide long-term storage of most sensory data, though they may store connections among modules. Instead, they coordinate the activation among widespread areas of the

cortex and produce a pattern of activation similar to that observed during the original experience (Greenberg et al., 2003).

The medial frontal cortex in particular has been further suggested to be associated with mentalizing i.e. representing one's own and other's mental states ("self-referencial mental activity") (Gündel, O'Connor, Littrell, Fort & Lane, 2003; Markowtsch et al., 2003). Moreover, the frontal lobe has been claimed to be a distinct neural substrate for mood-congruent processing biases in performance: "The medial and prefrontal regions may play a key role in mediating the interaction between mood and cognition in affective disorder" (Elliott, Rubinsztein, Sahakian & Dolan, 2002). This hypothesis lends itself to the present findings.

The other brain area that was activated under the negative AM condition in the reboxetine group compared to the placebo group was the insula, located within the cerebral cortex, beneath the frontal, parietal and temporal opercula, where parts of the corresponding lobes extend over the surface of the insula. This brain structure has been previously linked as a component of emotional behaviors by studies ranging from symptom provocation in anxiety-disordered patients to studies of emotion activation in normal individuals and to pharmacologically manipulated emotion (Davidson & Irvin, 1999; Fossati, Hevenore, Graham, Grady, Keightley, Craik & Mayberg, 2003). Namely, it has been associated with anxiety, depression and provocation of feeling of sadness (Mayberg, Liotti, Branna, McGinnis, Mahurin, Jerabek, Silva, Tekell, Martin, Lancaster & Fox, 1999) and the right insular has been specifically associated with grief (Gündel et al., 2003). The insula is well established as an area specialized for the processing of visceromotor information (Augustine, 1996) and it has also been suggested that it is generally involved in the integration of internal states (Fossati et al., 2003). It is known to receive afferents from several

major autonomic regions and to send efferents to a number of brain regions that play a critical role in regulating autonomic responses that accompany emotion, such as the central nucleus, the amygdala and the lateral hypothalamus.

However, it is not yet clear if the insular activation is primarily a function of visceral afferent feedback or rather is produced by the insular cortex issuing commands for autonomic change (Davidson & Irvin, 1999). One could thus claim that the differential activation of this brain area in the reboxetine group when compared to the placebo group could be informative of a greater difficulty to recall negative autobiographical memories or it could even demonstrate the recall of more specific representations.

4.2 Neural locus of autobiographical memory

Significant differences in the activation patterns that represent the activation for positive and negative AM after the substraction of the activation for neutral AM irrespective of the drug were also detected. To the best of the author's knowledge this is the first study that substracts neutral autobiographical memories from positive and negative memories. Piefke et al. (2003) and Markowitsch et al. (2003) have also investigated whether retrieval of both emotive forms of AM engages the same or different neural net as well, but they both substracted the positive and negative conditions from each other.

The activation for positive minus neutral AM included many areas that are known to mediate emotion, namely the right medial frontal cortex and the right insula whose mediating role has been discussed above as well

as bilateral anterior cingulate, the left declive, bilateral precuneus and the left cuneus.

The activation of the anterior cingulate cortex (ACC) during positive autobiographical memory replicates previous findings. For example, the ACC was found to be activated in comparison of the happy versus the rest condition in the ecphorizing of autobiographical memories (Markowitsch et al., 2003). Lepage, Ghaffer, Nyberg and Tulving (2000) found anterior cingulate activations during memory retrieval and induction by emotion recall/imagery as well as emotional tasks with cognitive demand (Phan et al., 2002).

The cingulate cortex is situated roughly in the middle of the cerebral cortex beginning below the rostrum of the corpus callosum and continuing posteriorly above the to the medial part of the temporal lobe. Its location makes the cingulate cortex "an excellent candidate for the brain's emotional control centre, which is what it seems to be" (Carter, Braver, Barch, Botvinick, Noll & Cohen, 1998). Its anterior part, the ACC, communicates with the prefrontal cortex (Pertides & Pandya, 1999). The ACC is thought to play a superordinate role in the executive control of attention (Davidson & Irvin, 1999; Gündel et al., 2003) and to be particularly involved in a form of attention that serves to regulate both cognitive and emotional processing (Whalen, Bush, McNally, Wilhelm, McInerney, Jenike & Rauch, 1998). It has also been proposed that neuronal activity in this region is correlated with the maintenance of the episodic memory retrieval mode, a condition necessary for remembering past episodes (Lepage et al., 2000).

Interestingly enough, abnormalities in the anterior cingulate have been consistenly associated with mood-congruent response biases in depression (Elliott et al., 2002; Davidson, Irvin, Anderle & Kalin, 2003). The

finding of the response bias has been shown to be not only a bias toward sad information in depression, but also a bias toward happy information in controls –a finding readily replicated by the present study.

The precuneus is part of the medial parietal cortex and is located superior and posterior to the retrosplenial cortex. It has widespread anatomical connections to the prefrontal cortex, the temporal and occipital cortices and the thalamus (Fletcher et al., 1995). The precuneus has been labelled the "mind's eye" and it is a principal area involved in the conscious recall of memory–related imagery (Fletscher et al., 1995) and may participate in the representation of polymodal imagery associated with successful retrieval (Maddock, Garrett & Buonocre, 2001). It has been further suggested that the precuneus cortex is more directly related to the actual experience of remembering a remote event in great detail (Gilboa, Winocur, Grady, Hevenor & Moscovitsch, 2004). The cuneus, located on the medial surface between the parietooccipital and calcarine sulci, has been suggested to attributed to imagery and retrieval success, in line with the activation of the precuneus (Cabeza & Nyberg, 2000).

The lingual gyrus lies inferior to the calcarine sulcus. It is adjacent to the posterior portion of the occipitotemporal gyrus and is separated from it by the collateral sulcus. This brain structure has been shown to be active during the encoding and recall of complex visual stimuli and has also been shown to be responsible for emotional salience at recognition (Gilboa et al., 2004). The latter seems to be the case in the present study. This area has been previously reported in only one other study of AM, the Gilboa et al. (2004) study. The authors suggest that this is possibly due to the shorter duration that was used in previous studies, which was not conducive to visual re-experience. Their study also provides evidence that this activation was specifically related to the re-experiencing component of

autobiographical retrieval, as lingual activation was associated with sensory-episodic memories that were attained.

The declive is the part of the vermis of the cerebellum just caudal to the primary fissue. The declive as such has not been previously identified, but left hemispheric cerebellar activation in general is thought to be engaged in several nonmotor activities, including episodic memory retrieval (Fink, Markowitsch, Reinkemeier, Bruchbauer, Kessler & Heiss, 1996; Bäckman et al., 1997; Andreasen, O'Leary, Paradiso, Cizadlo, Arndt, Watkins, Boles Ponto & Hichwa, 1999; Cabeza & Nyberg, 2000) and attribution or experience of emotion (Lane et al., 1997b). Andrease et al., (1999) have suggested the participation of the cerebellum in an interactive cortical-cerebellar network initiating and monitoring the conscious retrieval of episodic memory and Markowitsch et al. (2003) have further claimed that the cerebellar neurons provide a sequencing time code or a temporal programming to ecphorized events. Therefore, its contribution to cognition is modulatory rather than generative (Gündel et al., 2003).

Significant activation for the negative minus the neutral autobiographical memories was found in the bilateral medial prefrontal cortex, which is known to play a specific role in the cognitive processing of emotional stimuli (Lane et al., 1997a; Fossati et al., 2003), episodic memory encoding and retrieval (for a review see Cabeza in Tulving, 2000), consciousness, emotion processing, self-referential processing (Gusnard, Akbudak, Shulma & Raichle, 2001; Johnson, Baxter, Wilder, Pipe, Heiserman & Prigatano, 2002) and personal identity (Markowitsch et al., 2003). Interestingly enough, there is growing consistency between the lesion data on the mood consequences of small unilateral lesions and the findings from neuroimaging studies in supporting the view that several regions within the prefrontal cortex are active during experimental arousal

of negative emotion (Davidson & Irvin, 1999). Fossati et al., (2003) has suggested that this activation is not likely to be related to emotional content per se but it is due to the self-referential processing of the emotional stimuli.

The medial prefrontal areas have been also implicated in the pathology of affective disorders (Drevets, Price, Simpson, Todd, Reich, Vannies & Raichle, 1997; Drevets, Ongur & Proce, 1998) and have been proposed to play a key role in mediating the interaction between mood and cognition in affective disorder (Elliott et al., 2002). "The common role of the dorsomedial prefrontal cortex in evaluating both positive and negative stimuli suggests that the dysfunction of the dorsomedial prefrontal cortex frequently reported in mood disorders (Mayberg, 2003) may subserve the bias of emotional processing in depression" (Fossati et al., 2003). Moreover, "by providing a personal perspective in the evaluation of emotional stimuli, the right dorsomedial prefrontal cortex may mediate cognitive processes, such as those involved in psychotherapy, that guide regulation of emotional experience" (Fossati et al., 2003).

4.3 Behavioral results

The results in the behavioral level were discouraging. No significant difference in the specificity of the recalled memories between the reboxetine and the placebo groups was detected. As a matter of fact, rarely were any general memories reported, with the reboxetine group reporting specific memories for a mean of 10.25 out of the 12 words and the placebo group reporting specific memories for a mean of 9.16 out of the 12 words.

The rest of the words produced either specific extended memories, general memories or were missed data.

Several factors may account for this negative finding. Firstly, it should be emphasised that research evidence for the overgeneral bias in autobiogrpahical memory comes from studies of retrieval of personal experiences during depressed mood (e.g. Evans et al., 1992, Kuyken & Brewin, 1995; Calev, 1996; Goddard, Drotschel & Burton, 2001; Wessel et al., 2001; Hermans et al., 2004; Van Vreeswijk & de Wilde, 2004), or from studies of such retrieval in healthy volunteers during induced negative mood (Raes et al., 2003). This was the first study using healthy volunteers that were not induced in negative mood, but instead half of them were given an antidepressant drug. Another possible explanation is the fact that participants were given 20 seconds to search for a specific memory which they later reported. In contrast, previous studies used as the dependent variable the first event that was reported by each participant, even if later on they managed to retrieve a specific memory (e.g. Raes et al., 2003; An de Decker et al., 2003; Hermans et al., 2004). It could be further hypothesized that a single dose of reboxetine was not sufficient to produce significant differences.

It should be also kept in mind that the nuber of participants was rather limited, with each group comprising of just 12 people. Other studies that managed to reach significant results had noteably more participants. For example, Raes et al. (2003) had 36 participants in each of their experimental and control groups and Wessel et al. (2001) used 93 outpatients and 24 healthy controls.

As far as the recall times of the autobiographical memories are concerned, no significant interactions between them and the different valence of the cue words were to be found, but overall volunteers

receiving reboxetine were relatively quicker at recalling memories. This difference in recall times is likely to be due to the improved alertness of the reboxetine group, which in turn could have enhanced the speed of the memory retrieval. Nevertheless, it could be possible to claim that a single dose of reboxetine facilitated AM recall after all, by allowing for the participants under its effect to reach autobiographical memories (regardless of their emotional valence) significantly quicker –that is specific memories in their vast majority, as shown above.

4.4 Caveats and limitations

Some cautious remarks need to be made. There is no methodological venue via which controlling and equalizing responses between subjects could be made possible; each person has his/her own unique memories of their life experiences and hence they provide different responses. Moreover, as pointed out by Markowitsch et al. (2003), fresh experiences may have more detail and vividness whereas old experiences may still be remembered exactly because of their emotional severity.

A potential limitation of this study is the fact that positive and negative emotional words were not matched for the arousal associated with them. Negative stimuli are typically more arousing than positive words (Fossati et al., 2003) and fMRI differences between the word types may be due to this potential confound.

Furthermore, gender has been suggested to contribute towards enhancing or diminishing possible neural activation effects towards affect related information (Cahill et al., 2001, Killgore et al., 2001; Schneider et al., 2000; Markowitch et al., 2003). Consequently, it cannot be excluded that different aspects of emotional and memory variables cotribute differently

in male and female subjects and have acted as confound variables to our finding of the existence of distinct neural nets for positively and negatively valenced autobiographical memories.

Additionaly, the fMRI analysis was the primary endpoint of the present study and this led to a compromise in the collection and analysis of the behavioural data, i.e. the data was collected after the specific memory retrieval in the scanner, when the subjects had exited the scanner. Another drawback was the limited number of subjects which is also amongst the possible reasons why significant results could not be reached in the behavioural level.

4.5 Conclusions and future directions

In summary, the behavioural measures were not affected by the administration of a single dose of reboxetine, but the functional imaging data did reveal significant differences in the recall of positive and negative autobiographical memories under acute antidepressant action. These areas included the right insula and parts of the frontal gyrus. Additionally, brain areas that are implicated differentially in the processing of negative versus positive autobiographical memories were identified. With the exception of the cerebellar one, all activations involved the cerebral cortex and were largely confined to limbic or paralimbic regions, namely the frontal cortex, the right insula, the anterior cingulate, the declive, the lingual gyrus, the precuneus and the cuneus.

The present findings are consistent with the notion that reboxetine may work in a manner that redresses negative biases in information processing, since areas within the frontal cortex which have been found to be active in the recall of aversive memories, were also found to be effected

by acute reboxetine administration. Furthermore, the findings support theories which claim an involvement of a widely distributed set of brain regions in the processing of autobiographical remembering, which are distinct for the re-activation of positively and negatively viewed autobiographical episodes.

These findings have implications for understanding the neural substrates of both normal and pathological emotion. The new information which has been collected can provide a compelling foundation for theoretical advances in the basic understanding of the constituents of emotion under antidepressant action. It may further work towards bridging the existing gap between pharmacological theories of drug action and an understanding based on the function of brain networks of emotional processing. A better understanding of the neurobiological mechanisms involved in emotional processing may be imperant in the development of novel antidepressant treatments as well.

There are many ways in which this work can be carried forward and the recognition of its shortcomings could benefit future investigations. Thus, future studies need to consider possible differences in neural activations related to gender. Moreover, they should use a larger number of participants when testing for any behavioural effects of acute antidepressant administration. Further, they should assess primary effects of memory specificity.

In conclusion, neuropsychology stands in a unique position to explore the effects of antidepressants, increase the knowledge about their neurobiological mechanisms and by doing so work towards providing more efficient ways of antidepressant treatment so as to improve the lives of those touched by this rather common mood disorder.

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