A Psychopharmacological Exploration of Memory for Emotional Material

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Thesis submitted for the degree of Doctor of Philosophy
University College London
September 2003

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ABSTRACT

It is often assumed that emotional events are remembered in great clarity and detail. This thesis begins with a review of the literature on memory enhancement by emotional material. This enhancement may involve mechanisms that are psychologically and neurobiologically distinct from the mechanisms usually employed in memory for neutral material, such as modulation of consolidation by emotional arousal via noradrenaline action in the amygdala. Theoretically, pharmacological manipulation of noradrenaline by methylphenidate and benzodiazepines should affect the function of specialised 'emotional memory' mechanisms, altering the balance of emotional and neutral material remembered.

A set of four double blind, placebo controlled experiments were designed to investigate this theory. Each was carried out with three groups of 16 healthy human volunteers. **Experiment 1** produced some evidence that both 1.5mg lorazepam and 40mg methylphenidate reduced the mnemonic advantage of emotional sections of a story. **Experiment 2** compared diazepam (15mg) with placebo and propranolol (80mg) (a β-blocker which has been reported to impair emotional memory) on two new tasks. Diazepam left implicit memory intact, but impaired explicit memory, particularly for emotional material. In **Experiment 3** both diazepam (15mg) and methylphenidate (40mg) altered relative levels of recall for emotional and neutral pictures. In **Experiment 4** diazepam (10mg) clearly impaired fear conditioning. However there was no evidence that diazepam (10mg) or methylphenidate (40mg) affected emotional memory during consolidation.

Taken together these studies provide evidence for a pharmacological dissociation of fear conditioning and perceptual priming. There was some evidence that benzodiazepines disproportionately impaired explicit emotional memory. However these effects were subtle. Methylphenidate increased the relative amount of emotional material retained on some measures, and decreased or left it unchanged in others. This may be due to differing levels of arousal.

A central issue throughout the thesis was the difficulty of separating the 'emotional memory' mechanism from other co-occurring mnemonic properties of emotional stimuli. These may mask effects of the pharmacological manipulations that would be informative to any theory of 'emotional memory'.

ACKNOWLEDGEMENTS

First and foremost a large amount of credit for this thesis is due to my PhD supervisor Prof. Val Curran, without whose help it would not have been possible. For the time, help and encouragement, and for being the best advisor, teacher, proof-reader and guide I could have wished for – Thank you

I would like to gratefully acknowledge Dr. Joe Rosenthal for screening the volunteers, and Dr Chris Newman, Dr Rebecca Richell, Kate Hall and Karen Ashwood for their assistance with data collection.

Thank you to Dr James Blair for his help, and to Dr Jonckheere, and Dr Alastair McClelland for invaluable advice on data analysis. Many thanks are also due to several other friends and colleagues.

I am especially grateful to my parents for their understanding and support, and Mike for always being there and having absolute confidence in me.

And finally I would like to express my appreciation to all the people who voluntarily participated in this research.

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SELECTED ABBREVIATIONS AND ACRONYMS

SCR	skin conductance response
US	unconditioned stimulus
CS+	conditioned stimulus (previously been paired with US)
CS-	conditioned stimulus (not previously been paired with US)
BDZ	benzodiazepine
LZ	lorazepam
DZ	diazepam
MPH	methylphenidate
PL	placebo
ANOVA	analysis of variance
ANCOVA	analysis of covariance
GG	Greenouse Geisser correction used to compensate for possible violations of the sphericity assumption
MRS	mood rating scale
AG	affect grid
MRI	magnetic resonance imaging
FMRI	functional magnetic resonance imaging
PET	positron emission tomography
NA	noradrenaline
DA	dopamine
GABA	Gamma-aminobutyric acid
5-ht	serotonin
THC	tetrahydro-cannabinol
i.v.	intra-venous
i.m.	intra-muscular

CHAPTER 1: LITERATURE REVIEW

"An impression may be so exciting emotionally as almost to leave a scar upon the cerebral tissues" W.James, (1890)

"...above them waved hundreds of banners, and the sun, glinting on many thousand hostile spear-points, spread a sparkling cloud. It was, perhaps, the impression of a lifetime; nor do I expect ever again to see such an awe-inspiring or formidable sight...
....white banners tossing and collapsing; white figures subsiding in dozens to the ground; little white puffs from their rifles, larger white puffs spreading in a row all along their front from the bursting shrapnel. The picture lasted only a moment, but the memory remains for ever...."
W.S.Churchill (1899)

1.1. Introduction

Two years ago, at a scientific conference in Marseilles I was sitting in a symposium about the neurobiological basis of action recognition and imitation. One speaker finished, and before the next could start, a grave Frenchwoman interrupted the proceedings. With emotion audible in her voice and trembling hands, she announced that there had been a terrible 'air raid in New York' and we should return to the main auditorium.

Out in the bright Marseille sunshine I telephoned my partner as I crossed the lawn to the auditorium. We considered the world consequences of such an act. Was this world war three? Would things ever be the same again?

The main auditorium was dark, lit only by the flickering of CNN on the giant screen. It was showing thick clouds of smoke, rising from a tower on the Manhattan skyline. The light from the news broadcast strangely illuminated the terror in the upturned faces of distinguished academics. After the warm September day outside, the crowded room was eerily hushed and chilled. I watched, not knowing if, or how, to offer comfort to an eminent American neuroscientist as her face crumpled with despair and shock.

Searching the rows of seats looking for a familiar face, I found some students from the Institute of Psychiatry, who I had met the previous evening. We sat there and watched the devastation unfold, live on the huge cinema size screen. Far from home, we pieced together information about what was happening. Hijacked aeroplanes had destroyed the World Trade Center in New York. As the twin towers crumbled to earth, the camera zoomed in on the screaming

faces of desperate people, jumping stories to their death rather than be trapped inside.

There are probably few people who had access to a television set on the 11th September 2001 who feel they will ever forget these striking images. Are memories of events like these actually more vivid, or more enduring than less emotional memories? If so, how do they become so qualitatively different? This thesis focuses on the psychopharmacology of the interaction between emotion and memory. This first chapter presents an introduction to the topic, overviewing evidence from the available literature. The review concentrates on evidence for specific cognitive and neural mechanisms that may be activated by emotional stimuli to enhance memory. This is followed by a description of the prevailing theory of the underlying neurochemistry behind emotional enhancement of memory. Given the limitations of a thesis, the review focuses on studies with humans, only considering the animal work in any detail where no human data is available.

1.1.1.Memory

The penguin dictionary of psychology defines memory as '*the mental function of retaining information about stimuli, events, images, ideas etc after the original stimuli are no longer present*'. Since the 1960s the concept of memory has been fractionated in various ways. The debate about how precisely memory can be described in terms of systems, processes, and stores would itself merit an entire thesis. This thesis takes the pragmatic view that memory can be divided up into short and long term stores (e.g. Shiffrin & Atkinson 1969). Short term memory can further be divided up into components of working memory as described by Baddeley & Hitch (2000), and longer term memory as described by Squire (1992), Tulving (1985), Tulving & Schacter (1990).

1.1.2.Emotion

Dolan (2002) defines emotions as our ability to sense whether events in our environment are more or less desirable (their value). He argues that they are a product of evolutionary processes and evident across phylogeny. An emotion happens in reaction to a stimulus. Therefore it is different from a mood, which is longer lasting, and may be less directly related to external events. This literature

review is about the effect of *emotion* on memory and therefore will not discuss mood dependent or mood congruent memory.

Several influential psychological theories have reduced the range of human emotions to two dimensions. Russell & Mehrabian (1977) and Russell, Weiss, & Mendelsohn (1989) showed most of the reliable variance in 42 commonly used self report scales of affect could be predicted from scores of 'pleasure' and 'arousal'. Lang et al. (1993) and Lang, Bradley, & Cuthbert (1990) also use two dimensions labelled 'valence' and 'arousal'. Watson & Tellegen (1985) call their dimensions 'negative and positive affect', Gray (1985)(1990) 'anxiety and impulsivity', Eysenck & Eysenck (1969) 'neuroticism and extraversion', and Mogg & Bradley (1998) 'valence evaluation' and goal engagement'. Although there are some critical theoretical differences between these models, and they were constructed in different ways to have utilities in different areas, they can all be argued to be rotations of two orthogonal factors. For example Yik, Russell, & Barrett (1999) showed that subjects' ratings of current affect on Russell et al's (1989) affect grid could be integrated into a bipolar two-dimensional structure with three other popular two-dimensional scales: Watson and Tellegen's (1985) positive and negative affect, Thayer's (1989) tense and energetic arousal, and Larsen and Diener's (1992) 8 combinations of pleasantness and activation.

There are other theoretical frameworks, many of which do not take a factor analytic perspective. For example Ekman (1973) proposed six putative universal and biologically based emotions of happiness, sadness, anger, disgust, surprise, and fear, and Izard & Izard (1977) argued for ten fundamental emotions. However for parsimony and in line with much of the available literature, the current thesis takes the perspective that emotion can be conceptualised as a combination of two basic factors: valence and arousal Russell & Mehrabian (1977); Russell & Steiger (1982); Russell, Weiss, & Mendelsohn (1989) Lang, Greenwald, Bradley, & Hamm (1993). Affective valence runs from 'unpleasant' to 'pleasant', and arousal runs from 'calm' to 'excited'. Thus valence can be thought of as an evaluative aspect of emotion, (evaluating if a situation is good or bad) and emotional arousal can be thought of as intensity (how good or bad is the situation).

Emotional arousal is often thought to be associated with physiological arousal. However this is not a simple relationship, as arousal is a diverse concept.

Indices of physiological arousal include activation, cardiac and vascular activity, skin conductance, hormone and neurotransmitter levels. Measures like these do not often correlate (Lacey, 1967). Some theorists have proposed that patterns of physiological activation can differentiate subjectively different emotions e.g. Levenson et al. (1992). The concept of arousal can also be fractionated psychologically and neurochemically (Robbins 1997;Robbins & Everitt 1995). Hence arousal as a concept is actually a related collection of concepts and is difficult to define.

1.1.3.History

Emotion has long been though to have a facilitating effect on memory. For example in the 17th century Descartes wrote:

> *" .....the utility of all the passions consists alone in their fortifying and perpetuating in the soul thoughts which it is good it should preserve and which without that might easily be effaced from it. "*
>
> *(Descartes 1649, p.364)*

By the 19th century emotions began to be regarded as more of a hindrance to learning. Darwin (1872) carried out a large, cross-cultural study of emotion and concluded that the emotions were an evolutionary throwback, something like the human appendix.

At the end of the 19th century Sigmund Freud (1895) began writing about his theory of emotional trauma, a theory which he modified throughout the first part of the 20th century as evidence against it gradually accumulated. Influentially, he believed that some emotional traumas (usually sexual) were so damaging they would leave psychological scars that would affect the persons psychological functioning. In order to protect the psyche, traumatic events would be 'repressed' in memory and thus made inaccessible to intentional retrieval.

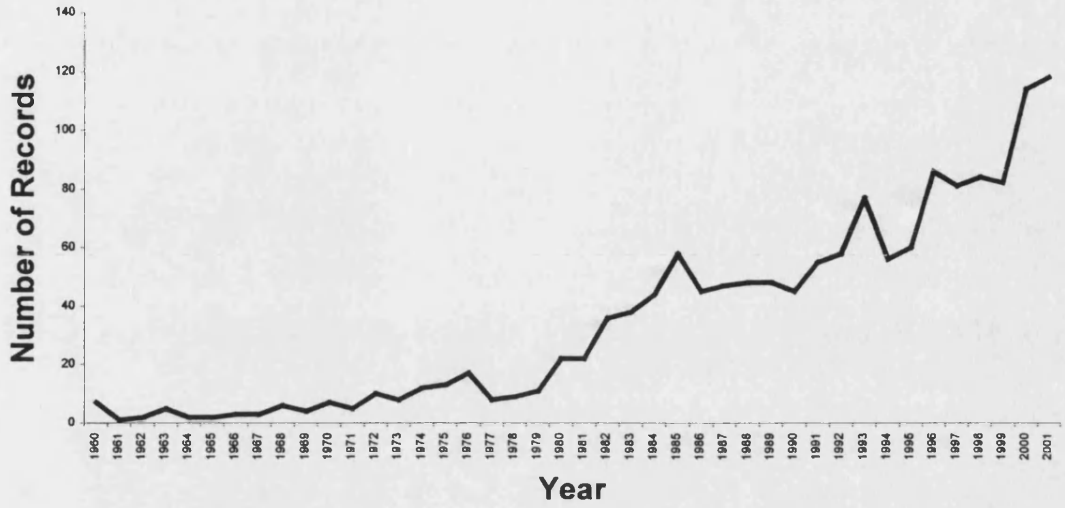
The ideas of behaviourism rose up in reaction to approaches based on subjective introspection. As neither 'emotion' nor 'memory ' are directly observable, they were not considered suitable topics for scientific study (Skinner 1938). However the work of the physiologist, Pavlov (1927) could arguably be interpreted in the light of these very concepts today. His description of classical conditioning forms the background for the fear-conditioning paradigm which has been used previously, (e.g. Hamann, Monarch, & Goldstein

2002; LeDoux 1998) and is one of the paradigms used in the current thesis to study the effects of emotion on memory.

In the latter half of the 20th century, the advent of cognitive psychology brought more structured theories of memory. Some cognitive theorists, notably George Mandler (1964,75), did include emotion in cognitive theory. However, much of this work conceptualised the mind in a mechanistic way and somewhat ignored the concept of emotion. Later cognitive theory began to include concepts of experience, consciousness, and meaning (e.g. Craik & Lockhart 1972, Tulving 1985) but there was still little consideration of emotion. In the 1980s an increase in interest in applied knowledge saw 'eyewitness testimony' and 'flashbulb memories' become popular as topics of research. There was debate about whether emotion facilitated (enhanced) or impaired (e.g. repressed) memory, and of the possible psychological mechanisms behind either action (e.g. Christianson 1992) More recently, advances in technology in the field of cognitive neuroscience have led to increasing research into neurocognitive models of the facilitation of memory by emotion.

Figure 1 shows how the number of records about 'emotion and memory', in the electronic database Psychinfo has increased consistently since the 1980s. Partly this may just represent the increasing use of electronic databases, but it does represent the recent explosion of interest in the field of emotion and memory.

Figure 1: Number of records returned by a Psychinfo search using the keywords 'emotion' AND 'memory' for each year from 1960 - 2001



Again, the apparently discrepant themes of memory enhancement and impairment are evident in this body of research. For example titles of influential publications include both '*Functional amnesia* as induced by a psychological trauma' (Christianson and Nilsson, 1984) and '*Enhanced memory* associated with emotional arousal' (Cahill and McGaugh, 1995).

Rather than reviewing the literature on the effects of emotional arousal on memory from a simple chronological perspective, it will be reviewed as it illuminates several specific issues. The first question to be considered is under what circumstances does emotion facilitate memory? Three variables that are believed to alter the way emotional arousal effects memory are:

- Time between encoding and retrieval
- Level of emotional arousal
- If the information is 'central' or 'peripheral'

It is argued that if these three variables are taken into account, there is evidence that memory for emotionally arousing stimuli is facilitated.

The second main issue to be considered is whether this facilitation of memory can be explained without the need to postulate special mechanisms of 'emotional memory'. Literature will be considered in terms what it reveals about alternative theoretical interpretations. The alternative interpretations discussed are whether apparent memory facilitation could actually be an effect of the *distinctiveness*, or *semantic cohesion* of emotionally arousing material or the

extra attention and rehearsal given to this material. Following this, the neurocognitive evidence that memories of emotional events may be qualitatively distinct from memories of non-emotional events will be addressed. Finally there is a discussion of the prevailing psychopharmacological hypotheses about the neurochemical mechanism of memory.

1.2. Factors influencing the effects of emotion on memory

1.2.1.Time between encoding and retrieval

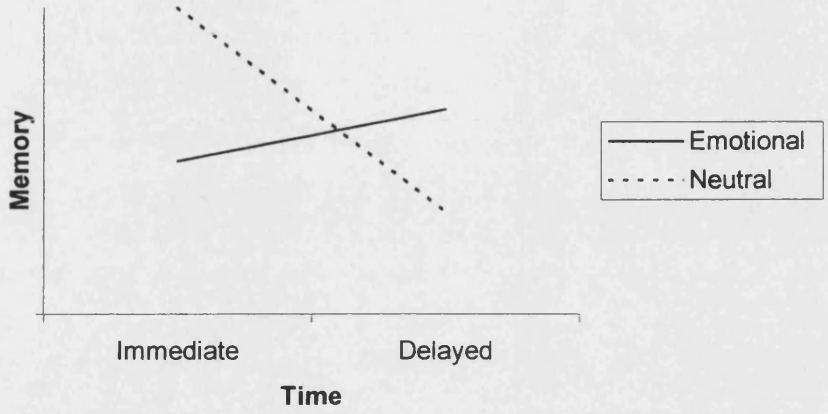
Kleinsmith & Kaplan (1964); Kleinsmith, Kaplan, & Trate (1963); Kleinsmith & Kaplan (1963) performed a classic set of experiments on the memory storage of paired associates of either arousing or non-arousing stimuli. Kleinsmith & Kaplan (1963) paired numbers with emotional and neutral words (*kiss, rape, vomit, swim, exam, dance, money, love*), and Kleinsmith & Kaplan (1964) paired numbers with nonsense syllables (*cef, qap, tov, jex, laj, dax*). Arousal was determined by the skin conductance deflection within 4 seconds of the stimulus presentation. The three stimuli with the smallest deflections were defined as low arousal; the three with highest deflections were high arousal. They found an interaction between the level of arousal and time of testing, which is shown in a simplified way in Figure 2.

Different groups of volunteers did the test at each time interval. It was found that the paired associates of low arousal stimuli were recalled well after a period of either 2 or 20mins. However when tested after a longer time interval (1 week) most of these pairs had been forgotten and recall was very poor.

In contrast paired associates of arousing stimuli showed low immediate (2 or 20 mins later) recall but higher levels of delayed (1 week) recall. The hypothesis put forward to explain this is a period of 'preservative consolidation' in conditions of high arousal, where the information is protected from interference while it is being consolidated in long-term memory. The interaction was surprisingly clear considering arousal levels would not be expected to vary

much amongst the words or syllables, and there were only three to-be-remembered items in each group.

Figure 2: Memory for neutral material tends to deteriorate over time, whereas memory for emotional material does not



However the effect seems to be reliable. Similar findings have since been described by Parkin, Lewinsohn, & Folkard (1982) who tested one group of participants immediately and a second group after a seven day delay, and by Bradley & Baddeley (1990) who tested volunteers either immediately or after 28 days. Both experiments investigated memory for the participant generated associates of emotional versus those of neutral words. The words were predefined as emotional or neutral. The findings were used to critique interpretations of an earlier study by Levinger & Clark (1961). Levinger & Clark found that associates given to emotional words were more likely to be forgotten than associates of neutral words. Some authors had taken this as evidence for the Freudian theory of repression. However, there was no delayed recall test in Levinger and Clark's study. Had there been, it would probably have found that the associates of emotional words would have been recalled better after a delay, a finding inconsistent with Freudian theory.

LaBar & Phelps (1998) give a recent description of the interaction between study-test delay and relative amounts of emotional and neutral material remembered. They found the memory advantage of emotional 'taboo' words (e.g. *shit, masturbate, whore, incest*) increases over time (one hour) in healthy volunteers. They attribute this to the arousing words receiving enhanced

consolidation compared to neutral words. Compared to the difference between taboo and neutral words at immediate recall the effect of 'arousal mediated memory consolidation' is quite small. The memory advantage of taboo words only grew by about 10 – 15% over the hour.

A study by Christianson (1984) provides evidence for this effect operating on memory for emotional pictures. His volunteers were shown either a neutral slide show or a slide show where the middle section was emotional in nature. Half of the people who saw each show had their memory for it tested by recall and by recognition 12 minutes later. The rest of the volunteers had their memory tested 2 weeks later.

There was no difference between the groups who saw the different versions on *recall* performance for the middle section of the show if they were tested 12 minutes later. However the group who were tested 2 weeks later and who saw the emotional version recalled more of this section than the group who saw the neutral version and were also tested at this time. On immediate test of *recognition* memory, the volunteers who saw the neutral slides recognised the middle section better than those who saw the emotional version. At delayed recognition testing the group who saw the emotional version performed better than those who saw the neutral version. However, it is worth noting that these results were not replicated by Christianson & Loftus (1987) who found emotional slides were recalled better both at immediate recall and after a 6 month delay.

Burke, Heuer, & Reisberg (1992) also found some evidence for an interaction between retention interval and emotionality for memory of an emotional versus neutral story. However, this finding was not very reliable over their series of experiments. They did conclude that, although there may be a stronger effect of emotion after one week than at immediate test, the pattern of results did not change from one week to two weeks delay.

Therefore, overall it seems that there is evidence that emotional arousal does enhance memory, although, if retention is tested soon after encoding, the emotional advantage is not as clear. If memory for the *associates* of the emotional stimuli is tested immediately after encoding, emotion can even be shown to have an impairing effect. However, given enough time between encoding and retrieval, emotional arousal has been shown in some studies to

have a facilitating effect on memory. The explanation usually given for this is enhanced consolidation associated with emotional arousal, however rehearsal processes may play a part (see section 1.3.2). One week appears to be sufficient time to show emotional facilitation of memory.

1.2.2.Arousal vs. valence, and level of arousal

Russell et al (1989) argue that studies which try to concentrate on a single dimension of emotion – either arousal or pleasantness (valence) - run the risk of confounding the two. In the valence dimension more studies have looked at the effects of trauma (extreme negative emotion) on memory than the effects of positive emotion. Where emotional stimuli with positive valence have been investigated, they have usually been found to have similar memory effects to negative stimuli.

Christianson (1986) found memory was impaired[1] for verbal descriptors that accompanied 'positive' emotional events (erotic pictures). Both male and female participants had higher heart rates and reported higher levels of 'happy, lustful, sexually aroused, and sexually excited' emotions when exposed to the erotic pictures. A range of other (positive and negative) emotions were also rated, and did not show any significant differences. However, notably, the emotions rated did not include embarrassment. Participants were asked informally if they experienced embarrassment at the end of the study. However this may be subject to underreporting as easily embarrassed participants may have been unwilling to discuss this. Therefore it is possible that some participants experienced negative emotion and this contributed to the mnemonic effect.

A similar pattern of memory performance has been observed by the same group in studies about memory for verbal descriptors accompanying negative emotional pictures (horribly disfigured faces) (e.g. Christianson & Nilsson, 1984).

Bradley & Baddeley (1990) found that both positive and negative words had similar facilitating effects on memory. Their stimuli had previously been rated on

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[1] The verbal descriptors are associates, or peripheral details of the emotional material itself, causing memory for them to be impaired

two scales: (1) very unpleasant – very pleasant, and (2) unemotional – highly emotional by Brown & Ure (1969). The latter scale can, in retrospect, be seen as similar to Russell's arousal dimension of emotion, and it was words that were rated 'highly emotional' on this scale that led to a facilitative effect on long term memory. The study did not demonstrate differential effects of positive versus negative material. As mentioned above (section 1.2.1) this study was an effort to debunk the idea of Freudian repression as positive emotional events are not supposed to be repressed.

More recently Hamann, Ely, Grafton, & Kilts (1999) showed similar neuroanatomical and functional effects of both positive and negative pictures. They also used erotic stimuli, and therefore may be subject to the same criticisms as Christianson et al discussed above, but as this was an imaging study they were able to use a small sample of right handed, heterosexual, male volunteers. Phelps et al. (1998) argued that it is only physiologically arousing stimuli rather than emotional stimuli of either valence, that require specific neuroanatomical structures for memory facilitation[2].

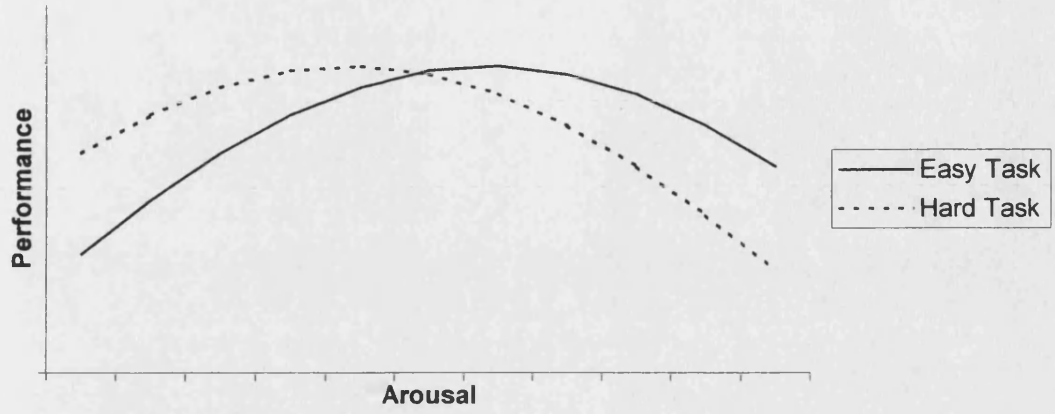
Therefore it seems that it is the arousal dimension of emotion, rather than valence that is associated with facilitation of memory. The relationship between arousal and memory may be complicated. Several theorists (e.g. Deffenbacher, 1983; Christianson, 1992; Mandler, 1992) have proposed the Yerkes Dodson law as an explanation for many discrepancies in the research about the effects of emotion on memory. This law quoted in textbooks is that performance varies as an inverted U –shape function as arousal increases. Therefore at low levels of arousal (boredom/ uninvolvement) there will be a low level of performance. High arousal (e.g. panic) also leads to poor performance. Optimal performance stems from arousal levels between these two.

Task difficulty also has an effect, so for easy tasks the curve will be shifted along the arousal axis and higher levels of arousal will be required to provide optimal performance (see Figure 3). This makes intuitive sense. As Loftus (1979) points out, under high stress, a person would have little difficulty

[2] Memory for non-arousing but semantically emotional stimuli may be facilitated by other mechanisms – see section 1.3 below.

remembering their name but would find it very difficult to remember how to play a Beethoven piano sonata.

Figure 3: Yerkes Dodson Law



There are two main problems with the literature applying the Yerkes Dodson law. First, it is difficult to quantify the difficulty levels of qualitatively different tasks. Second, it is very difficult to quantify arousal levels in individuals across tasks. In practise the method usually used is to quantify these measures by their fit to the inverted U-shape curve, and then use their fit to the curve as evidence that the law is correct. This can be seen as circular and in this way the Yerkes Dodson Law is unfalsifiable.

Winton (1987) describes how the Yerkes-Dodson law is often defined in textbooks as a relationship between general arousal and performance. Yerkes and Dodson performed their research in 1908, several decades before an arousal construct existed. The experiment they performed was about habit forming in mice. They never mention the term arousal; the closest they come to it is 'strength of electrical stimulation'. Their findings can retrospectively be interpreted in terms of an arousal-performance relationship, but these findings are not evidence for such a law.

1.2.3.Central vs. peripheral information

According to Mandler (1975, 1992); Bower (1992) Tobias, Kihlstrom, & Schacter (1992) and other cognitive emotion theorists, emotion uses up cognitive capacity, and therefore thoughts and problem solving may become impaired. This is consistent with the Easterbrook (1959) cue utilisation hypothesis, which states that there is a progressive restriction of the range of cues used or

attended to as a function of emotional arousal. This has often been used to justify the application of the Yerkes Dodson law, as, at states of moderate or optimal arousal, the restricted number of cues used should benefit performance because only relevant information is attended to, and irrelevant cues are excluded. At higher levels of arousal the cues used are restricted such that important cues are also excluded and so performance deteriorates.

This hypothesis is supported by a wide body of work (see below) on memory for the central and peripheral details of emotional information. When stimuli have emotional content, memory for central details tends to be superior to that for a similar non-emotional stimulus. However memory for peripheral details tends to be worse when the stimuli are emotionally arousing than when the stimuli are neutral.

Heuer & Reisberg (1990) tested subjects' memory for central and peripheral details of a set of slides depicting a story. They found that although central details were remembered better in the emotional version, peripheral details in that version were also remembered better. Burke, Heuer and Reisberg (1992) used the same story but tested memory after different time periods (for effects of time to testing see section 1.2.1.). They also reclassified what was central and peripheral information and found the expected result of central details being remembered better than peripheral details in the emotional condition.

This illustrates an important problem in this research area, which is how to define what is central and what is peripheral information. In field studies it is usually impossible to decide in advance what is central and what is peripheral. In laboratory studies, normative data can be collected in advance about what is central or peripheral information.

Another problem is that the categorisation may also change with the emotional valence of the material. Information which is peripheral in the neutral condition may become central in the emotional condition.

In a widely cited study by Christianson & Loftus (1991), the central and peripheral details were kept constant in all the alternative stimuli employed. They showed their volunteers three pictures where the central information was a girl and her bike. In the *neutral* condition she was riding her bike along a road. In the *unusual* condition she was carrying her bike on her shoulder and in the *emotional* condition she was lying injured beside her bike as if she had had an

accident. The peripheral details (the road, a car in the background) remained constant. The results of a series of experiments carried out with these stimuli showed that central details were better retained in the emotional versions but that peripheral details were better retained in the neutral and unusual conditions.

Attention may have some role in causing the enhanced retention of central details. Wessel, van der Kooy, & Merckelbach (2000) found some evidence that participants' eye movements show they fixate more on the central emotional details of emotional material. However Christianson et al. (1991) controlled for exposure duration and eye fixations and still found that central information of traumatic events was better remembered than peripheral information. Safer et al. (1998) conducted an experiment into the focus of memory for emotional vs neutral material and found that memory for neutral pictures tends to be subject to 'boundary extension'. Because participants understand pictures in a wider context they 'remember' information that is likely to exist just outside the camera's view. In contrast heightened elaborative and emotional processing of the critical details of emotional pictures leads to 'tunnel memory' and only the central details are remembered. They propose that the narrowing of focus happens during elaboration after encoding. However this was not explicitly tested.

Another aspect of this is the phenomenon known as the 'weapon focus ' effect. This has been studied many times using various techniques. Studies have used films and slide shows (Loftus et al, 1987; Cutler et al, 1987), staged scenarios (Maass and Kohnken, 1989; Tooley et al, 1987), and analysis of real life police interviews. (Kuehn, 1974). Essentially, when a weapon is present in a scene it is remembered better than other parts of the scene. Thus, in support of the Easterbrooke hypothesis, the weapon could be thought of as the central detail, and other aspects of the scene as peripheral details. However this interpretation is not without its critics. It is circular to define the weapon as the central detail because it is the best remembered detail, and then to say that central details have a memory advantage in emotional situations because the weapon is remembered best. Loftus et al (1987) debate whether the weapon focus phenomena actually requires emotion at all. They remark that they get the same

results, even when the weapon does not cause emotional arousal. Other reasons for this effect are discussed below (section 1.3.1).

1.3. Alternative Theoretical Interpretations for the Enhanced Retention of Material

Therefore in order to achieve facilitation of memory by emotional material it is necessary to (1) test memory after a relatively long period of time (e.g. 1 week); (2) induce an optimal level of arousal i.e. above normal, but not blind panic; (3) test memory for central (as opposed to peripheral) information. When these points are met, the evidence suggests memory is enhanced by emotional arousal. However there are other characteristics which tend to covary with the emotionality of material which may contribute to this effect. These are:

- Distinctiveness
- Increased attention and rehearsal
- Semantic Cohesiveness

The following discussion debates whether some or all of these three processes can explain the enhanced retention of material without the need to resort to a mechanism specific to emotional arousal.

1.3.1.Distinctiveness

Brewer (1988) carried out a study in which participants carried a beeper, which sounded at random intervals. When the alarm went off the participants had to record exactly what they were doing at the time. Their memory for these events was then assessed in a cued recall test 23 or 46 days later. Memory performance was best for incidents that had aroused high levels of emotion (positive or negative) when they happened. Another determinant of successful recall was the infrequency (uniqueness or distinctiveness) of an event. High frequency routine events (e.g. studying) aroused little emotion and were poorly remembered. Distinctive events that occurred infrequently (e.g. an argument) aroused higher levels of emotion and were remembered much better.

Therefore one factor which could lead to emotional events being better remembered than other events could be their distinctiveness. Are the news broadcasts of the afternoon of 11th September 2001 memorable because I had never seen anything like them before? No one I spoke to could remember a similar event, where a foreign act of terrorism had stopped a scientific conference. If emotional events are more distinctive than other events this would give them a retrieval advantage. This is demonstrated by the von Restorff (1933) effect: In a series of stimuli (e.g. a word list) where one word is very different from the others, (e.g. presented in French, rather than English) the distinctive one will be more likely to be recalled. Memory for stimuli on either side of the distinctive one will be slightly poorer than the rest of the group.
Many models of emotion attribute emotion to a discrepancy. A perceptual or cognitive discrepancy or the interruption or blocking of some ongoing action violates expectations and therefore it is distinctive. It also often leads to the autonomic nervous system (ANS) arousal, which Mandler argues is necessary for emotion to occur. Discrepancies can be thought of as violations of schemata. Many models of learning consider this to be the condition in which learning occurs. Mandler (1984) describes how expectation failures cause learning, and through arousal of the autonomic nervous system, they also cause emotion.
As mentioned above the effect of weapon focus does not need to be emotionally arousing. This is because it may be due instead to the *distinctiveness* of the weapon-stimulus. Indeed Loftus (1987) argued that the effect would probably have been the same if a banana had been produced rather than a weapon.
However there have been experiments which try to match the emotion condition with the control condition for distinctiveness. As already mentioned Christianson and Loftus (1991) performed a study in which subjects had to study three pictures which featured a woman with a bicycle. In the emotional condition she appeared to have had an accident, and in the control condition she was riding the bicycle. The *distinctiveness* control condition was the picture showing her carrying the bicycle on her shoulder. Memory performance for these three pictures showed that the unusual picture did give a memory advantage but that there were still differences in the pattern of memory performance (for central vs.

peripheral details discussed above) between the unusual condition and the emotional condition.

Hamann et al (1999) showed that although memory is superior for emotional pictures and for distinctive 'interesting' pictures, memory for emotional pictures uses different neuroanatomical substrates (see below: section 1.4.4.).

Studies of memory for emotionally arousing words have used published 'frequency' statistics to try to control for distinctiveness. For example Phelps, LaBar, & Spencer (1997); Doerksen & Shimamura (2001); Maratos, Allan, & Rugg (2000); Bradley & Baddeley (1990) all balanced emotion categories for word frequency in the language and found that more emotional than neutral words were remembered (after a delay). Therefore although distinctiveness does give material a retrieval advantage it does not fully account for the phenomenon of enhanced memory for emotionally arousing material.

All the studies mentioned in this section have the problem that, although the emotional and neutral stimuli are matched in some way for distinctiveness, they are still essentially different stimuli. Therefore there may be other extraneous variables that covary with emotion to produce the actual cause of the observed memory (or neurological) effects.

1.3.2.Extra Attention and Rehearsal

The same reasons that make events emotional also make them worth attending to at the time and ruminating over afterwards.

How often have we seen the footage of the crumbling Twin Towers in New York? Many people made catastrophic predictions that day, and two wars have since been waged, motivated partly by that act of terrorism. Emotional events are usually more important than neutral events in terms of their consequences for our daily life. Due to its importance, we pay attention to an emotional stimulus while it is ongoing. Mandler (1975) would argue that emotional reactions are mechanisms that have evolved to direct our attention to events that are important to be learned. Anything that sets in motion autonomic nervous system activity also sets in motion searches for the causes of the activity. Thus we focus on the source of the failed expectation or interruption. What one remembers from an emotional situation depends on what features of the episode the emotion causes one to focus on.

Bower (1992) describes how emotion controls both present and future attention. He argues that emotional systems react quickly to an event and focus on the anomaly or cause of the discrepancy. Autonomic nervous system and hormone systems are then activated and this induces recycling and rehearsal of the events leading up to the emotional reaction. This rehearsal promotes transfer of material to long term memory. After the physiological arousal has passed, our minds still repeatedly return to the emotional events. This allows more possibilities for rehearsal, which improves retention. Bower gives the example of rumination over negative events, possibly as a mechanism of trying to habituate to an experience.

However Bower offers no evidence for the claim that activation of the hormone system promotes rehearsal. Many other theorists (e.g. Easterbrook) would argue that the elated arousal levels would do exactly the opposite and leave less processing capacity for rehearsal.

Emotional events often have ongoing effects on our personal life and the lives of others. There are thus environmental cues which reactivate the memories and mean they are rehearsed time and again. In this way, we are self-exposed to these events repeatedly and this means that we eventually reduce the amount of anxiety or perhaps other emotions that are associated with these events.

A critical difference between laboratory experiments and real life may be that experimenter-generated emotional experiences (for ethical reasons) should never have lasting consequences for the participant. However, the emotion-inducing material in many laboratory experiments may require the participant to perform more elaboration in encoding the stimulus. For example in the Christianson and Loftus (1991) study with the girl and her bike, the emotional condition seems to require the subject to think about what had just happened to cause the injuries, whereas the neutral condition is just 'a girl riding a bike'. A photographer would probably tell you that the emotional picture 'told a story' but the neutral picture was just a photograph.

In this way, emotional material is more likely to be attended to and more likely to be rehearsed. However, evidence from Heuer and Reisberg (1990) shows that this does not fully explain the retrieval advantage of emotionally arousing information. Subjects were either (1) told to watch a *neutral* slide show closely,

(2) told to watch an *emotional* slide show closely (3) told to memorise the slide show (supposed to increase rehearsal) or (4) told to try and work out what the slide show was trying to 'mimic'. Both groups (3), and (4), recalled the gist of the slide show better than the control group (1) who were just told to watch the stimuli carefully. However neither of these experimental groups (3) and (4) showed the memory advantage for detail demonstrated in the emotional group (2). This experiment was criticised by Cahill and McGaugh (1995) because there were systematic differences between the neutral and emotional slide shows.

Guy & Cahill (1999) showed participants emotional and neutral sets of film clips. They found that all participants recalled more emotional than neutral clips regardless of whether they were allowed to talk about (and therefore rehearse) the film clips. However they mention in their discussion, that it was not possible to control participants' covert rehearsal of the emotional films. This is an important point as participants probably spent more time thinking about the emotional films. It is even conceivable that the participants who were instructed not to discuss what they had seen may have rehearsed the information even more than the participants instructed to talk about it. Wegner et al. (1987) report how trying to suppress thinking about a white bear makes the thought occur more frequently. Guy & Cahill (1999) do not report any measure of how much participants talked about each category of films, merely that the participants who were instructed to talk, discussed them with at least 3 other people. Thus it is possible that they talked about the emotional films with more than three people.

Schmolck, Buffalo, & Squire (2000) carried out a study in which participants' memories of how they heard the verdict of the OJ Simpson trial were recorded both soon after the event, and again after a delay of either 15 months or 32 months. Amount of rehearsal was indexed by a self-report rating of how much they had talked about the event. Although such ratings are inherently problematic this may have been a more reliable index of rehearsal than in the study described above. As participants were not asked to suppress their talking, it would have been a reflection of what was actually going through their minds. However, there is the issue of whether participants' retrospective memories (for the amount of discussion of the verdict) were accurate. After 15 months

rehearsal, interest in, and strength of opinion about the trial were all predictive of memory consistency. Both rehearsal and interest were correlated with the strength of emotional reaction at first hearing. After 32 months *only* emotion was predictive of memory accuracy.

Overall, although extra attention and rehearsal may aid memory for emotional arousing material they still do not fully explain the phenomenon.

1.3.3.Semantic Cohesiveness

Category membership enhances memory. This is partly because the category provides a cue to prompt recall. Category membership also acts as a basis for 'chunking' at encoding. Emotional events are naturally related (they are all emotional), and therefore this can be a mechanism by which memory for them is enhanced. This would particularly be an issue in experiments where memory for a group of 'emotional' stimuli is compared to memory for other stimuli.

Phelps, LaBar and Spencer (1997) conducted two experiments on memory for emotional (e.g. *lucky, funny, victim, error*) and neutral words (e.g. *stamp, spare, switch, locate*) in patients who had had unilateral temporal lobectomies leading to unilateral amygdala damage, and in matched healthy controls. Despite deficits in memory consistent with hippocampal damage, the patient groups showed the same pattern of memory for emotional and neutral words as the control groups. Affect words, or neutral words embedded in affective sentences, were recalled significantly better than words that did not have an emotional valence. This is discrepant with the large body of work which has led to the conclusion that the amygdala is a necessary structure for enhanced memory performance associated with emotional stimuli. (see section 1.4).

Amongst other hypotheses put forward to explain this discrepancy, Phelps et al proposed that although the emotional stimuli were emotional in meaning, they did not actually cause emotional *arousal* in the subjects. The emotional component of the stimuli was their meaning. Because the emotional stimuli all belonged to the same semantic category, there would have been strong inter-item associations between the stimuli. Therefore organisational strategies would have given these stimuli a memory advantage. Phelps et al hypothesised that words belonging to the category 'emotion' benefits encoding and/or retrieval in much the same way as words belonging to any other semantic category.

This hypothesis was supported by a later case study of a patient with bilateral amygdala damage conducted by Phelps et al (1998). In a series of emotional episodic memory tasks it was found that the patient was only impaired in a subset of these tasks. These were restricted to tasks when episodic memory benefits from arousal. Therefore they concluded that a specialised 'emotional memory' system is only active when retention is enhanced by arousal. They postulated that emotion can enhance episodic memory by contributing an organising principle such as a schema or category to the material, and that this does not require the amygdala.

Maratos, Allan, & Rugg (2000) argue that high levels of semantic cohesion can also lead to a high false recognition rate for emotional words. This is explained using ideas from the area of false memory (reviewed by Johnson and Raye, 2000). In a typical false memory experiment (e.g. Milani & Curran, 2000) subjects study several lists of related words. Each list contains one 'critical lure', a word which is semantically related to the words on the list, but not presented on the list. For example if the presented words were *thread, pin, eye, sewing, sharp, point, pricked, thimble, haystack, pain, hurt, and injection*, the critical lure would be *needle*. Memory of the word lists is tested by free recall and/or recognition. Subjects usually 'falsely' produce several of the critical lures in the memory tests.

Therefore, Maratos et al (2000) argue that if emotional stimuli in a memory test are semantically related, (as proposed by Phelps, et al, 1997 and Phelps 1998), then emotionally valenced words may act as 'related lures'. This should lead to recollection of emotional stimuli that were not presented. They tested this hypothesis with a recognition test for emotionally negative and neutral words. They found that although a greater number of negative words were correctly recognised, there was a much greater false alarm rate for these emotional words. Thus recognition *accuracy* was better for the neutral items.

To try and control for this effect Maratos and Rugg (2000) performed an experiment where all the stimuli were neutral words. Therefore there would have been no 'emotional' semantic category. These neutral words were then embedded in emotional sentences. For example for the critical word '*gas*' the sentences used were '*she put the pan on the stove and turned on the gas*' and '*she put her head in the oven and lit the gas*'. Recognition memory for the

critical words was tested. Although there was no behavioural difference between recognition of words from the two contexts, brain event related potential (ERP) data indicate a qualitative difference between remembering words from emotional contexts and words from neutral contexts. Left parietal effects were larger and more sustained for words that had been embedded in emotionally negative contexts, and a right frontal effect was exclusively elicited by these words.

Therefore overall although the semantic cohesiveness of material can aid the retention of emotional material, it does not fully explain the enhancement of memory.

1.4.Neuroanatomical substrates

It is apparent that none of the factors - distinctiveness, extra attention and rehearsal or semantic cohesiveness - can alone account for al the findings of enhanced memory for emotional material. Although there remains the possibility that an interaction between these may still underpin the observed memory facilitation, there is further evidence that there is a specific 'emotional memory' mechanism. This comes from research suggesting that memory for emotional material has specific neural and hormonal mechanisms Hamann (2001). In other words, there is some evidence that memory for emotional material has qualitatively different neuroanatomical substrates from memory for neutral material, and the two can also be dissociated pharmacologically.

1.4.1.Animal work

Since 1939 when Kluver and Bucy described the consequences of temporal lobe damage in monkeys, a large body of animal studies have been carried out investigating the sites in the brain important for emotional processing.

More recently studies of fear conditioning in the rat have described the neural pathways that can be used for emotional learning, (reviews: Gallagher & Chiba, 1996; LeDoux 1998; LeDoux 1999; LeDoux 2000; Fendt & Fanselow 1999). The role of the amygdala has featured largely in this research. A vast amount of work has also isolated the basolateral nucleus of the amygdala as important for the instrumental learning of emotionally motivated responses (for review see McGaugh, 2003). Furthermore, the participation of the amygdala in rat learning

depends on the degree of arousal induced by the training (Cahill & McGaugh 1990). When stimuli are not arousing (e.g. the location of a drink) the amygdala is probably not involved. Although it is acknowledged that human studies have been guided to some extent by concepts arising from the animal work, the details and controversies of animal research on the neuroanatomy of emotional memory will not be discussed in any depth here, and the reader is referred to McGaugh (2003), or LeDoux (1999).

1.4.2.Emotional memory and amnesia in humans

There is some evidence that profoundly amnesic patients still retain some memory for emotional information. An early and often cited example of this was Clarapede (1911) who pricked his densely amnesic patient with a pin as they shook hands. Later she refused to shake hands with him, although she did not know why.

Korsakoff's syndrome is a degeneration of the mammiliary bodies, and anterior thalamus, and sometimes frontal lobes related to thiamine deficiency, mainly in alcoholism. In an early study of emotional memory in amnesia, Korsakoff's patients were shown pictures of faces, matched with descriptions of the persons' characters as essentially good or bad. Although the patients showed no explicit memory for the descriptors they still retained a sense of liking 'good guys' and disliking 'bad guys' (Johnson, Kim, & Risse,1985). More recently Candel et al. (2003) have described how Korsakoff's patients remember the destruction of the twin towers on 9/11/03 despite being densely amnesic. However in comparison to control subjects, their memories of the event were not as consistent over time. The first question used to test patients memories in this study was *'what happened on September 11, 2001'*. It could be argued that this was not a very good a cue for personal emotional memories. The salience of the date may have been added later by the media. Thus this could perhaps have been a test of the patients' memories for highly rehearsed information, rather than 'emotional' memory.

The classic neuropathology associated with amnesia is hippocampal damage. Fear conditioning can be thought of as an implicit emotional memory, a basic form of remembering an emotion. In this paradigm an innocuous stimulus such as a tone, or light is paired with an aversive event such as an electric shock or

loud noise. After a few pairings, if the 'fear' is 'remembered', the subject starts to make fear responses such as increased skin conductance, or potentiated startle to the aversive (previously neutral) stimulus when it is presented alone. Bechara, Tranel, Damasio, Adolphs, Rockland, & Damasio (1995) found that a patient with selective bilateral damage to the hippocampus showed fear conditioning, despite being unable to explicitly recall which stimulus predicted the aversive event.

Hamann, Cahill, & Squire (1997) showed that despite remembering a lower overall number of pictures amnesic patients still showed a proportional enhancement of memory for emotional pictures. Similarly, Hamann et al. (1997) described that, despite having low overall levels of explicit memory, amnesic patients still show relatively facilitated memory for the middle emotional section of a story with emotional and neutral elements. This story task was designed by Cahill & McGaugh (1995) and consists of 11 or 12 slides with accompanying audio narration. Slides 1-4 are neutral describing a little boy leaving home and walking with his mother. Slides 5-9 are emotional; the boy gets hit by a car and has to be rushed to hospital to have his severed feet reattached. The final few slides are supposed to be neutral and show the mother leaving the hospital to collect her other child from nursery. Using this story task, people with amygdala damage or healthy people given ß-blockers (see below, sections 1.4.3., and 1.5.3) show impaired emotional memory. However its use with the small samples of amnesic patients is problematic as the group of patients participating was too small to use the available non-emotional control stimuli. A further criticism that applies to both experiments is that because the patients were amnesic the memory test had to take place very soon after the studying of the pictures. Therefore it is possible that the additional coherence or category fluency of the emotional stimuli, may have contributed to the effects.

Emotional memory has also been investigated in Alzheimer's disease - a common form of dementia which frequently involves early degeneration of the amygdala. A naturalistic study investigating Alzheimer's patients' memories of the Kobe earthquake in Japan, found that their emotional memories, but not general knowledge, of the event were correlated with normalised (averaged across both sides) amygdala volume (Mori et al. 1999). Interestingly, normalised hippocampal volume was unrelated to either type of memory.

Hamann, Monarch, & Goldstein (2000) showed that in early Alzheimer's disease, memory for emotional (particularly negative picture) stimuli was disproportionately impaired, compared to neutral stimuli. Hamann, Monarch, & Goldstein (2002) found this effect extended to fear conditioning. Patients with suspected Alzheimer's disease were impaired at acquiring a skin conductance response to a coloured circle that had previously been paired with an aversively loud noise.

However, Moayeri et al. (2000) and Kazui et al. (2000) used the Cahill & McGaugh (1995) story task with Alzheimer's patients and found facilitation of memory for the emotional middle section was spared. This can be explained in terms of non-emotional properties the emotional section of the story may have had, that make it more memorable. Possibly it is more semantically coherent. Thus there is some evidence for a dissociation between memory for emotional and neutral material from some amnesic patients, whose memory advantage for emotional material has been relatively spared. The exception to this is patients with early Alzheimer's disease, where impairments of emotional memory are associated with amygdala atrophy.

1.4.3.Emotional memory and amygdala damage

Patients with damage exclusively to the amygdala, particularly bilaterally are rare. Early research found that the amygdala did not have a role in memory. For example, Scoville & Milner (1957) concluded that *'Removal of the amygdala bilaterally does not appear to cause memory impairment'*.

More recent studies have found selective deficits to emotional memory after amygdala damage. Babinsky et al. (1993) reported that their patient, a woman with bilateral temporal lobe damage where the main region affected was the amygdalae showed normal intelligence and memory, excepting a specific impairment of memory for emotional material.

Markowitsch et al. (1994) studied two patients with Urbach-Wiethe disease, a very rare congenital lipoid storage disease, that can selectively damage the amygdala bilaterally. They found some impairments in memory exclusively for emotional pictures and words, and concluded that the amygdala added an 'affective flavour to memories'. Another Urbach Wiethe patient tested by Cahill, Babinsky, Markowitsch, & McGaugh (1995) showed selectively impaired

memory for the middle emotional section of a story (the same story as was discussed above in section 1.4.2). Further, Adolphs, Cahill, Schul, & Babinsky (1997) found that memory for the middle emotional section of the story was impaired in two more similar patients.

Bechara et al (1995) famously tested three patients. One, an amnesic, had fairly selective damage to the hippocampal region. This was the patient discussed above. The second had damage localised to the amygdalae, and the third showed damage to both these regions. In a fear conditioning paradigm, the amygdala damaged patient showed impaired ability to form the association between the stimulus and fear response, despite having the explicit knowledge of which stimulus predicted the aversive event. This was in contrast to the patient described above with hippocampal damage. The patient with brain damage in both areas was not able to form either the explicit memory or the conditioned response. LaBar et al. (1995) tested a slightly larger sample of patients with unilateral amygdala lesions, and found impaired fear conditioning. Although this shows a dissociation between emotional and non-emotional memory, it should also be noted that it also follows the classic implicit / explicit memory dissociation.

As discussed above (section 1.3.3), Phelps et al. (1997) observed memory facilitation for emotional words in their unilateral lobotomy patients, and proposed that when emotional material gained its advantage through normal cognitive processes such as semantic grouping, the amygdala was not involved. Phelps, LaBar, Anderson, O'Connor, Fulbright, & Spencer (1998) reported a case study which further confirmed the amygdala only has a role in memory when an advantage was gained from emotional arousal. The patient described had bilateral amygdala damage due to Urbach Wiethe disease. She exhibited deficits in a fear conditioning task and the Cahill & McGaugh (1995) story task, but not in tasks where emotional material had a memory advantage that could have been due to semantic emotionality.

Patients with amygdala damage seem to *experience* a normal range of affect, both in response to the emotional stimuli, used in the studies described above (Adolphs et al, 1997; Cahill et al, 1995; Phelps et al, 1998; Phelps, LaBar, & Spencer, 1997; LaBar & Phelps,1998) and in their day to day lives Anderson &

Phelps (2002). Thus poor memory for emotional stimuli does not reflect a lack of emotional reaction to these stimuli.

Thus although amygdala lesions, particularly bilaterally are fortunately very rare, they have consistently been reported to lead to memory deficits restricted to emotional information.

1.4.4.Imaging studies with healthy volunteers

Imaging studies have demonstrated amygdala involvement in memory for emotional material in healthy volunteers. Cahill et al. (1996) demonstrated that glucose use by the (right) amygdala observed using positron emission tomography (PET) correlated with memory for emotional (but not neutral) films. Hamann, Ely, Grafton, & Kilts (1999) found that there was a relationship between degree of amygdala activity (PET) and memory for emotional picture stimuli. They found that amygdala activity was related to long-term (but not immediate) recognition memory of both positive and negative emotional pictures. They included an 'interesting' condition of pictures that were emotionally neutral, but interesting. Although this improved memory, the improvements were not associated in any way with increased oxygen utilisation by the amygdala.

Canli and associates in two functional magnetic resonance imaging (fMRI) studies, also found that reactivity of various brain regions including the (left) amygdala was related to long term retention of both blocks of (Canli et al. 1999) and individual (Canli et al. 2000) emotional stimuli. In the latter study, memory was only facilitated by the stimuli that both caused the most activation and were rated as the most subjectively emotional. This led them to conclude that there was a minimum threshold of emotional arousal that had to be surpassed before the 'emotional memory' system would be activated.

Tabert et al. (2001) also described (right) amygdala activation during the encoding of negative words in right handed women, and found this correlated with long term, but not immediate recall for the words. Thus any emotional memory system is not just activated for pictures but also by language stimuli.

Canli et al. (2001) also described how differences in reactivity were related to personality variables. Reactivity to positive stimuli was related to extraversion and to negative stimuli to neuroticism. Later studies (Cahill et al, 2001; Canli et

al, 2002) have shown that there is a gender difference in lateralisation of amygdala activation during encoding of emotional stimuli, and that this may be related to functionality (Cahill & van Stegeren; 2003). Therefore there are individual differences in activation, even in healthy volunteers, and two variables that may help explain them are personality and gender.

In a review of imaging studies of fear conditioning Buchel & Dolan (2000) report that a feature of the early PET studies of human fear conditioning was the absence of the expected amygdala activation. However these early studies compared activation before conditioning (habituation) with activation after conditioning (extinction). These conditions are not equivalent. More recent imaging studies use a different classical conditioning paradigm. They compare activation to a stimulus that was previously paired with an aversive experience, with a similar stimulus which had never been paired with the aversive experience. Buchel & Dolan (2000) report that studies like this show the predicted amygdala activation, even when the stimuli are presented out of conscious awareness. Even newer imaging techniques with greater temporal resolution, show that amygdala activation to the conditioned stimulus decreases over time. This is suggestive that the amygdala is most active during *encoding* of emotional memories. However this suggestion is currently the subject of heated debate (for example by LeDoux, 1999; Vazdarjanova, 2000).

Findings from imaging studies, taken together with the data from brain damaged patients and data from rats and monkeys thus strongly implies that the amygdala plays a crucial role in the formation of emotional memories, a part it does not play in the formation of memories about neutral events. Taken with the evidence from cognitive psychology, it appears that there is a mechanism active when remembering emotional events that is neuroanatomically and functionally distinct from the well established memory processes active when remembering neutral events.

1.5.Neurochemical Research

One of the earliest explicit hypothesis for a specific neurochemical mechanism of emotional memory was put forward by Kety (1970) who hypothesised that, during emotional events, noradrenaline in the forebrain acts to selectively

enhance cell firing in neurons receiving environmental inputs. Persistent facilitation of firing during these events leads to enhanced memory.

Since then research into neurochemical systems that modulate emotional memory has mainly concentrated on the roles of glucocortoid, adrenergic, opioid peptergic, GABAergic and cholinergic systems. This review will focus mainly on the actions of catecholamines and GABA. (Although it is accepted that no neurochemical system acts in isolation and therefore other systems will be mentioned in passing, but not dealt with as thoroughly.)

Animals have no ability to give informed consent, no right to withdraw, and no possibility of being successfully debriefed. It is unlikely that the knowledge gained will be applied to the long-term benefit of the animals' own species, and possible that it will not generalise to humans. Thus the ethics of submitting animals to emotional memory experiments, where they may experience levels of stress, discomfort, and pharmacological treatments deemed unacceptable for human volunteers are dubious. However the majority of the testing of psychopharmacological hypotheses of emotional memory has taken place in animals, so unlike the previous sections that work will be discussed alongside the human research.

Most of the animal studies described tested the behaviour of rats in an 'inhibitory avoidance' test. This is done with a box containing two compartments; the first compartment is small and brightly lit (mice and rats are afraid of brightly lit spaces), with a door leading to a second compartment. The animal starts each trial placed in the first compartment, and when it enters the second compartment it receives an electric shock. Memory is quantified by time taken to enter the second dimmer compartment when the rat is later reintroduced to the box. Rats who 'remember' the shock take longer to enter the compartment where it happened, and do not enter this compartment within a criterion time. As much of the interest has been the effect of various compounds on consolidation, in most of the animal experiments drug treatments were administered shortly after training, and given time to clear from the animal before retention was tested. This removes the possibility that the drugs affect memory through some non-specific process (for example altering the amount of exploratory behaviour in the box).

1.5.1.Stress hormones

A clear candidate for a pharmacological basis for emotional memory is the endogenous stress hormone, adrenaline. Adrenaline is widely accepted to be released in stressful circumstances, and studies looking at the its role in memory consolidation in animals have confirmed that post-learning injections of adrenaline enhance retention of the aversive event in the inhibitory avoidance task (Gold & van Buskirk 1976; Gold & van Buskirk 1978a; Gold & van Buskirk 1978b; Gold, van Buskirk, & Haycock 1977; Gold & Van Buskirk 1975; Gold, Van Buskirk, & McGaugh 1975; Van Buskirk, Gold, & McGaugh 1975). Christianson & Mjoerndal (1985) compared the effects of adrenaline (0.007 mg/kg) with saline on memory for verbal descriptors accompanying faces. Despite having observable physiological and subjective effects, the adrenaline injections did not affect memory for these verbal descriptors. Christianson et al. (1986) performed a similar study where they compared memory in adrenaline (0.007 mg/kg) treated volunteers on a similar stimulus set, with memory in a group of saline treated volunteers who were shown grotesquely disfigured faces as some of the stimuli. These emotionally arousing stimuli impaired memory for the accompanying descriptors. However no memory effect of adrenaline was found. There was no group of adrenaline treated volunteers who saw the emotional stimuli. Adrenaline treated volunteers only ever saw neutral faces. The main finding of this work was that the adrenaline injections had no effect on memory.

The hypothesis put forward by Christianson and Nilsson to explain this finding was that the volunteers in the adrenaline group might not have attributed their increased arousal to the pictures, as the injections were a possible cause of arousal. Thus the (neutral) stimuli would have been unlikely to be attributed as a cause of arousal (this comes from the theory of Schacter and Singer, 1965). Although Christianson et al (1986) report that 'almost all subjects injected with adrenaline attributed the autonomic changes as symptoms of nervousness due to the experimental situation itself' any perceived nervousness would be unlikely to be attributed to the stimuli. More plausible factors to attribute increased arousal could have been the EEG apparatus used or personal performance on the task.

A further reason for the findings would be that Christianson was trying to find emotionally induced amnesia (for the accompanying verbal descriptors) in his subjects via adrenaline. As discussed above, arousal is associated with memory detriments when memory for peripheral information is tested immediately. The stimuli used (verbal descriptors accompanying faces) were peripheral for the saline treated volunteers when arousal was induced emotionally (by the pictures of horribly disfigured faces). However in the adrenaline-arousal, condition the verbal descriptors would have been central information as the task set at encoding was to choose a descriptor to fit the face. Because memory was tested after a short time interval (12mins) the effect of adrenaline on consolidation would not have time to be assessed. It is conceivable that memory for the verbal descriptors might have been *improved* in the adrenaline group had they been tested after a longer delay.

A more recent study studied the number and type of traumatic memories held by patients who had been in intensive care (IC) (Schelling, 2002). Adrenaline, noradrenaline, and hydrocortisone are frequently given to IC unit patients with serious cardiac or vascular failure. The number of types of traumatic memory increased with the dose of all three of these drugs, although interestingly pharmacologically increased cortisol levels seemed to be associated with decreased levels of PTSD. A more experimental study of the effects of cortisol on human memory was carried out by Buchanan & Lovallo (2001) who found that pharmacologically raised cortisol levels at encoding led to enhanced memory for emotionally arousing (but not neutral) pictures. However the cortisol manipulation also caused participants to rate unpleasant pictures as more emotional, which makes interpretation of any subsequent memory effect problematic.

The two main hypotheses for a mechanism by which adrenaline affects the brain are by inducing glucose release (e.g. Gold 1995) and by activating ß-adrenoceptors on the vagus nerve which leads to the amygdala via the nucleus of the solitary tract (e.g. Jensen 1996). Both hypotheses have found support coming not only from animal studies (see review by McGaugh 2003), but also studies with humans (Clark et al. 1999; Blake, Varnhagen, & Parent 2001; Parent, Varnhagen, & Gold, 1999).

1.5.2.Stimulant drugs

"This is a call to all my
past resignations ....
... Ritalin is easy
Ritalin is good..."
FooFighters (1995)

There are many stimulant drugs which easily cross the blood brain barrier. McGaugh has accumulated a vast body of evidence from animal research that post-training injections of many stimulant drugs facilitate learning in the inhibitory avoidance task, (reviews: McGaugh 1973; McGaugh et al. 2000; McGaugh 2000; McGaugh, Roozendaal, & Cahill 2000). His first study tested the effects of strychnine, but subsequent work showed that drugs that stimulate catecholamine receptors (e.g. amphetamine), block GABA receptors (picrotoxin and bicuculine), block opiate receptors (naloxone and naltrexone) or facilitate cholinergic transmission (oxotremorine and physostigmine) all enhance memory when given in aversively motivated learning tasks such as the inhibitory avoidance task described above.
The neuroanatomical locus of action of these drugs has been investigated in rodents. Packard, Cahill, & McGaugh (1994) showed that in an aversively motivated task (forced swimming) amphetamine injected into the hippocampus facilitated memory for a spatial location (the location of a platform), and amphetamine injected into the caudate-putamen facilitated memory for a cue (a symbol marking the platform), but not *vice versa*. However injections of amphetamine into the amygdala facilitated both types of memory. Using new techniques (Gallagher et al, 1981; Gallagher & Chiba 1996) it has been possible to further isolate the important region for this action to the basolateral nucleus of the amygdala. McGaugh's (2000) review of relevant studies concluded that in this type of research there is little evidence for modulation of memory by the central nucleus, but intrabasolateral injections of stimulants enhance memory.

These types of highly invasive procedures are never used with humans. In humans tests of the effects of stimulant drugs investigate systemically administered drugs, given either orally or by intravenous (i.v.) or intramuscular (i.m.) injection. Studies of the effects of stimulant drugs on human memory have found more mixed results. Most of the work examining the effects of

amphetamine on human memory has concentrated on patient groups. For example children with ADHD (for review see Barkley, 1997), patients with schizophrenia (e.g.Kirrane, 2000), Alzheimer's disease (e.g. Kittar and Hauser, 1999), clinical depression (Little, 1993), and patients receiving high doses of opiates (e.g. Bruera et al 1992). Other studies have assessed effects in severely fatigued soldiers who had not slept for several days (e.g. Giam, 1997).

As baseline neurotransmitter function and memory performance can effect the memory modulating effects of stimulant drugs (Mehta et al. 2000;Mehta 2002, Fleming et al. 1995) these results should be generalised with caution.

Soetens and colleagues carried out a series of five experiments on the effects of amphetamine on human memory looking at the long-term retention of lists of unrelated words (Soetens et al. 1995; Soetens, D'Hooge, & Hueting 1993). The elegant design of the series of experiments allowed the observed facilitation on this task to be attributed to the effects of amphetamine on consolidation in the hour after learning.

In the first experiment of the series subjects given amphetamine and control subjects (placebo and no drug controls were used in this experiment) remembered the same percentage of words in an immediate free recall test. A delayed free recall test at the end of the session showed that the amphetamine group had forgotten marginally fewer words than the other groups. When tested 24 hrs later, the control and placebo groups had forgotten significantly more words than the amphetamine group.

The second and third experiments manipulated the timing of drug administration. This narrowed down the time window when amphetamines aid learning to the hour *after* list exposure, and suggested that consolidation is still taking place more than 30 minutes after learning.

Their fourth experiment confirmed previous results, demonstrated that the recall advantage persisted for at least three days, and showed that the effect increased with longer presentation times. The fifth experiment demonstrated that the effect generalised to recognition, and was not due to enhanced encoding due to earlier recall acting as a form of rehearsal.

Analysis of false positives in each of the five experiments confirmed that the improved recall scores were due to improved retention rather than readiness to

guess words. During experiment 3, (i.m. injection) the period between learning and test was filled with unrelated questions. This confirms that these results were not due to increased rehearsal in the amphetamine group. This series of experiments seem to confirm the results of the animal experiments reported by McGaugh (2000) that amphetamine can improve memory through a post-learning consolidation process.
Two other studies have explicitly reported improvements in human memory by single dose of a stimulant drug. Rapoport (1980) reported improvements on a learning task in healthy men after a single oral dose of dextroamphetamine. Camp-Bruno & Herting (1994) found improved performance on the Buschke selective reminding task in healthy volunteers given methylphenidate.

In contrast, Wetzel, Squire, & Janowsky (1981) report impaired memory after a single (0.5mg/kg i.v.) dose of methylphenidate, and no effects of smaller doses of methylphenidate. The results showed that there were no differences between methylphenidate and placebo groups on retention of material learned before administration of methylphenidate. Impaired memory following methylphenidate was observed in the immediate recall of paired associates, and story recall. What is more interesting, and not discussed by Wetzel et al, is that there was no difference between the groups on recall of the same information 24 hours later. Therefore it appears that although subjects given methylphenidate recall less at immediate test, after a longer delay they do not differ from the placebo group. This may be an effect of 'time between encoding and retrieval' effect as discussed previously (section 1.2.1).

There is also a possible influence of 'level of arousal' at the immediate test. Participants in the methylphenidate group had just received the drug intra - venously[3]. Their pulse rate increased from approximately 65bpm to 115bpm. Although other drug effects were not reported, these could be assumed to have gone through the same dramatic changes. These were drug naïve subjects and it would not be surprising if during the 'rush' of their first i-v injection of stimulant drugs their attention was not fully on the test. Therefore although Wetzel et al's

[3] Where injections of amphetamine were given by Soetens (1993,1995) they were intramuscular.

hypothesis of disruption of attention during learning is reasonable, their claim that methylphenidate 'impairs learning and memory' is premature. The evidence that the memory deficits are much less apparent after 24hrs could perhaps be taken as evidence for methylphenidate induced enhanced retention. This would be consistent with the view that stimulant drugs have a facilitating effect on memory consolidation and with Soeten's (1993,1995) findings with amphetamine.

However none of these tests are analogous to the intensely stressful inhibitory avoidance paradigm used in McGaugh's series of animal experiments. There are doubts about how similar any test of human episodic memory can be to the (procedural) learning undergone by a rat. It can also be questioned how closely human emotion resembles the stress experienced by an animal. However, there have been two studies of noradrenaline agonists in humans on an emotional task: one by O'Carroll et al (1999) who tested the effects of yohimibine and the other by Papps et al. (2002) who tested the effects of reboxetine. These are discussed below.

1.5.3.Noradrenaline

Most of the stimulant drugs described above increase levels of noradrenaline in the amygdala[4], some, such as amphetamine do this directly by promoting noradrenaline release, others such as bicuculine and naloxone do it indirectly by blocking the action of inhibitory neurotransmitters. McGaugh et al. (1993) report that intra-amygdala injections of ß-blockers can block the memory enhancing effects of systemic injections of naloxone, and this is also true of bicuculine (Dickinson Anson & McGaugh, 1997). ß-blockers also attenuate the memory enhancing effects of adrenaline and the stress hormones McGaugh, Roozendaal, & Cahill (2000). McGaugh proposes that the mechanism by which all these drugs enhance retention and the way that emotional arousal facilitates memory is that consolidation is modulated by raised levels of noradrenaline in the amygdala (see Figure 4).

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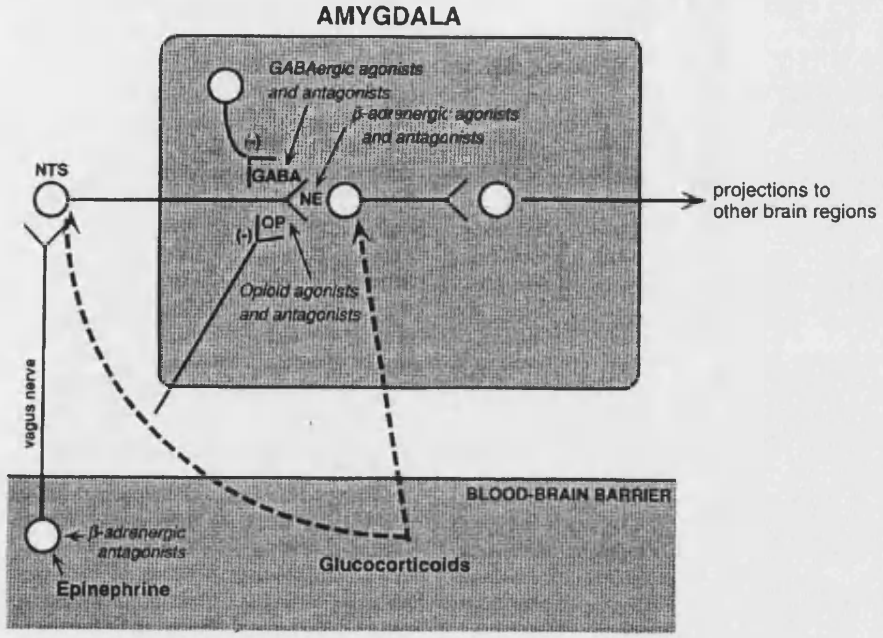
[4] The exception to this is the drugs acting on cholinergic receptors. To date the evidence suggests that the noradrenergic influences on memory are mediated through a subsequent step, through cholinergic influences. The amygdala has projections to several brain regions that are rich in cholinergic neurons.

Figure 4: Diagram illustrating the theory of the interaction between neurotransmitters promoting memory enhancement by emotional material: Reproduced from McGaugh (2000)



Early studies of the effects of ß-blockers on human memory had mixed results. Ghoneim et al. (1984) found some impairing effect on free recall of words, but Madden et al. (1986) found no significant effects on memory in a group of hypertensives. However these early studies were again not analogous to the stressful aversively motivated tasks used with animals.

Research by Cahill et al (1994) found more convincing evidence for a role of adrenergic hormones in the enhancement human of memory by emotional arousal. They used propranolol, a β-adrenergic antagonist that acts both peripherally and in the central nervous system and blocks the action of adrenergic hormones. They performed a study where 15 healthy volunteers received placebo and 20 volunteers received propranolol before watching a story with emotional and neutral sections (as described in section 1.4.2 above.). Half of each drug group saw an emotional and half saw an equivalent neutral version of the story. The subjects were then given a surprise memory test one week later.

Results showed that subjects who received propranolol had significantly impaired memory for the emotional story, but that memory for the neutral story was unimpaired. The impairment was due to a lack of enhanced performance in the middle emotional phase. Because propranolol did not impair memory for the neutral story or for the neutral phases of the emotional story, Cahill et al (1994) claim that the results cannot be due to non-specific sedative or attentional effects. One problem with this task is that the three story phases were predefined as emotional or non-emotional. The validity of this categorization has not been tested. A further issue is whether Cahill & McGaugh (1995) actually managed to keep both versions of the story the same (except for the emotionality). Although the pictures were identical and the narratives closely matched for grammatical and syntactic structure and for comprehensibility, there are still differences between the two stories. Critical differences may have been the coherence of the story, the amount of personal versus technical information, how interesting the story was, novelty of the material, and centrality of the boy character in the story.

Further use of the same task has been made to investigate the effects of central *versus* peripheral nervous system manipulations of arousal. Both vanStegeren et al (1998) and O'Carroll et al (1999a) used three subject groups. One group were given propranolol a β- adrenergic agonist which acts both centrally and peripherally, one group were given placebo, and one group were given nadolol. Nadolol is a water-soluble β-adrenergic agonist which does not cross the blood brain barrier but has similar peripheral effects to propranolol.

The results of the vanStegeren et al (1998) study confirm those of the previous study by Cahill et al (1994). Propranolol but not nadolol reduced memory for the emotional component of the story. These results were interpreted as showing that central β-adrenergic receptors are responsible for the enhanced storage of emotional material.

In contrast, a study by O'Carroll et al (1999a) used the same three drugs, but found that in all conditions subjects showed *better* memory for the emotionally arousing material. This finding is clearly discrepant with both Cahill et al (1994) and vanStegeren et al (1998).

O'Carroll et al (1999b) compared stimulation with blockade of the central noradrenergic system. The β-blocker given was metoprolol. Metoprolol is

selective to the β1 receptor whereas propranolol is non-specific and acts on both β1 and β2 receptors. The noradrenergic system was stimulated with the central adrenergic agonist, yohimbine. There was also a placebo group. The experiment used the same story paradigm, however this time only the emotional version of the story was used.

Like O'Carroll et al (1999a) the findings of this experiment showed a memory improvement for the central emotional part of the story in all of the drug groups. However differences between groups were that the volunteers given Yohimbine performed best in both the recall and recognition tests, and volunteers given the β-blocker performed worst on both tests. (The placebo group performed in between these two groups.) There were no differences between the groups for the initial non-emotional story phase. The differences in recall performance (which were in the predicted order of yohimbine, followed by placebo, followed by metoprolol) were only just statistically significant for the emotional second phase of the story and not the other phases.

In the recognition memory test O'Carroll et al (1999 b) found that the predicted order effect was only statistically significant for the final phase which had been classified as neutral. Although the groups were ordered in the expected way, there was barely a difference between them, on recognition memory for the middle emotional phase of the story. Thus as the metoprolol group performed worst and the yohimbine group performed best on the (supposedly neutral) final phase, it could be argued that the difference between recognition memory for emotional and neutral phases was smallest in the yohimbine group and largest in the metoprolol group. This is the opposite of what was predicted by the hypothesis. However this is probably not a reasonable conclusion as (1) it is debatable whether the final story section really is neutral (2) the results are confounded as the middle emotional section received extra rehearsal as more of it was retrieved during the recall part of the experiment.

A more recent study by Papps et al, (2002) investigated the effects of reboxetine, a noradrenaline reuptake inhibitor on memory in an emotional task. They found that the effects of reboxetine on memory were opposite to those predicted. Reboxetine impaired memory. Reboxetine also did not alter the relative facilitation of memory for the middle emotional section of the story. Although reboxetine increased blood pressure throughout the story

presentation, it did not alter subjective emotion ratings of the story. This finding was discussed in the light of possible anticholinergic effects and in terms of the level of arousal may have been 'too high', taking participants to the declining side of the arousal-performance inverted U shaped curve. However as it stands the study does not support the hypothesis that increased noradrenaline levels facilitate consolidation.

The evidence from three of these studies (Cahill et al, 1994; van Stegeren et al, 1998; & O'Carroll et al, 1999b) and from animal research (e.g. McGaugh, 1989,1990,1992) points to the involvement of the noradrenergic (NA) system in the enhancement of memory by emotional arousal. Thus in retrospect Kety's (1970) ideas were in part correct. However the research in humans has not had consistent findings, and two, perhaps three of the published studies found results that do not support the hypothesis.

1.5.4.GABA (Gamma-aminobutyric acid) and Benzodiazepines

"My mind is wide asleep,
My conscience deep awake..."
NOFX: Pump up the Valium (2000)

In rodents, GABA-ergic agonists (muscimol, bacolofen) and antagonists (bicuculine, picrotoxin) impair and enhance memory storage respectively (McGaugh 2000 p. 396; McGaugh, Introini-Collison, Cahill, Castellano, & et 1993; McGaugh & Cahill 1997). As mentioned at the beginning of the previous section McGaugh proposes that this is due to the effects of GABA on noradrenaline release. Evidence for this is as follows.

Early research by Breen & McGaugh (1961) found facilitation of maze learning in rats given picrotoxin. This finding was replicated and extended by Brioni & McGaugh (1988) who found post-training injections of GABAergic antagonists (picrotoxin and bicuculline) dose-dependently enhanced retention of an inhibitory avoidance task. However in a Y maze discrimination task, the results were not as clear, possibly because the Y maze is not as emotional (animals had to learn the location of a food reward). In contrast to the facilitation of learning due to the antagonists, Castellano et al. (1989) report that the GABA agonist Baclofen impairs retention on the inhibitory avoidance task.

Consistent with the idea that these mnemonic effects are due to the drugs acting on an 'emotional memory' mechanism, they appear to require an intact

amygdala. Bilateral lesions of amygdala block the effects of the GABAergic agonist muscimol and the antagonist bicuculline on retention of an inhibitory avoidance task (Ammassari-Teule et al. 1991).

Drugs whose main action is assumed to be noradrenergic reverse the actions of GABAergic drugs. Introini-Collison, Castellano, & McGaugh (1994) showed that propranolol blocked the enhancement due to post training bicuculline, and clenbuterol blocked the impairment due to muscimol.

The GABA-ergic drugs mentioned above are not licensed for use in humans. GABA levels are more often manipulated in human psychopharmacology with the benzodiazepine class of drugs. Benzodiazepines act on the $GABA_A$ receptor to increase the frequency of chloride channel opening (Cooper et al, 1991).

The benzodiazepines are a very widely prescribed class of drugs. From 1960 until around 1980 their use increased exponentially and they became the most widely prescribed psychotropic drug in the world. Their main clinical utilities are promoting sleep and alleviating anxiety. However they also have a range of cognitive effects, particularly the dose-dependent impairment of episodic memory (for review see: Curran 1999; Curran 2000; Curran & Weingartner 2002). Curran (1999) reports that other memory systems are preserved relatively intact. An interesting effect is the relative facilitation of memory for information learned shortly before administration of a benzodiazepine (Weingartner et al. 1995). There have been hundreds of studies on the effects of benzodiazepines for neutral information. However, the effects of benzodiazepines on human memory for *emotional* material have been less thoroughly investigated.

There are some animal studies of benzodiazepines and inhibitory avoidance. An early study in mice, was carried out by Jensen et al. (1979). They found that systemic injections of either diazepam or lorazepam administered prior to training increased the number of trials needed to acquire an inhibitory avoidance response. Further flurazepam administered immediately after training (consolidation) impaired retention of the avoidance response. This is one of only two studies to report retrograde impairment of memory after a benzodiazepine. (the other was by Platel and Porsolt, 1982) However, according to Cahill, Brioni, & Izquierdo (1986) the (1.0 mg/kg) dose of flurazepam used by Jensen

and colleagues was very high and therefore may account for the unusual results.

Decker, Tran, & McGaugh (1990) compared diazepam with scopolamine on the inhibitory avoidance paradigm. The rats received systemic injections of the drug before learning. Scopolamine impaired learning of the inhibitory avoidance response (i.e. increased the number of times the rat was shocked before they learned). Diazepam however impaired retention but did not slow acquisition of the avoidance. Tomaz, Dickinson Anson, & McGaugh (1991) found that the amnestic action of the benzodiazepine diazepam on the inhibitory avoidance task is dependant on the animal having an intact amygdala. Tomaz et al. (1993) further isolated the locus of action of benzodiazepine amnestic effects on this task to the amygdala. Silva and Tomaz (1995) found that, like propranolol, intra baso-lateral amygdala injections of benzodiazepines impaired memory on the task, but intra central nucleus injections had no effect.

Flumazenil is a benzodiazepine antagonist, thus it should block the action of endogenously released benzodiazepine-like compounds. Da Cunha et al. (1999) found that flumazenil enhances memory for inhibitory avoidance training when injected post-training to the basloateral amygdala, but has no effect in the central amygdala. They report that it is an 'interesting paradox' that flumazenil should have an effect post training, when benzodiazepine agonists do not. Dickinson Anson & McGaugh (1993) showed that as with other benzodiazepines, a systemic injection of midazolam injected (before training) into the amygdala impairs memory for an inhibitory avoidance task. They also found that bicululine (a GABA antagonist) reversed midazolam induced amnesia when injected into the amygdala (Dickinson Anson, Mesches, Colman and McGaugh, 1993), and the effects can still be observed even with post training injections (Dickinson Anson & McGaugh, 1997). This is not the case with the medial septal area Dickinson Anson & McGaugh (1994). Thus although benzodiazepines administered post-learning do not have an effect on memory, their effect when given pre-learning can be blocked post-learning by giving a GABA antagonist.

Thus there is evidence from animal studies that benzodiazepines may block the facilitation of memory by emotion. This is over and above the standard memory impairing effects of this class of drugs. The mechanism for this has been

hypothesised by McGaugh to be due to enhanced GABA action, blocking the effect of noradrenaline in the amygdala, on consolidation. However the fact that benzodiazepines do not cause retrograde memory impairments (if anything causing retrograde memory facilitation) can be seen to present problems for this theory. The only evidence that benzodiazepines can impair memory consolidation comes from animal studies and is indirect.

Despite the wide interest in the memory impairing effects of benzodiazepines, in humans their effects on memory for emotional material have only been investigated once. Zangara and Curran (2000) in a published abstract, report that the effects of diazepam on the Cahill & McGaugh (1995) story task are comparable to propranolol: The benzodiazepine disproportionately impaired memory for the emotional story section. Although diazepam also impaired memory for all sections of the story there was no relative facilitation for the emotional material.

1.6.Conclusions and Research Questions

In summary, there is a variety of evidence that memory can be facilitated by emotion. As discussed in this chapter the criteria for observing this phenomena are: a long enough time being left between encoding and retrieval, level of arousal being raised, and memory for central 'gist' information being tested. The facilitation is clearly due in part to the enhanced attention and rehearsal that emotional material receives. The effect may also, at least in part, be due to the material's distinctiveness and semantic cohesiveness. However, memories of emotional material show a distinct pattern of central and peripheral material being remembered, and rates of forgetting over time are different from neutral material. Therefore memory for emotional material does appear to be not just quantitatively, but also qualitatively psychologically different from memory for less arousing material.

There is evidence from animals, brain damaged patients, and neuroimaging of healthy volunteers that memory for this type of material also has dissociable neuroanatomical substrates from memory for less arousing material. Therefore there is evidence that suggests that 'emotional memory' is a mechanism that is functionally and neuroanatomically distinct.

The dominant theory of a neurochemical basis of this mechanism is that adrenaline and corticosterone are associated with noradrenaline release in the amygdala. This noradrenaline release promotes enhanced consolidation of emotional material (possibly by activating projections to other brain structures where memory is modulated by acetylcholine.) Levels of noradrenaline in the amygdala are modulated by opioid and GABA systems, and benzodiazepines affect this system by facilitating GABA action.

The vast majority of the evidence for this theory comes from work with rodents. The hypothesis originated with findings from animal work that post-learning injections of stimulant drugs in animals enhance memory for the inhibitory avoidance task. As reviewed in this chapter the interactions of various drugs in these experiments suggest that the common action of stimulants is increasing noradrenaline levels. The implication is that noradrenaline agonists should facilitate consolidation in humans. However, as discussed, the findings from human studies of memory following noradrenergic stimulation (by drugs such as the amphetamines and methylphenidate) are sparse and findings have been equivocal. Nearly all the human work has used tasks which are not emotional such as learning word lists. As the 'emotional memory' mechanism is presumably only active for arousing stimuli, noradrenergic manipulations would not be expected to alter memory for non-arousing word lists. However as the two studies where stimuli have been arousing and where levels of noradrenaline have been pharmacologically increased have not provided constant results. Therefore the question of whether increased noradrenaline levels enhance human memory remains unanswered.

The hypothesis that reducing noradrenaline release impairs the action of the 'emotional memory' mechanism has been tested in humans. Reducing CNS noradrenergic action disrupted the effect of emotion on memory in three out of the four studies that have been carried out to date. The implications of the theory for GABA and opioid systems have not been tested in humans. The idea that benzodiazepines may affect consolidation processes is particularly questionable because benzodiazepines have not been shown to cause retrograde memory impairments. Although there is a vast body of research indicating that benzodiazepines cause anterograde amnesia, the question of

whether benzodiazepines disrupt the 'emotional memory' system in humans is also unanswered to date.

1.6.1.Research Hypotheses

This thesis will address some of the unanswered questions identified above by exploring the effects of benzodiazepines and the stimulant methylphenidate upon 'emotional memory'. An experimental perspective will be taken by using a battery of neurocognitive assessments in drug challenge studies. A placebo control will be employed and studies will follow double blind procedures.

As emotion is theorised to enhance memory consolidation through an amygdala based noradrenaline system, it is predicted that participants administered placebo will have superior memory for emotional material. This will be tested by presenting participants with comparable neutral and emotional material, and comparing the amounts remembered from each emotional category. As conventional psychological mechanisms such as semantic grouping may also play a part in memory facilitation, effort will be made to control for these.

The animal work concerning the effects of stimulant drugs on memory points to the hypothesis that stimulant drugs will enhance memory in humans. As the animal studies use stimuli that are emotional for the animal (e.g. electric shock), enhancement of memory for emotional material might be expected. However given that one human study O'Carroll et al (1999b) found weak support for this and another Papps et al (2002) found the opposite, it may be premature to predict this result.

The stimulant drug used will be methylphenidate, a dopamine and noradrenaline reuptake blocker, which can be administered in tablet form. According to McGaugh's research, by blocking noradrenaline uptake methylphenidate should enhance memory for emotional material. As a stimulant drug, methylphenidate is also expected to increase arousal. Methylphenidate is a commonly prescribed drug and therefore results may have clinical implications.

Orally administered benzodiazepines will be used as a tool to explore the action of GABA on the emotional memory system. Benzodiazepines facilitate GABA action, and this theoretically should reduce amygdala noradrenaline levels. Therefore they are hypothesised to block the operation of the 'emotional

memory' mechanism. It is predicted therefore that benzodiazepines will block the superiority of memory for emotional material compared with neutral material. As noted previously, benzodiazepines act in many areas of the brain, they sedate, reducing arousal, and impair episodic memory for all kinds of information. However they tend to impair most types of memory equally. For example a stimulus that has received increased elaboration will be remembered better than a stimulus that has received little elaboration, in a volunteer given a benzodiazepine; however memory for both would have been better if the volunteer had not been drugged. Thus it is predicted that benzodiazepines will impair memory globally. However, if they act as hypothesised to block the emotional memory system they will disproportionately impair memory for emotional compared with neutral material. As benzodiazepines are widely prescribed drugs, findings will also have clinical implications.

CHAPTER 2: A STIMULANT, A SEDATIVE, A STORY, AND SOME SENTENCES: Pharmacological manipulations of arousal and memory for emotional events (EXPERIMENT 1)

2.1.INTRODUCTION

2.1.1.Rationale

The aim of this first experiment was to investigate (1) the feasibility of significantly increasing as well as decreasing arousal pharmacologically, and (2) the impact of these arousal manipulations on memory for emotional and neutral material.

As discussed in Chapter 1 the most developed neurochemical theory of the basis of emotional memory is that advocated by Cahill and McGaugh (e.g. McGaugh et al. 2000; McGaugh & Cahill 1997). They propose that adrenergic activation in the basolateral amygdala is the mechanism by which consolidation of long term episodic memory for emotionally arousing events is enhanced. In three separate experiments they demonstrated that blockade of CNS β1-receptors resulted in a reduction of the memory enhancement associated with emotional material (Cahill et al, 1994; O'Carroll et al, 1999b; van Stegeren et al. 1998).

Noradrenaline release is not the only way in which the brain responds to stress. As discussed in chapter 1, there are many other neurochemical bases of arousal (review: Robbins, 1997). McGaugh et al propose that drugs that increase GABA and the opioid peptides modulate noradrenaline release, and therefore should produce the same effect as noradrenergic antagonists, on memory for emotional versus neutral information. The theory originated in early work by McGaugh with stimulant drugs, which suggested that the amphetamines also modulate the effects of emotion on memory.

Although the noradrenergic part of the theory has been tested in humans, to date the predictions concerning GABA and the amphetamines have only been

tested with rodents. This study was designed to address whether (like the noradrenaline part of the hypothesis), these predictions also apply to humans. Therefore, this experiment used a single dose of a benzodiazepine (lorazepam 1.5.mg) to facilitate GABA action, and test whether this has a disruptive effect on emotional memory, similar to drugs that more directly block noradrenaline. Methylphenidate 40mg was used to test whether McGaugh's findings relating to stimulant drugs in rodents generalise to humans.

Both these drugs are expected to alter arousal. Indeed changes in arousal may well play a part in the way they may modulate emotional memory. Thus increases and decreases in arousal will be assessed. A range of arousal indices (physiological, motor, subjective) will be used as it has been argued e.g. Lacey (1967) that various indices of arousal do not often correlate. Of interest also is how these pharmacological manipulations of arousal may alter the valence (positivity or negativity) as well as the 'activation' quality of mood. Thus the subjective effects scales used required ratings of both arousal and valence aspects of mood.

2.1.2.Choice of Drugs

2.1.2.1.Lorazepam

The benzodiazepine to be used in the current study is lorazepam 1.5mg. Lorazepam was selected as the period of peak drug action is long enough to allow the 1hr battery of tests. Because lorazepam comes into the category of 'short' action benzodiazepines it is expected that this will be more acceptable to volunteers than a drug that takes longer to clear from the body. The 1.5mg dose was selected because on the one hand, a higher dose may cause floor effects on memory (Curran, 1999) and, on the other hand a lower dose may not induce significant effects on memory and arousal. As benzodiazepines are known to impair memory, participants given lorazepam were expected to show poorer memory performance than the placebo group for both emotional and neutral material.

Investigations of emotional memory in healthy volunteers under the influence of benzodiazepines have been carried out by Curran and Zangara (2000). Using Cahill & McGaugh's (1995) story task they demonstrated some reduction in

memory facilitation by emotional material in volunteers who had been given diazepam (15mg). Taken together with the theoretical work by McGaugh this leads to the prediction that, in the current study, lorazepam would disrupt emotional memory, and participants would show a different pattern of results from the placebo group.

The alternative hypothesis is that benzodiazepines do not differentially affect memory for emotional and neutral information. For this to be supported the same pattern of results (i.e. better memory for emotional as compared to neutral material) would have to be observed. If this is the outcome of the experiment, it would be evidence against the theory that pharmacological manipulations of GABA can disrupt the noradrenergic mechanisms responsible for the facilitation of memory by emotional material.

However if, as predicted, benzodiazepines mediate the effect of emotion then there should be no significant difference between memory for emotional and neutral elements in the lorazepam group.

2.1.2.2.Methylphenidate

The stimulant drug chosen was methylphenidate 40mg. Methylphenidate acts in a very similar way to amphetamine, raising synaptic levels of both dopamine and noradrenaline. There is some evidence to suggest that amphetamine may enhance memory consolidation in human subjects (Soetens et al. 1995;Soetens, D'Hooge, & Hueting 1993) but this is not consistent (e.g. Wetzel, Squire, & Janowsky 1981). Reports in the literature about the effects of methylphenidate on memory in healthy humans are sparse, suggesting evidence is hard to find.

As discussed in the previous chapter only two studies have assessed effects of pharmacologically increased arousal on human memory for emotional stimuli. O'Carroll et al (1999b) only found significant evidence for memory facilitation by 20mg yohimbine for material they had classified as neutral[5]. Papps et al (2001) found slightly decreased memory overall, but still relative improvements for emotional material with volunteers given 4 or 8 mg Reboxetine. As no study to date has explored the effects of methylphenidate on memory for emotional

[5] Although this classification may be incorrect, see appendix 1

material, two possible hypotheses are given. It may be that under the influence of methylphenidate all material is encoded under increased arousal. If so, memory for both emotional and neutral material would be equally enhanced. The pattern of emotional facilitation would be the same as placebo. Alternatively, in line with Cahill and McGaugh's theory and the findings of (O'Carroll, 1999a) it could be hypothesised that the prevention of reuptake of noradrenaline caused by methylphenidate will enhance memory for the emotional material even further.

Therefore it is possible that arousal induced pharmacologically with amphetamine or methylphenidate may facilitate long term memory through a noradrenergic mechanism, in a similar way to emotionally-induced arousal. However the main action of methylphenidate is to prevent dopamine reuptake. Rolls (2000) and Everitt et al (2000) argue that dopamine may play an important role in memory for emotional material as dopamine release is strongly associated with reward (e.g. Everitt et al, 1989; Phillips et al, 1989) and possibly punishment, (Rada et al, 1998, Gray et al, 1997) value of an event. Dopamine levels are also high during novel events and hence may be associated with promoting interest in a situation and hence learning. Therefore any observed effect of methylphenidate on emotional memory could be due to both (or either) noradrenergic and dopaminergic mechanisms.

2.1.3.Choice of Test Battery

The tasks chosen to investigate emotional memory were the story task (Cahill and McGaugh, 1995), and the sentences task (Maratos & Rugg 2000). A 5 X 5 picture grid was also used to assess memory. Subjective effects of the drugs were measured using visual analogue scales (Bond and Lader, 1974), and Affect Grids (Russell et al, 1989). Heart Rate, blood pressure, and tapping speed were taken as measures of arousal. In addition a variation of the profile of mood states (POMS) (McNair et al, 1971), a facial expression processing task (Calder and Young, 1996) and a variation of the autobiographical memory test (AMT) (Eich, Macaulay, & Ryan, 1994) were also administered, but provided no useful data, and are not discussed here. A brief description of each task, and the rationale for selecting each task is presented below.

2.1.3.1.Memory Tests

2.1.3.1.1.Story Task

This paradigm was chosen because it is one of the more widely used methods of demonstrating facilitation of memory by emotional material and therefore findings can be compared with others in the literature. Some examples of its use are (Heuer & Reisberg, 1990; Burke, Heuer, & Reisberg, 1992; Cahill et al, 1994; Cahill & McGaugh, 1995; Adolphs et al, 1997; van Stegeren et al, 1998; O'Carroll et al, 1999a; O'Carroll et al, 1999b, & Zangara and Curran, 2000). Cahill and McGaugh (1995) designed the task in its present form. A story comprising some emotional and some neutral elements is presented as a set of slides with accompanying audio narration. Participants watch this slide show and seven days later are given a surprise memory test. In healthy participants memory performance indexed by both free recall and multiple-choice recognition has been demonstrated to be superior for the emotional elements compared to the neutral elements. Patients with amygdala damage, and healthy volunteers given ß-blockers show less differentiation between memory performance for both emotional and neutral story elements.

Emotional responsiveness to the story has usually been assessed by asking participants to fill in a rating scale ranging for 0 'not emotional at all' to 10 'highly emotional' immediately after presentation of the story. To allow comparison with the literature this scale will also be used in the present experiment. However there are two problems with this way of measuring emotional reaction. (1) It may be that this rating scale captures subjects' intellectual knowledge that they were presented with an emotional story. It is conceivable that in a drugged state a participant may know that the story was emotional, but not actually experience the emotion. (2) The rating scale probably captures the valence aspect of emotion, but whether it captures the arousal dimension of mood is doubtful. Theoretically arousal may be more important than valence for enhanced memory consolidation. Therefore to address these two points, affect grids marked directly before and after the story presentation will also be used as a measure of how the story affected participants mood.

2.1.3.1.2.Sentences task

Maratos & Rugg (2000) follow Phelps et al. (1998) in criticising the majority of conventional emotional memory tasks for having too many possibly confounding variables which covary with emotionality (see Chapter 1). Hence they designed a task in which the to-be-remembered material (neutral words) remains constant in all conditions. Embedding these words in either emotional or neutral sentences created the emotional and neutral conditions. They performed an ERP study presented 260 words, and tested word recognition. Fewer stimulus presentations are necessary for behavioural than ERP studies. Therefore a shorter version of this task was developed using 20 sentences (10 negative, 10 neutral). Retention will be assessed by free recall which is more sensitive than recognition to emotional manipulations (Bower, 1981).

2.1.3.1.3.Picture Grid Memory Task

A memory task with a short study-test interval, and no emotional component was used as a control condition to compare the groups.

2.1.3.2.Measures of Arousal

2.1.3.2.1.Visual Analogue Scales – Mood Rating Scale (MRS)

Bond & Lader (1974) developed this scale as a measure of the effects of benzodiazepines on mood. Principal components analysis of the 16 scales yields three mood factors: alertness, contentedness and calmness. Although this scale has been widely used and validated with benzodiazepines and other sedative drugs, it has not often been used and is unvalidated with stimulants such as methylphenidate. Therefore this was not the only mood scale used.

2.1.3.2.2.Affect Grid (Russell et al 1989)

Russell, Weiss, & Mendelsohn (1989) describe how most of the variance in mood described by established mood scales can be represented in a (9x9) grid showing the dimensions of valence and arousal. Participants will be taught to use this grid and will fill in grids at several points during the experiment. This method of measuring mood is particularly relevant to the present study because of the emphasis it puts on the arousal dimension of mood. Balch, Myers, &

Papotto (1999) argue that this dimension is often neglected or confounded with the dimension of valence.

2.1.3.2.3.Physiological and Motor Arousal

Finger tapping speed (motor arousal) pulse and blood pressure (physiological arousal) will be taken both pre and post drug to compliment the subjective measures of arousal.

2.2.METHOD

2.2.1.Participants

Volunteers were recruited from advertisements placed around the university. Prospective volunteers were informed that the study was part of a research programme investigating how drugs affect mood and information processing. They were told they would need to participate in two separate sessions 7 days apart, and that during the first session they would be asked to swallow two capsules. The contents of these capsules could include a sedative or a stimulant or an inactive placebo, and no participant would receive two active drugs. The possible side effects of the drugs were described.

Potential participants who reported psychiatric history, any history of drug or alcohol abuse, pregnancy, risk of pregnancy due to inadequate contraception, diabetes, hypertension, hyperthyroidism, glaucoma or any other medical problem were excluded from the study.

Volunteers who met the inclusion criteria were sent or given an information sheet detailing all the above information and the standard information given to all volunteers for studies involving drugs at UCL. Thus student volunteers were instructed to inform their tutor of their participation and to ensure that taking part in the study would not interfere with their normal studies. All volunteers were informed that they must agree not to take any mood altering drug (including alcohol) the night before and on the day of each test. They also agreed not to drive any vehicle or make any important decisions on the day of the first test session. On test days they were asked to consume only light, low fat meals and no more than their usual amounts of caffeine.

Forty-eight participants (23 males and 25 females) completed the study. They ranged in age from 18-35 years with a mean of 22.77 years.

2.2.2.Design

Volunteers were randomly allocated to one of three parallel groups (methylphenidate, lorazepam, or placebo). A double blind, placebo controlled design was used, and a double dummy procedure was utilised to allow for the different absorption rates of the two drugs (see below). Where tests were repeated, 2 parallel versions were counterbalanced across subjects and conditions.

2.2.3.Procedure

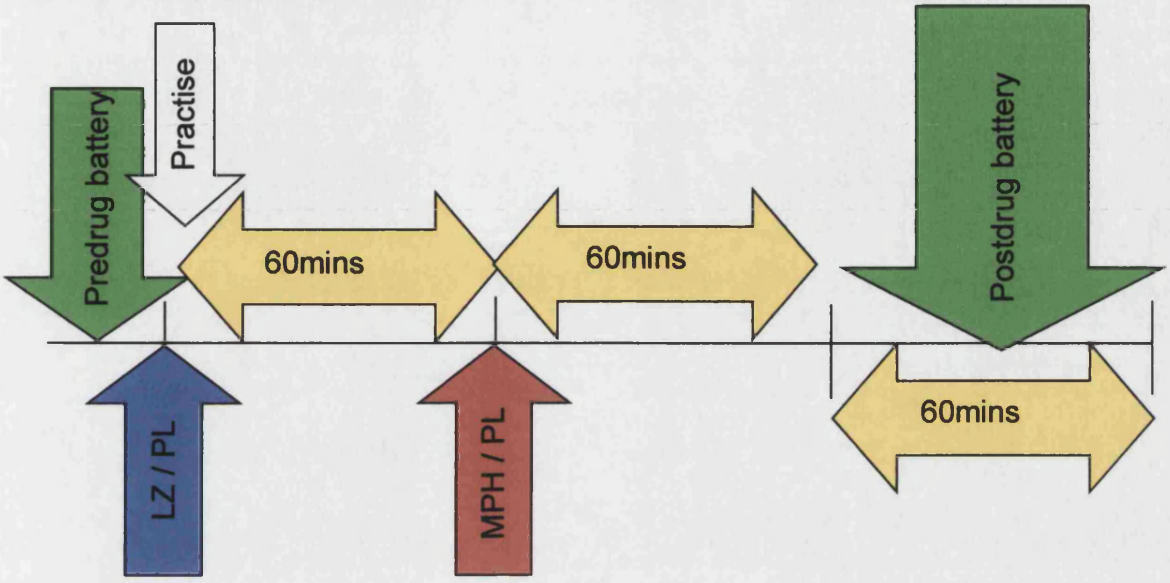
The UCL/UCLH committee on the ethics of human research approved the study (Appendix 12) and all participants gave written informed consent. They then performed the pre-drug battery of tests, which gave base-line measures of mood, motor arousal (tapping), heart rate, blood pressure, and recall performance (see below).

To allow for the different absorption times of the two drugs a double dummy procedure was used. Lorazepam (1.5mg) or lactose placebo formulated in identical gelatine capsules was ingested at time zero (T_0). Sixty minutes later (T_{0+60}) participants received either Methylphenidate (40mg) or lactose placebo also formulated in identical gelatine capsules. Thus treatments were defined as lorazepam (lorazepam T_0 + placebo T_{0+60}), methylphenidate (placebo T_0 + methylphenidate T_{0+60}), or placebo (placebo T_0 + placebo T_{0+60}).

Whist waiting to perform the post-drug test battery participants practised marking the affect grids, and then practised the emotional sentences test.

Two hours later (T_{0+120}) pulse rate and blood pressure was recorded using an OMRON R2 blood pressure monitor and the post-drug battery given below was carried out. The tests were performed in the order in which they are described below. (Test order is given in Appendix 3, timings are represented in Figure 5)

Figure 5: Representation of test timings and administration of lorazepam (LZ), methylphenidate (MPH), and placebo (PL)



2.2.3.1.Mood Rating Scale (Bond & Lader 1974)

This scale consists of 16 visual analogue scales and measures subjective feelings of mood. Participants were presented with 100mm lines anchored at each end with adjectives describing opposing moods. They were asked to take the centre of the scale as representing how they usually feel and to place a vertical line on the scale to describe how they were feeling 'right now'. Scores were measured from the left of the scale in mm. Bond and Lader (1974) constructed three scales from the 16 items: alertness, contentedness, and calmness. The mood rating scale was filled in pre-drug, post-drug and on day 7

2.2.3.2.Finger Tapping Speed (Frith, 1976)

This was used as a measure of manual motor arousal. The participant was instructed to continuously tap the spacebar of a computer keyboard using the first two fingers of the hand they use to write. They were asked to do this as fast as possible for one minute and number of taps made in 60s was recorded automatically. This test was completed pre-drug and post drug.

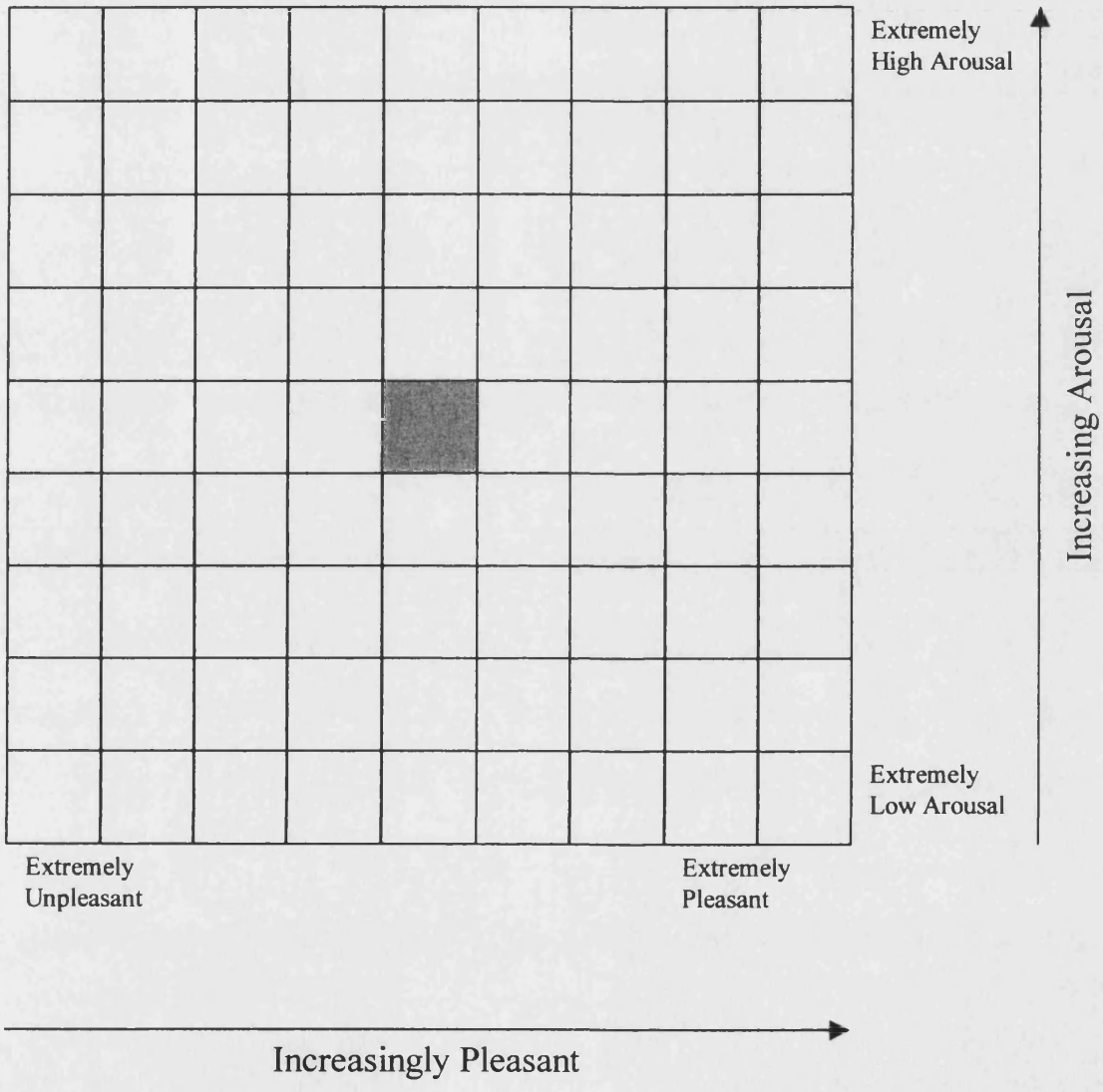
2.2.3.3.Affect Grid (Russell, Weiss, & Mendelsohn 1989)

Participants were presented with a grid as shown in Figure 6. They were told that the grid measured two aspects of their prevailing mood - arousal and pleasure. The extremes of the mood are represented at the edges of the grid and the centre (shaded) square represents a neutral mood in both dimensions. Participants were asked to mark the one square that best corresponds to the levels of pleasure and arousal that they were experiencing at that precise moment. Affect grids were completed pre drug and at 5 time points during the testing battery. Two affect grids were completed on day 7.

Figure 6: Affect Grid

AFFECT GRID

Name_____ **Subject No.**_____ **Time**_____



2.2.3.4.Emotional sentences

In the practise phase of the experiment the participant was informed that one of the tests in the battery would be a memory task, and that it would include emotionally negative sentences. An example of the study phase consisting of the presentation of 2 neutral and 2 negative sentences was then given. The neutral words and emotional sentences were taken from Maratos, Allan & Rugg (2000) (Appendix 7). Participants were presented with 20 sentences in 22 point type on a computer screen. Sentences were presented approximately every 10-15 seconds. Each sentence contained an underlined target word. Ten of the sentences were neutral, and 10 were negative. Sentences were counterbalanced between subjects so that each target word appeared in each emotional context half of its presentations.

Participants were instructed that when each sentence appeared they should read it out loud and try to remember the underlined word in the context of the sentence. They were also asked to give each sentence an affective rating. Ratings were made on a Likert scale (ranging from -3 'negative' to +3 'positive). This scale was presented on an index card, participants reported their ratings verbally, and the experimenter recorded these.

Retention of the words was tested both immediately and after a delay of approximately 20 mins. (This time period was filled with a non-verbal task) Participants were asked to recall as many of the target words as possible. The experimenter recorded words recalled and errors made. On day 7 participants were asked to recall anything they could remember (i.e. this was not usually the target words, but the sentences) from this test and responses were recorded.

2.2.3.5.Memory span task

Participants were presented with a card printed with a 5x5 grid. Each square of the grid contained a picture of a common object. Pictures were taken from the Kendrick object learning test and the Snodgrass and Vanderwart (1981) picture set. Participants were instructed that they would have 75 seconds to look at the objects and try to remember as many of them as possible. When the time was up the card was turned over and the participant was asked to tell the experimenter as many of the things s/he saw as possible, in any order. Recall was scored by awarding a point for each item correctly recalled and deducting a

point for each error. Two parallel versions of the task were used pre and post drug.

2.2.3.6.Emotional story task (Cahill & McGaugh 1995)

Participants watched a slide show with audio narration. The slides and story describe a young boy being involved in a terrible car accident. There are 11 slides consecutively presented, the middle four of which (slides 5-8) are described by Cahill et al as emotional story elements. However rating of the slides for emotionality by 100 independent raters (Appendix 1) have led to a different classification of 2 of the slides. This is 2 groups with slides 1-4 and 11 being 'neutral' and slides 5-10 being 'emotional'. Therefore the volunteers are expected to achieve higher memory scores on slides 5-10, if their memory is facilitated by the emotionality of the material. However if they do not experience emotional facilitation of memory, slides 1-4 and 11 should be better remembered due to primacy and recency effects.

Immediately after watching the show participants rated their emotional reaction to the story on an 11 point scale anchored with 0=not emotional at all, and 10=extremely emotional.

During the follow up session 7 days later, participants were told that their memory for the story was to be tested. The memory test followed the standard multiple-choice format with 5-9 questions per slide presented on a computer screen (Cahill & McGaugh 1995). There were 4 possible answers for each question, and participants gave their answer verbally.

Participants were also asked if they had guessed that their memory for the story would be assessed during the second session.

2.2.4.Statistics

The tests which were administered both predrug and post drug (pulse, blood pressure, Tapping, Affect grid, MRS, Picture grid memory) were analysed using the general linear model (GLM) Repeated Measures procedure in SPSS. Drug group (3 levels) was used as a between subjects factor and 'time' (2 levels, except for affect grid which had 6 levels) was used as the within subjects factor. The GLM repeated measures programme was also used for the emotional memory tasks. Again drug group (3 levels) was used as the between subjects

factor. Emotion was used as the within subjects factor (2 levels in the sentences task, the new categorisation of slides and, the analysis of slide 8, and 3 levels in the Cahill and McGaugh categorisation of slides). In addition the sentences task had a further within subjects factor, test occasion (3 levels). Where required, simple effects of emotion in each drug group were analysed. Where there were more than 2 levels of emotion (the Cahill and McGaugh 1995 categorisation of slides) a priori planned comparisons were used to compare phase 2 (the emotional phase) vs phases 1 and 3 (the neutral phases).
Where Mauchley's W indicated the sphericity assumption had been violated significance levels were corrected using the Greenhouse Geisser method.
For the subjective response to the emotional story a straightforward comparison of the three drug groups was carried out using oneway ANOVA. Descriptive statistics calculated were mean and standard deviation. Unless otherwise specified graphs display means with standard errors displayed as error bars. Change scores are displayed where a reduction in the number of data points enhanced clarity. $p<0.05$ was considered the cut off point for statistical significance throughout.

2.3.RESULTS

2.3.1.Demographics

The groups did not differ in gender ($X^2_2=0.67$, $p=0.72$), or age ($F_{2,47}=1.31$, $P=0.29$) (Table 1).

Table 1: Mean (SD) age and no. of males and females in each group

	Age Mean (sd)	Males	Females
Methylphenidate	23.44 (1.03)	7	9
Placebo	23.56 (1.45)	9	7
Lorazepam	21.31 (0.70)	7	9

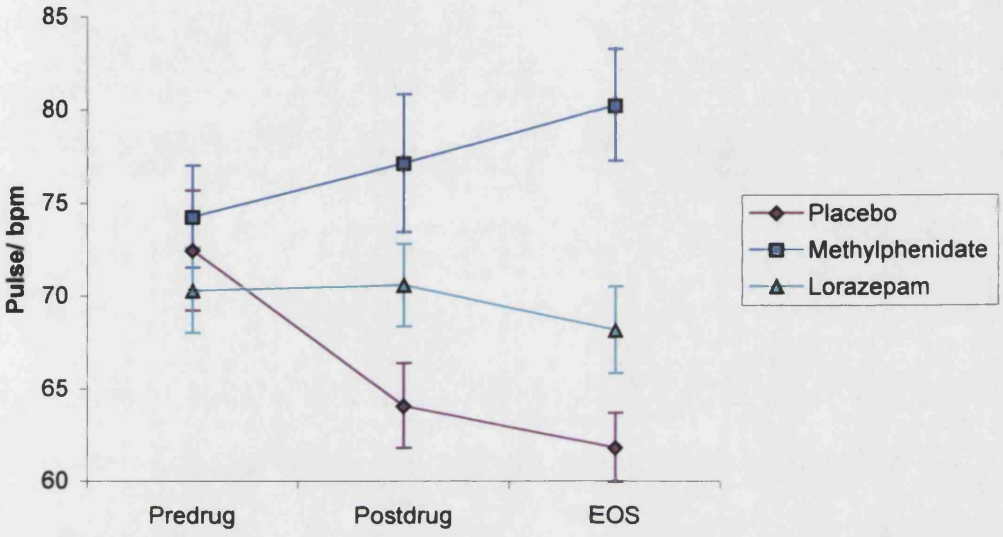
2.3.2.Arousal Measures

2.3.2.1.Physiological Data

As seen in Figure 7 pulse rate dropped over time in the placebo group, increased in the methylphenidate group and remained relatively unchanged in

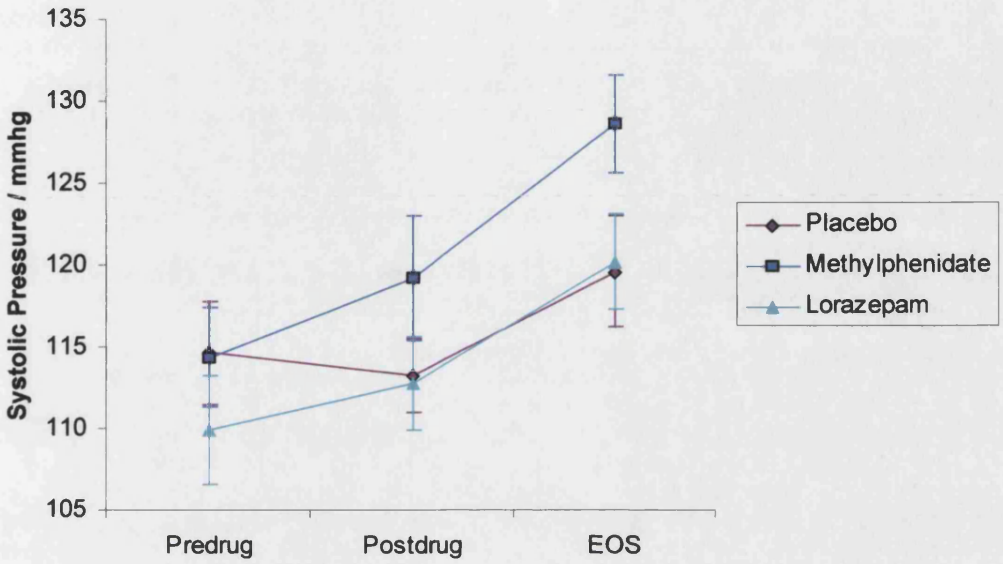
the lorazepam group. This is supported by a highly significant drug x time interaction ($F_{4,90}$=6.95,p<0.001)[GG] and a significant main effect of drug ($F_{2,45}$=5.94,p=0.005) [GG]

Figure 7:Mean (s.e.) Pulse Rate in Each Drug Group PreDrug, At the Beginning of the Main Test Session, and At the End of the Main Test Session.



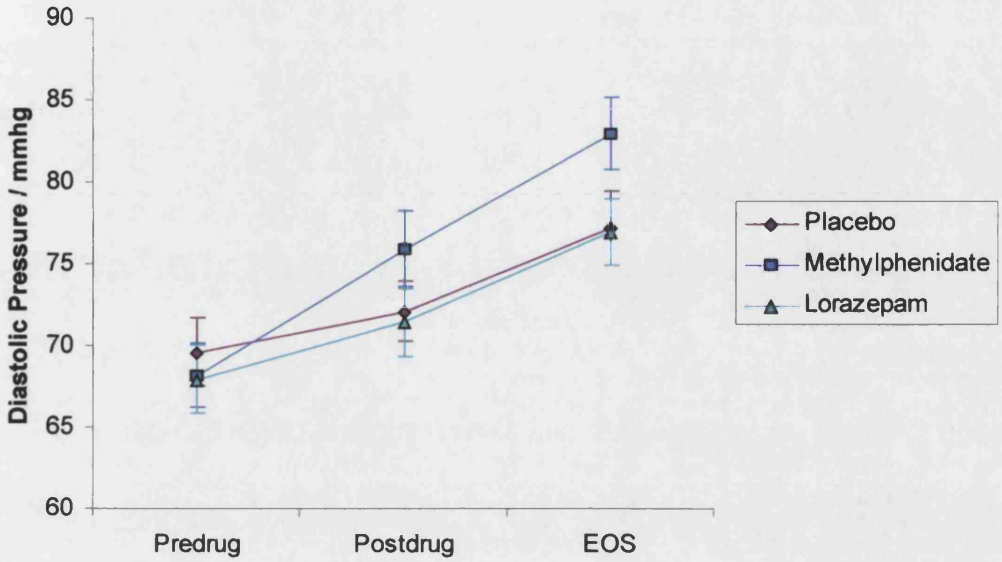
A significant drug x time interaction ($F_{4,90}$=2.64,p=0.039) and main effect of time ($F_{2,90}$=36.687,p<0.001) are evidence for an increase in systolic blood pressure in all drug groups. From Figure 8 it can be seen that the interaction reflects different rates of increase in the three groups with greatest increase in the methylphenidate group, followed by the lorazepam group, with the smallest increase in the placebo group.

Figure 8: Mean (s.e.) Systolic Blood Pressure in Each Drug Group PreDrug, At the Beginning of the Main Test Session, and At the End of the Main Test Session



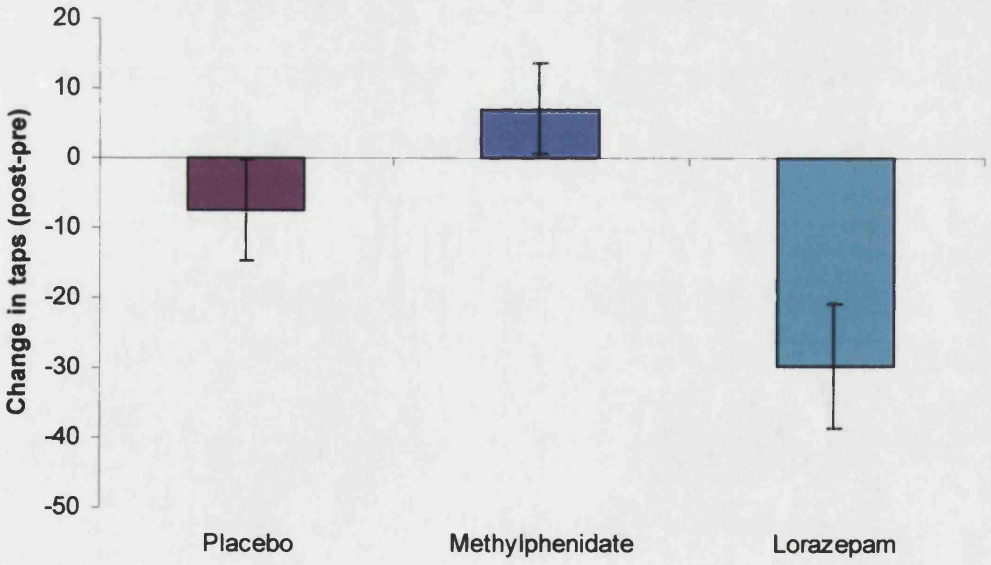
The diastolic blood pressure data showed a similar pattern with a greater increase in the methylphenidate group than in either of the other two groups. (drug X time = $F_{4,90}=3.657, p=0.016$ [GG], main effect of time = $F_{2,90}=77.84, p<0.001$ [GG])

Figure 9: Mean (s.e.)Diastolic Blood Pressure in Each Drug Group PreDrug, At the Beginning of the Main Test Session, and At the End of the Main Test Session



2.3.2.2.Motor Arousal Finger: Tapping Speed (Frith, 1976)

Figure 10: Mean (s.e.) Change in number of taps



There was an interaction between drug and time ($F_{2,45}$=5.89, p=0.005) as well as a main effect of time ($F_{1,45}$=5.25, p=0.027). Change scores (postdrug-

predrug) are shown in Figure 10. Lorazepam decreased and methylphenidate slightly increased motor arousal compared with placebo.

2.3.3.Subjective Ratings of Mood

2.3.3.1.Affect Grid Russell and Weis (1989)

Six affect grids were marked during the first session of the experiment. 1) Predrug, 2) Post drug (after POMS and MRS), 3) After the sentences task, 4) After the emotion perception task 5) After the memory span test and delayed recall of sentences (Immediately before story task), 6) After the story task. The dimensions of pleasure and arousal were analysed separately. For the arousal dimension there was a highly significant drug X time interaction ($F_{10,225}$= 4.59, $p<0.001^{GG}$) and main effects of drug ($F_{2,45}$ = 4.42, p=0.018) and time ($F_{5,225}$=4.54, P=0.003). As seen in Figure 11, compared with placebo there was a fairly steady increase in arousal in the methylphenidate group, and a fairly steady decrease in arousal in the lorazepam group. Ratings of arousal in the placebo group show much more variation which may link to the tasks they completed prior to each rating[6]. In contrast the two drug groups are much less responsive to the individual tasks.

[6] Arousal drops between points 1 and 2 (during this time participants sat quietly and read or relaxed). It then increases slightly as the test session starts and they begin to interact with the experimenter and work on the tests (point 3). Arousal then drops quite dramatically during the emotion perception task (point 4) this was the longest of the tasks taking about 15mins. Arousal then raises slightly after two more short tasks which involve interacting with the experimenter (point 5). Arousal rises again at (point 6) either because the participants are perking up because they know they are about to finish the experiment, or because they are emotionally aroused by the story task (further discussion of points 5 & 6 in the story task section).

Figure 11: Mean Affect Grid Measure of Arousal- Change Scores

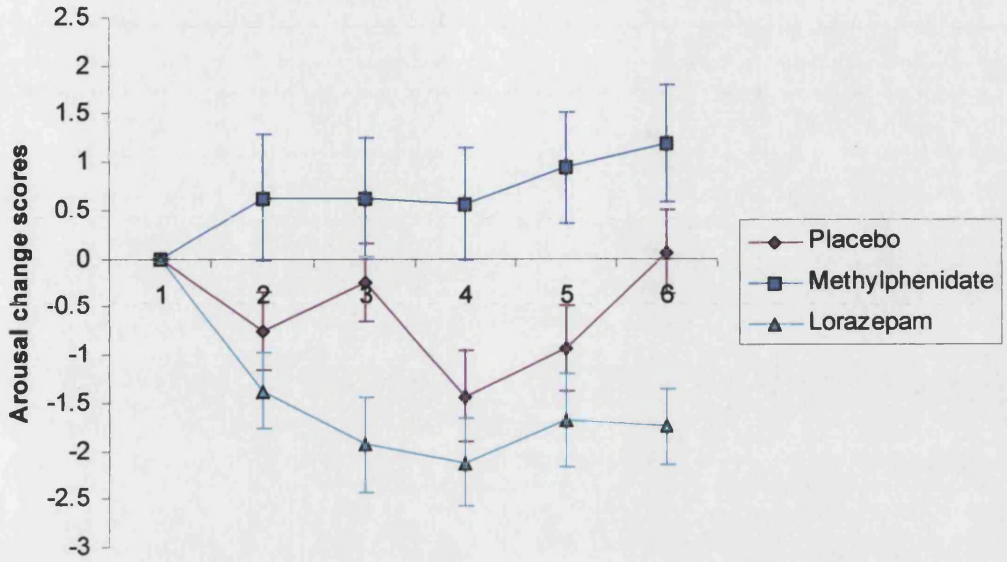
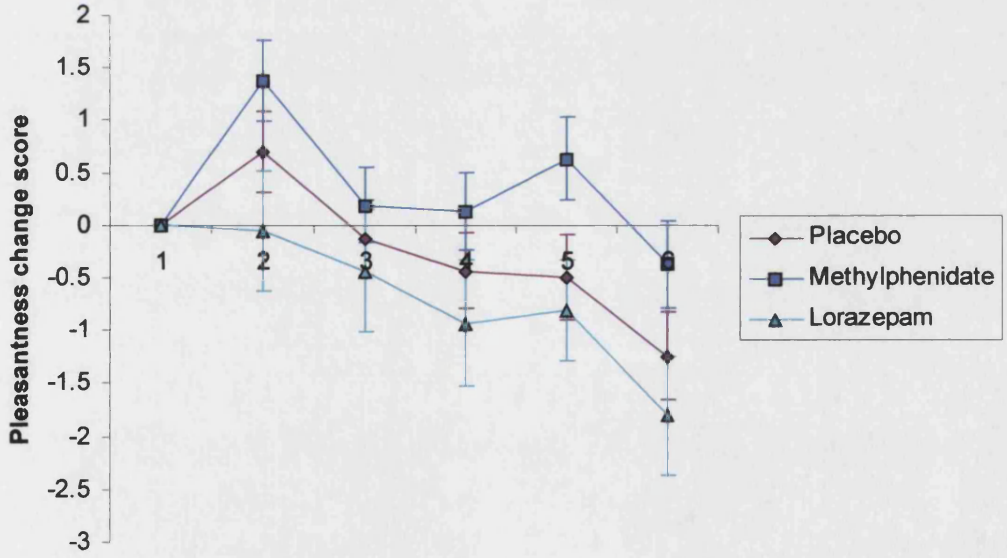


Figure 12: Mean Affect Grid Measure of Pleasantness - Change Scores

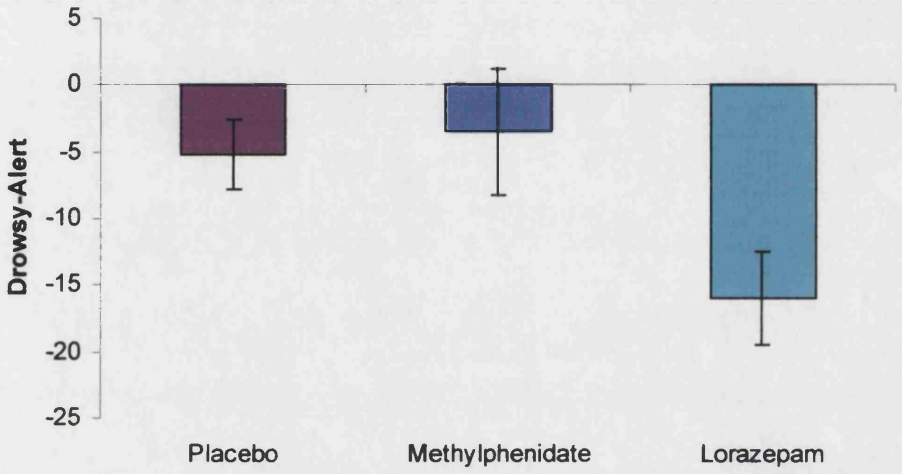


The pleasantness dimension (Figure 12) only showed a main effect of time $F_{5,225}$= 13.95, P<0.001, reflecting a decline in all groups throughout the main test session. (For further discussion of the drop in pleasantness between points 5 and 6 see the story task section.)

2.3.3.2.Mood Rating Scale (Bond & Lader 1974)

The three mood factors were calculated. The only factor to show significant drug effects was alertness with a drug X time interaction ($F_{2,45}$=3.32, p= 0.045) and main effect of time ($F_{1,45}$=14.79, p<0.001). This was due to a large decrease in alertness in the lorazepam group (Figure 13)

Figure 13: Mean (s.e.) Alertness Change Scores



There was no difference between the groups in change in contentedness or calmness (Table 2).

Table 2: Mean (SD) change scores on the contentedness and calm factors

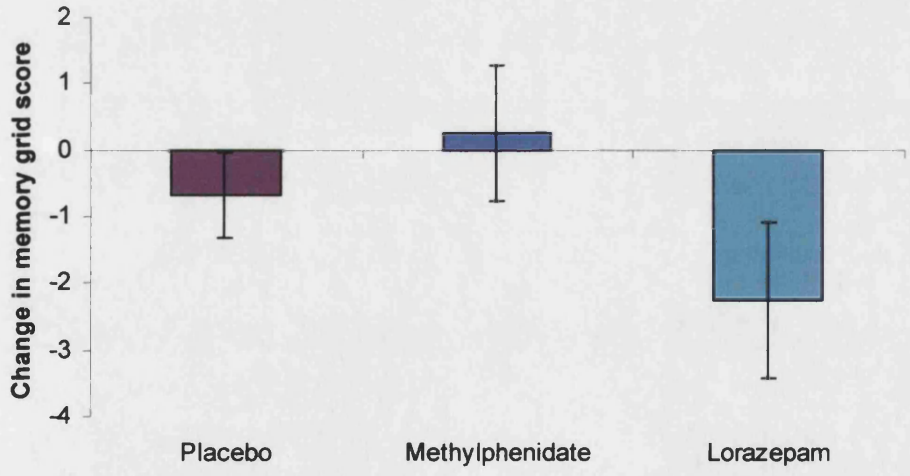
	Contentedness Change /Mean(sd)	**Calm** Change /Mean (sd)
Placebo	-5.33(8.68)	-9.41(14.33)
Methylphenidate	-2.34(9.82)	-1.06(24.46)
Lorazepam	-2.09(8.95)	-8.50(15.81)
ANOVA	F<1, P=0.54	F<1 P=0.39

2.3.4.Memory Measures

2.3.4.1.Picture Grid Memory Task.

There was a trend towards a time x drug interaction $F_{2,45} = 2.54$, p=0.090, and a main effect of time $F_{1,45} = 5.57$, p=0.023. As seen in Figure 14, picture recall deteriorated most after lorazepam, slightly under placebo, and remained unchanged after methylphenidate.

Figure 14: Mean (s.e.) Change in picture grid memory score



Following Mehta et al (2000), and Kimberg et al (1997) a possible relationship between baseline working memory performance and improvement in spatial working memory under methylphenidate was investigated. Participants were divided into 2 groups 'low' baseline working memory (predrug memory span scores <=16) and 'high' baseline working memory scores (predrug memory

span >16). There were 8 participants in each of these categories in each of the methylphenidate and placebo groups.

Figure 15: Mean Memory Span Change Scores for the participants with 'high' and 'low' baseline working memory in the Methylphenidate and Placebo Groups.

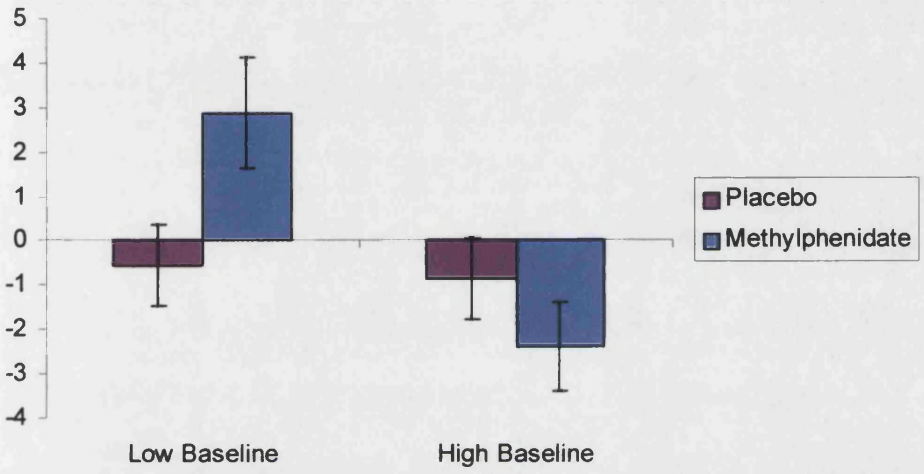


Figure 15 shows that participants with a 'low' baseline memory span score appeared to improve under the influence of methylphenidate. Participants with a 'high' baseline memory span score appear to get worse under the influence of methylphenidate. As baseline memory span does not appear to affect change scores in the placebo group, this effect cannot be explained in terms of regression to the mean. A trend towards a Drug X Baseline working memory interaction was observed $F_{1,28}=3.74$, $p=0.06$, and there was a main effect of baseline working memory $F_{1,28}=4.98$, $p=0.034$, no main effect of drug was observed.

2.3.4.2.Emotional sentences

The number of words recalled at each time point are shown in Figure 16 Figure 17 and Figure 18.

Figure 16: Mean (SD) Words Recalled at Immediate Recall

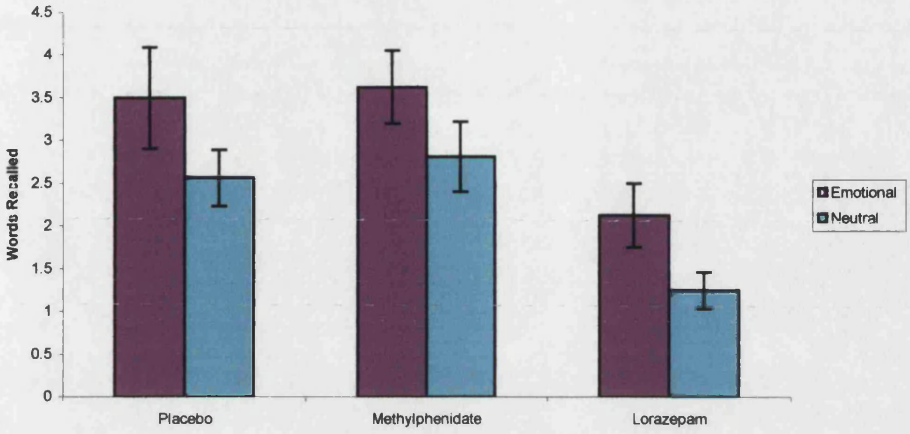


Figure 17: Mean (SD) Words Recalled At Delayed Recall

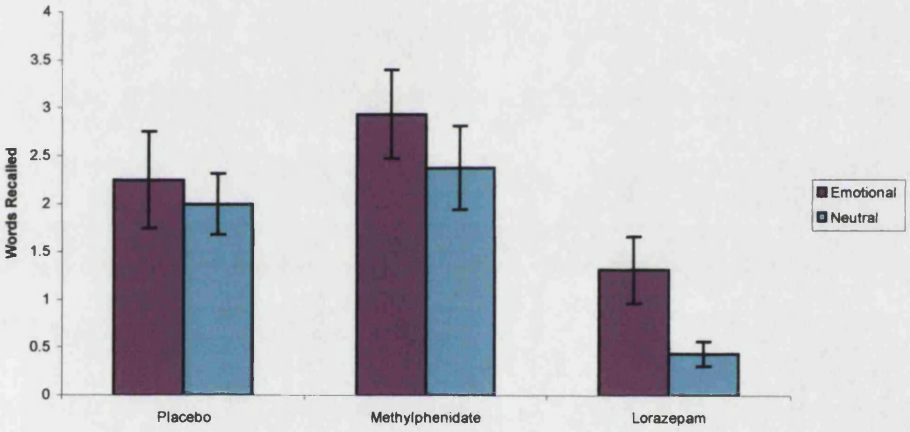
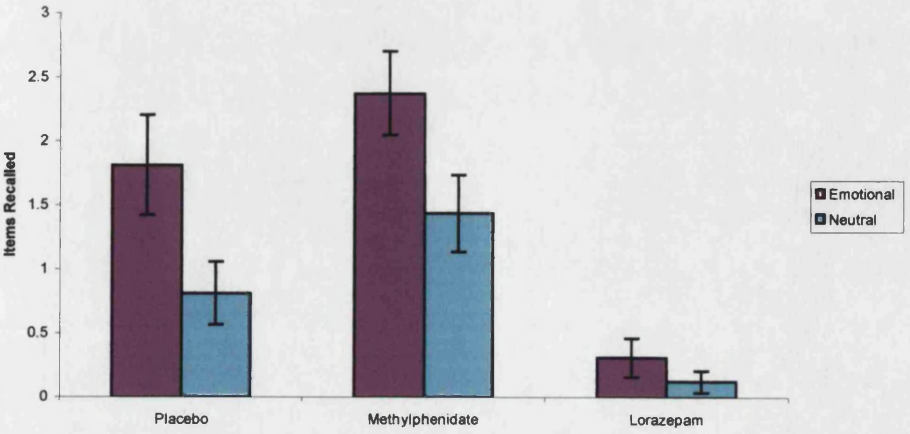


Figure 18: Mean (SD) Words Recalled on Day7



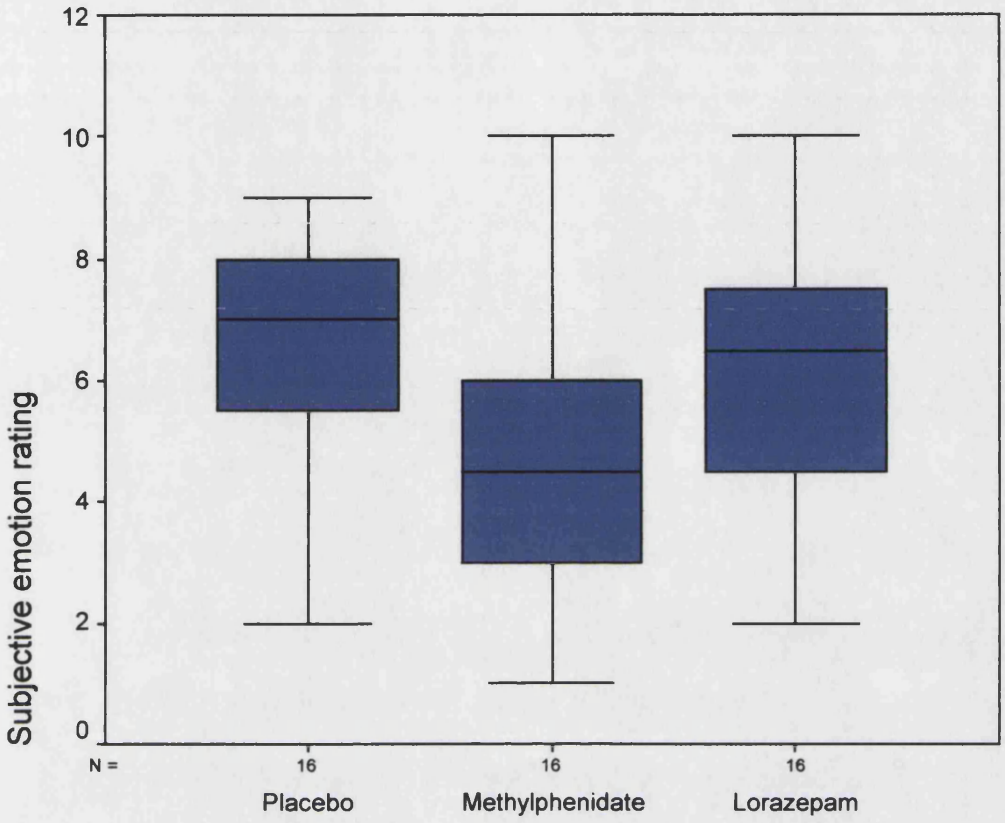
The data were entered into 3 x 2 x 3 ANOVA with two within subjects factors (delay and emotionality) and one between subjects factor (drug group). Main effects of all three factors were found (Emotionality $F_{1,45}$=12.23, p=0.001, Delay $F_{2,90}$=64.79, p<0.001, Drug $F_{2,45}$=10.08, p<0.001) but there were no interactions between the factors. Therefore all groups remembered more words from emotional sentences on all occasions. Participants remembered more words at immediate recall than at delayed recall, and more at delayed than on day 7. The lorazepam group remembered less words on each occasion and in each emotion category than the other 2 drug groups.

2.3.4.3.Emotional story task (Cahill & McGaugh 1995)

2.3.4.3.1.Story Task: Subjective Ratings

Figure 19 shows the distributions of the subject ratings (median, range, and quartiles) of how emotional they found the story (0 = not emotional at all, 10 = highly emotional). ANOVA of these scores showed that the difference between the groups almost reaches statistical significance ($F_{2,45}$=2.81, p=0.071), and Dunnetts test shows that the difference between the methylphenidate and placebo groups almost reaches significance (p=0.057, two-tailed as this was not a predicted effect).

Figure 19: Mean, Range, and Quartiles of Emotion Rating



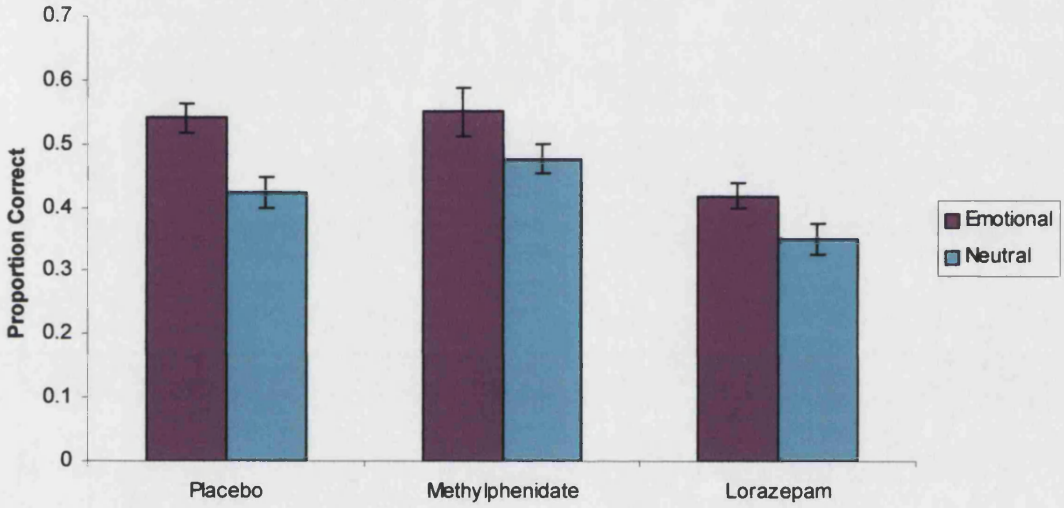
Affect grids were taken directly before and after presentation of the slides and story. These are shown as time points 5 & 6 on Figure 11 and Figure 12. Repeated measures ANOVAs were used to give an index of how the story altered participants' mood. Analysis of the pleasantness dimension showed that all groups reported a less pleasant mood after seeing the slides, than they did before (main effect of time $F_{1,45} = 24.4$, $p<0.001$). There were no effects of drug group or evidence for an interaction.

Analysis of the arousal dimension of the two grids showed a main effect of time ($F_{1,45}=4.705$, $p=0.035$), whereby arousal appears to increase during the story. There was also a main effect of drug ($F_{2,45}=6.325$, $p=0.004$). The interaction between drug and time almost reached significance ($F_{2,45}=2.984$, $P=0.061$) and this appears to be due to a greater increase in arousal in the placebo group than in either of the two drug groups.

2.3.4.3.2.Story Task: Memory Performance: New Categorisation of Slides

Figure 20 shows the proportion of recognition questions correctly answered for emotional material (slides 5-10) and neutral material (slides 1-4 & 11) in each drug group. It shows all three drug groups showing an apparent facilitation of memory for emotional material, main effect of Emotion, $F_{1,45}=29.51$, $p<0.001$). There was a main effect of drug, $F_{2,45}=9.650$, $p<0.001$, but no evidence for an interaction between Emotion and Drug ($p=0.40$).

Figure 20: Proportion of Each Type of Story Material Correctly Recognised



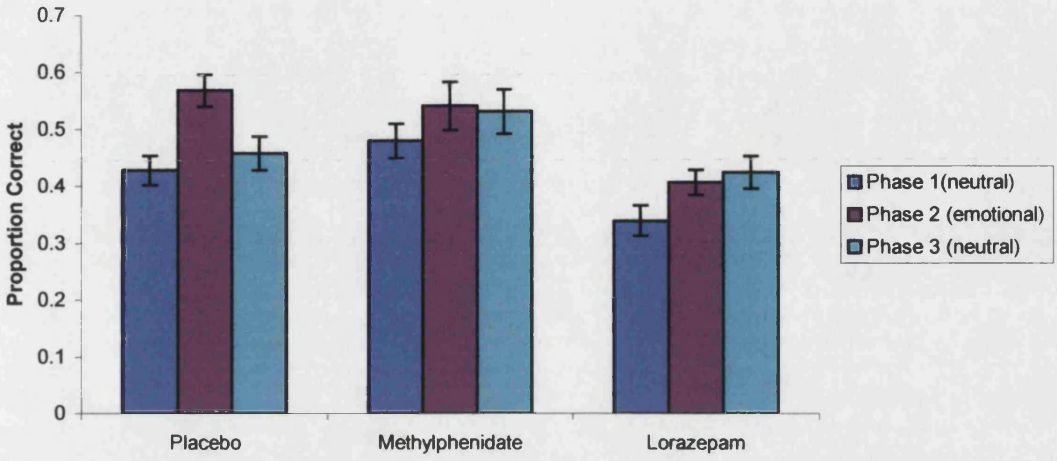
Story Task: Correlations Between Memory Performance and Subjective Ratings

As there was marginal evidence for a difference between the groups on reported subjective emotionality of the story correlations were calculated between these ratings and memory performance. Ratings of emotionality of the slides and story did not correlate with memory for neutral ($r=0.009$, $p=0.952$), or emotional material ($r=-0.129$, $p=0.384$), or with difference between recognition scores for emotional and neural material ($r=-0.142$, $p=0.335$).

Use of an ANCOVA analysis using subjective emotion rating as the covariate was considered. As subjective emotion does not correlate with any of the memory scores, this analysis was rejected.

2.3.4.3.3.Story Task: Analysis Using Original Cahill and McGaugh (1995) Categorisation of Slides

Figure 21: Cahill and McGaugh (1995) Categorisation of Slides



Analysis of these results was also performed using the original 3-way division of slides described by Cahill and McGaugh (1995). Similar to the new classification, the interaction between the factors did not reach significance ($p=0.15$) and there were main effects of Emotion ($F_{2,90}=8.746$, $p<0.001$), and Drug ($F_{2,45}=9.103$, $p<0.001$). However, Inspection of Figure 21 suggests different conclusions from the new classification of slides, as emotionality appears to have a much greater facilitative effect on the performance of the placebo group.

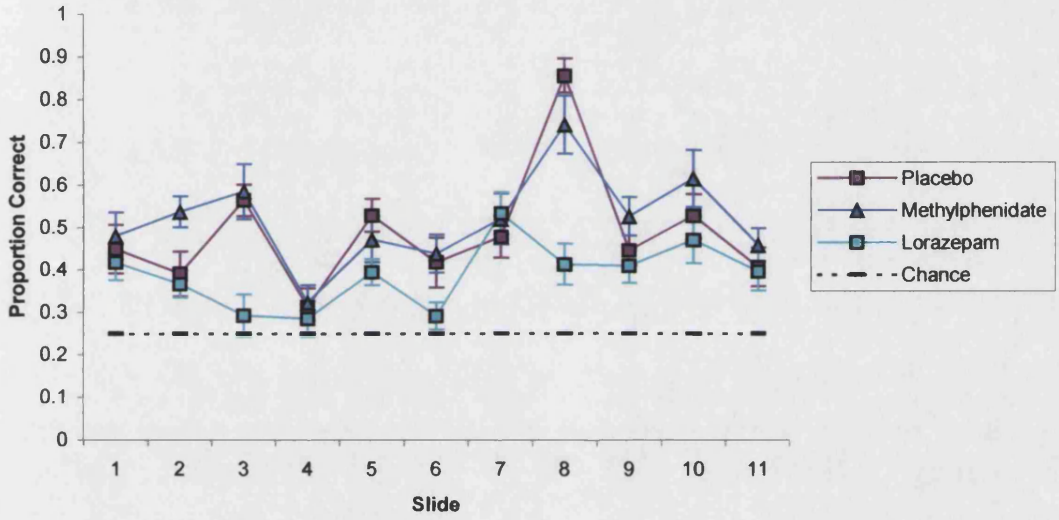
When the effect of emotion category was tested for each drug group separately using the a priori comparisons of phases 1& 3 vs. phase 2 in each drug group, a significant effect was found in the placebo group ($t_{15} = 3.90$, $p=0.001$), but there were no significant differences in the lorazepam group ($t_{15}=0.99$, $p=0.338$), or the methylphenidate group ($t_{15}=1.00$, $p=0.344$)

2.3.4.3.4.Story Task: Slide 8

The mean and standard error of each drug group on each individual slide of the story task is shown in Figure 22. The most notable feature of the graph is the performance of the placebo and methylphenidate groups on slide 8.

These two groups show dramatically enhanced memory on just this slide which depicts a child's 'reattach[ed]... severed feet'. To explore this effect further, post hoc analyses were conducted to see if slide 8 was better remembered than the other 'emotional' slides in this task. The difference between slide 8 and the mean of the scores on the other emotional slides (slides 5,6,7 and 9) was therefore tested.

Figure 22: Mean Proportion Correct on Each Slide



The results of this test show a highly significant interaction ($F_{2,45}$=15.232, p<0.001), and main effects of both emotion ($F_{1,45}$=48.149, p<0.001), and drug ($F_{2,45}$=15.228 p<0.001). An acceptable critical probability for these comparisons might be p=0.0045, to allow for a possible 11 slides, as the decision to analyse slide 8 in this way was made post-hoc. This is surpassed on each comparison. There were clear differences between performance on slide 8 and the other emotion slides in the placebo ($F_{1,15}$=105.44, p<0.001) and methylphenidate ($F_{1,15}$= 14.43, p=0.002) groups. However there was no difference in the lorazepam group F<1, p=0.884.

When the a priori planned comparisons for the Cahill and McGaugh (1995) 3 phase division of slides were repeated omitting this slide 8 from the analysis (i.e. recognition performance for phase 2 is calculated as the mean of slides 5,6,&7) the superiority of phase 2 in the placebo group disappears (t_{15} = 0.87,

p=0.399), and there is still no effect of phase 2 in the methylphenidate group (t_{15} = -0.78, p=0.447), or the lorazepam group (t_{15} = 1.03, p=0.319)

2.3.5.Results summary

- Table 3 shows a ✓ if the measure did or a X if it did not, show the predicted
    - Arousal increase relative to placebo in the methylphenidate group.
    - Arousal decrease relative to placebo in the lorazepam group.

Table 3: Summary of arousal measures

	Methylphenidate	**Lorazepam**
Pulse	✓	X
Systolic blood pressure	✓	X
Diastolic blood pressure	✓	X
Tapping	✓	✓
AG: Arousal	✓	✓
MRS: Alertness	X	✓
MRS: Calmness	X	X

- Memory Grid
    - Lorazepam impaired performance
    - Methylphenidate did not change performance in terms of means of the whole group. However, low baseline scorers performance improved after methylphenidate and high baseline scorers performance deteriorated after methylphenidate
- Emotional sentences
    - Lorazepam decreased the number of words recalled
    - More words from emotional than neutral sentences were recalled
- Story Task
    - Subjective emotionality of the story did not correlate with memory for the story.
    - Lorazepam impaired memory overall
    - The new categorisation of slides showed evidence for similar emotion facilitation in all groups
- Cahill and McGaugh's 1995 Original classification

- Although there was no significant interaction between drug and emotion, planned comparisons showed an effect of emotion in the placebo group, but not in the lorazepam or methylphenidate groups
- The emotion effect was mainly due to superior memory for slide 8
- Emotion ratings
  - There was a trend towards lower emotionality ratings from the methylphenidate group.
  - Story caused decreased pleasantness indexed by affect grid in all groups
  - The placebo group showed the greatest increases in affect grid arousal over the story

2.4.DISCUSSION

This study aimed to determine the effects of methylphenidate and lorazepam on arousal, and on memory for emotional versus neutral material. The data from the various measures of subjective, motor and physiological arousal are evidence that the pharmacological manipulations altered arousal in the expected ways. There were clear increases in arousal in the methylphenidate group and clear decreases in the lorazepam group.

Although one way of analysing the story task suggests that both pharmacological manipulations had disruptive effects on emotional memory facilitation, the evidence for this is less clear. This section will start with a discussion of the findings from the measures of mood and arousal, followed by a discussion of the measures of emotional memory.

2.4.1.Subjective Effects (Mood and Arousal)

The mood measure which showed the clearest drug effects was the affect grid (Russell and Weis, 1989). This simple scale had an advantage in that it was quick to complete and it could be administered several times during the experiment. Therefore it was possible to demonstrate how the arousal levels of the three drug groups changed as the experiment progressed. The stimulant effect of methylphenidate and the sedative effect of lorazepam persisted throughout the entire experiment. Interestingly, this scale also provides information about how the three drug groups' arousal ratings varied over the test session. The two active drug groups showed fairly consistent patterns of

increasing and decreasing arousal relative to placebo. However there was more variation in the placebo groups' ratings which may indicate they were much more responsive to the individual tasks than either drug group.
The mood rating scales (Bond and Lader, 1974) demonstrated the predicted reduction in alertness following lorazepam but no change following methylphenidate or placebo. Why did this scale not show the predicted increase in alertness in the methylphenidate group? There are two possible explanations for this (1) The mood factors were initially constructed and validated by Bond and Lader (1974) by measuring decreases in alertness associated with benzodiazepines. Therefore it is possible that the adjectives anchoring the opposite ends of the scales did not match up with the spectrum of subjective alertness increases associated with methylphenidate. (2) The scales were completed at the beginning of the test session. As previously discussed, the affect grids show the difference in arousal between the groups became larger as the experiment progressed. This suggests that had the mood rating scale been completed later in the test session there may have been more marked group differences. Although studies reviewed by Koelega (1993) tested effects of methylphenidate after one hour, Hardman et al (2001) state that peak plasma concentration of methylphenidate is reached approximately two hours after ingestion, and more recent studies (e.g. Mehta,2000) start testing after 90mins. The factors 'contentedness' and 'calmness' showed no difference between the groups. The only other notable finding that emerged from these scales were the very large standard deviations of the post drug scores in the methylphenidate group. This is a recurring feature of the pattern of results for the methylphenidate group and is believed to reflect individual differences in response to methylphenidate.

2.4.2.Physiological and Motor Arousal

The physiological measures provided evidence for the predicted increase in arousal associated with methylphenidate. Pulse and blood pressure was increased by methylphenidate throughout the experiment. There was no evidence for the predicted decreases in arousal associated with lorazepam. Pulse and blood pressure stayed about constant in this drug group, whereas pulse dropped slightly in the placebo group, perhaps as they relaxed into the

experiment. However the tapping task showed clear motor sedation in the lorazepam group and a trend towards increased arousal in the methylphenidate group. Taken together with the data from the subjective scales it appears that the drugs had their predicted effects on arousal. That there were some differences between the indices of arousal supports the decision to use several different measures of arousal and supports the notion that arousal is not a homogenous construct.

2.4.3.Picture Grid Memory Task

There was no clear difference between the groups in the number of pictures they recalled. This was as predicted. However the hypothesis that the arousal manipulations would not affect this memory task was possibly not upheld. The lorazepam group recalled slightly (non significantly) less pictures post drug than they did predrug. Although the methylphenidate group did not significantly change as group on this task, when the group was split into 'low baseline memory' and 'high baseline memory' on the basis of their predrug performance on this task, it could be seen that the low baseline memory group improved under the influence of this drug, and the high baseline memory group got worse. This is in accordance with the findings of Mehta et al (2000) and can be explained in terms of endogenous dopaminergic tone (section 2.1.2.2).
This is an unusually clear finding considering the small size of the groups and the crude index of memory.

2.4.4.Measures of Emotional Memory

2.4.4.1.Emotional story task

Story Task: Subjective Effects

The tendency for the drug groups to differ in ratings of the emotionality of the story was interesting. No previous study has reported any drug to reduce subjective ratings on this part of the test, and all groups in this experiment showed similar decreases on the affect grid measure of pleasantness while watching the story. Methylphenidate is similar to amphetamine which is taken recreationally to promote feelings of well being and elation (Tyler, 1986). Perhaps therefore it is not surprising that participants who received

methylphenidate tended not to experience as much negative emotion as the other participants. Because emotionality ratings did not correlate with any of the memory measures it appears that subjectively rated emotion did not affect memory for emotional material. This is surprising as theoretically emotion is directly linked to memory facilitation.

Affect grids completed directly before and after the story presentation were compared to give a measure how the story changed the participants mood. The affect grids are expected to represent the change in experienced emotion, rather than just perceived emotionality of the story. All three drug groups reported a less pleasant mood after being presented with the slides and story. In contrast to the pleasantness dimension of the affect grid, the arousal dimension showed the drug groups tended to differ in how the story affected their arousal levels. The placebo group rated a greater pre-post story increase in arousal than the methylphenidate and lorazepam groups. This lends support to the criticism that Cahill and McGaugh's (1995) subjective scale does not capture the change in arousal which is more likely than the valence to be associated with memory facilitation. It also suggests that the active drug given was more of a determinant of arousal levels than external stimuli in the lorazepam and diazepam groups.

Story Task: Memory Performance

Using Cahill and McGaugh's (1995) classification of slides, although there was no overall interaction between the drug and story phase, the planned comparisons of the effect of emotion in each drug group separately, only found a significant difference between memory for emotional and neutral material in the placebo treated participants. This analysis shows the predicted enhanced memory for the middle 'emotional' section relative to the beginning and end 'neutral' sections in the placebo group. In the methylphenidate group memory for the middle 'emotional' section was not different to the two other sections. There is also no evidence for emotional facilitation in the lorazepam group. This provides some evidence albeit not strong that methylphenidate and lorazepam impaired emotional memory

The main finding from the analysis of the new and arguably more valid classification of slides was superior memory for emotional material in all three drug groups. This was contrary to the initial hypothesis, and was particularly

unexpected in the lorazepam group. Previous work by Zangara and Curran(2000) indicated that benzodiazepines reduce the effect of memory facilitation by emotional material, perhaps even more so than β-adrenergic blockade. It was also unexpected that analysis using Cahill and McGaugh's (1995) categorisation of the slides showed the hypothesised reduction in the emotional memory effect whereas the new more valid division of slides did not. However when the effect of 'slide 8' is considered these observations become interpretable, as slide 8 has heavier weight in Cahill and McGaugh's (1995) categorisation of slides (as they categorise a smaller number of slides as emotional). Slide 8 (a picture of grotesque injury to a small child's legs) appears to have a different impact from the other slides. Cahill and McGaugh (1995 p.414 & p.418) and Hamann et al. (1997) describe how this slide was much better remembered than the others, and the raters in our pilot study who rated the slides for emotionality gave this the highest mean score. It is proposed that this slide 8 is analogous to Phelps et al's 'taboo' words, whereas slides 5,6,7,9, &10 are analogous to Phelps et al's semantically emotional words.

As described in Chapter 1 there are many mechanisms by which memory is facilitated by emotional material. Phelps et al (1998) argue the amygdala is not involved when emotion enhances episodic memory primarily by contributing an organising principle such as a schema or category. It is proposed that this is the main process by which memory is facilitated for slides 5,6,7, 9, & 10. These slides together form a coherent story schema. It is argued that the only slide to cause significant activation of the hypothesised stress hormone/ amygdala based emotional memory system is slide 8. It is different from the other slides because the picture itself contains emotional information (a child's bloody injured ankles) whereas the other ones are only emotional in conjunction with the narration (e.g. a picture of the front of a hospital). The other slides possibly have a high negative valence, but are not particularly arousing. However, as the 100 raters were only asked about the valence dimension of emotion it is impossible to say. These arguments are supported by the analysis comparing slide 8 with the other 'emotional' slides. Recognition performance for slide 8 is higher than for any other slide in the placebo and methylphenidate groups - but not in the lorazepam group. This could be seen as evidence that lorazepam disproportionately impairs 'emotional memory'.

In contrast memory for slide 8 was relatively enhanced for the methylphenidate group, although this was not quite as clear as the placebo group, and despite them showing no difference in memory for the emotional slides overall. Why the latter was found is still unclear. It could be (1) because this group did not find this material as emotional as the other groups, or (2) because there was a relative facilitation of the neutral material in this group.

2.4.4.2.Emotional sentences

This task showed memory facilitation for words from emotional sentences in all three drug groups. Lorazepam impaired memory globally, but words from emotional sentences were still recalled more than neutral words suggesting that the drug did not disproportionately affect emotional memory. The methylphenidate group showed a very similar pattern of results to the placebo group. Further the words from emotional sentences showed as much memory advantage at immediate as at delayed recall, suggesting that words from both types of sentences were equally forgotten over time.

The immediate recall test was carried out straight after participants had finished studying the sentences. McGaugh (2000) and others proposed that the stress hormone / amygdala based emotional memory system acts on the consolidation of information. Therefore the words produced by participants in the immediate test would not have had time to be influenced by this system. Although information produced at the delayed, and day 7 recall tests would have had time for the enhanced consolidation to give them an advantage this would have been concealed by the much bigger effect of recalling the words at immediate recall acting as rehearsal. This effect is discussed by Grober et al. (1988) and it was noticed in the current study that if a participant produced a word at immediate recall they were much more likely to produce it in the two later tests.

As the lorazepam group showed memory facilitation associated with emotional material, this also suggests that it must have been due to some other mechanism of memory facilitation[7].

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[7] It is accepted that both of these points may be false. If benzodiazepines do not affect the stress hormone / amygdala based emotional memory system, and the memory facilitation in this test was due to that system this would lead to the same observation of memory facilitation in the lorazepam group.

The reason for using neutral words as the stimuli was to make the material that was stored in memory and recalled equivalent in both the emotional and neutral conditions. The only way in which the conditions are supposed to be different is the emotional state the participant is in at encoding. However, it is possible that participants recalled the emotional context and then used this as a cue to aid recall of the target word. Some participants were obviously doing this for example one participant said "something about a man beating up his wife....stairs". The stimulus sentence was 'He threw the woman down the stairs and watched her hit every step'. The elaboration about the battered wife suggests that it was an emotional chunk of information (not a neutral word) that was encoded and recalled. This position is also supported by the pattern of emotional and neutral errors made. Participants produced more non-target words from emotional sentences.

Overall, the facilitation of recall of words from emotional sentences in all drug treatment groups could be due to one or more factors. Perhaps emotional sentences received increased attention, and/or greater elaboration. There may also have been more spontaneous rehearsal of emotional sentences. Cued recall from recollecting the emotional sentences themselves may have been aided by 'emotional sentences' being a semantic category.

2.4.5.Conclusions

Taken together, the various measures of subjective, motor, and physiological arousal demonstrated clear increases in arousal in the methylphenidate group and clear decreases in arousal in the lorazepam group compared with placebo. However the study was less successful at providing clear evidence of how these pharmacological manipulations affected the interaction of emotion and memory. Only one analysis (the predefined and presumably less valid categorisation of story phases) demonstrated a reduction in emotional facilitation of memory in the lorazepam and methylphenidate drug groups. The other emotional memory task and analyses showed facilitation of memory for emotional material in all three groups.

It is possible that the pharmacological manipulations of arousal did not produce the predicted effects on emotional memory because of methodological issues rather than because the hypothesis was not correct. In order to confirm that

these arousal manipulations do not affect emotional memory a task would need to be designed where the memory facilitation due to emotional material could be differentiated from memory facilitation due to other factors (e.g. semantic cohesiveness, enhanced self reference, etc.). Only if the memory facilitation shown in this way could be suppressed by one drug (possibly propranolol), but not by methylphenidate or lorazepam could it be concluded that these drugs do not affect emotional memory.

The current study was very effective in demonstrating enhancements in memory associated with emotional material. These effects appear to be highly robust, appearing in all three drug conditions. This discussion has somewhat dismissed these effects. However it should be noted that although in the animal brain emotional memory may be greatly influenced and controlled by a noradrenergic amygdala system, there is likely to be a much greater cortical influence on human emotional memory. Therefore it is worth considering that the clear effects of emotionality that were uninfluenced by the drugs in this study are not artefacts but worthy of investigation themselves.

In conclusion it was found that methylphenidate increased and lorazepam decreased arousal. There was a subtle suggestion on one analysis of the story task that these pharmacologically induced changes in arousal could affect emotional memory, but the evidence for this was ambiguous. In order to reach more definitive conclusions about the neurochemical basis of emotional memory it would be necessary to have a task where the facilitation of memory could be definitely attributed to the emotional content of the material itself.

CHAPTER 3: TRANQUILLIZING EMOTIONAL MEMORIES: A comparison of the effects of diazepam with propranolol and placebo on memory for emotional and neutral material (EXPERIMENT 2)

3.1.INTRODUCTION

3.1.1.Rationale

In experiment 1 (Chapter 2) the sentences task and the analysis of the new categorisation of slides in the story task showed that memory was facilitated by emotional material despite administration of lorazepam or methylphenidate. However there was also some limited evidence from the Cahill & McGaugh story task that memory deficits in volunteers given lorazepam were greater for material pre-classified as emotional than material that had been classified as neutral. For volunteers given methylphenidate there was a small memory advantage for this neutral material, but none for emotional material. However, using this particular task it was impossible to totally rule out alternative explanations for the memory facilitation attributed to emotional material.

This second experiment had three main aims. The first was to design a novel task (the picture colour test) to investigate the effects of emotion on explicit memory. Previous tasks have suffered from the problem of extraneous variables such as semantic cohesiveness and distinctiveness co-varying with emotionality. The new task aimed to overcome this and create two emotion conditions where the memory demands were equivalent, the only difference being the emotionality of material.

The second aim was to design a novel task to investigate the effects of emotion on implicit memory. Implicit memory is when past experiences unconsciously influence our perceptions, thoughts, and actions (Schacter 1996). In practice there is no pure test of any memory system, and implicit memory can influence performance on emotional 'explicit' memory tasks and vice versa. Currently there is no existing test that probes the effect of emotion on implicit memory.

Therefore in this experiment implicit memory was investigated using an adaptation of the sentences task from the previous experiment.
The third aim was to directly compare the effects of a ß- blocker (propranolol) with a benzodiazepine on performance of these tasks. Therefore the drug conditions included a benzodiazepine (15mg diazepam) group, a placebo control which is expected to show the standard effect of facilitation of memory for emotional material and a propranolol (80mg) group.
Propranolol is a non-selective (equal infinity for β_1 and β_2 receptors) adrenergic antagonist. It has successfully been used by Cahill et al. (1994) to reduce the effect of emotion on memory, leaving memory for neutral events intact. Therefore propranolol provides a useful control condition. If no evidence for disruption of emotional memory is found in this condition then limited conclusions can be drawn about similar results in the diazepam condition.
The benzodiazepine administered in the current experiment was diazepam. Diazepam is expected to have similar effects on emotional versus neutral memory as lorazepam, and therefore should provide confirmation that benzodiazepine treatment disrupts the emotional facilitation of memory. Diazepam was selected because the present study employed an implicit memory task and in contrast to lorazepam, diazepam has been shown to disrupt explicit memory, but leave priming intact Vidailhet et al. (1996).

3.1.2.Choice of tasks

3.1.2.1.Picture Colour Task

The finding in experiment 1 that all three drug groups showed memory facilitation for 'emotional' chunks of information in the sentences task, and information from the emotion category in the new, more valid categorisation of the Cahill and McGaugh (1995) slides highlighted the need for a task where the memory advantage due to the emotionality of material could be dissociated from other mnemonic advantages of emotional material. If emotional material is remembered differently from neutral material for reasons other than its arousing nature, pharmacological manipulations designed to interrupt the enhanced consolidation due to emotionality cannot be expected to reduce memory facilitation due to these processes. In other words drugs can modulate relative

catecholamine levels on presentation of an emotional slide, but they are unlikely to make an unusual slide any less distinctive. Manipulations that enhance normal memory (e.g. semantic cohesion, increased rehearsal, deeper encoding) usually have parallel effects under the influence of benzodiazepines (review: Curran 1999), and the same applies to psychostimulants (e.g. Soetens et al. 1995).

A recent study by Doerksen & Shimamura (2001) demonstrated a facilitation of memory tested by free recall, not only of emotional words compared to neutral words, but also the *ink colour* in which the emotional words were presented. A further experiment showed this effect extended to the 'frame', a coloured border around each word. They explain this effect in terms of the emotional words increasing "arousal or attention" to the stimuli. Ink colour, particularly that of the frame might be construed as a peripheral detail, and thus could be expected to be less well remembered than the central detail of the word itself. It is possible that the difference between this prediction and the enhancement observed by Doerksen and Shimumura may be because the ink colour effect was due to a more conventional *non-emotional* mnemonic advantage of the emotional words. Evidence from LaBar and Phelps (1998), and Phelps et al (1997) suggests that amygdala based emotional memory facilitation does not occur with individual words (with the exception of taboo words, which cause autonomic arousal). The words used by Doerksen & Shimamura (2001) although emotional in meaning (e.g. adorable, wedding, agony, wrong) are unlikely to be associated with large changes in arousal. Memory for non-arousing emotional stimuli may be enhanced because emotional stimuli all belong to a cohesive semantic category (LaBar & Phelps, 1998; Phelps, LaBar, & Spencer, 1997). Thus emotional words would show the same episodic memory facilitation as any other stimuli that could be clustered together. Doerksen & Shimamura (2001) addressed this possibility by demonstrating that although exemplars of the neutral categories 'vehicles' and 'dwellings' were more likely to be recalled in a free recall test, neither recognition memory nor source (ink colour) memory was enhanced by category membership.

Clustering by category membership is not the only factor by which memory has conventionally thought to be enhanced. Other accepted mechanisms are increased rehearsal (e.g. Baddeley & Hitch, 2000) (c.f. Guy & Cahill 1999),

greater depth of processing (Craik & Lockhart 1972), and more self-referent encoding (Rogers, Kuiper, & Kirker 1977). These encoding factors are often thought to be more likely to apply to emotional rather than neutral material (review: Christianson, 1992) and thus may provide the basis for the enhanced source memory in Doerksen & Shimamura's (2001) subjects.

Hamann (2001) argues that enhancement of memory for emotional verbal stimuli appears to be less dependent on the amygdala than for picture stimuli. He cites work by Phelps et al. (1998), Phelps, LaBar, & Spencer (1997) who demonstrate intact enhancement of verbal emotional information in a patient with bilateral amygdala damage.

There is other evidence to suggest that the emotional memory system is more likely to be activated by pictorial visual information than by semantic language information. The most successful emotional memory task to date is the story task designed by Cahill and McGaugh (1995), which is a graphic story, emotional information is presented in pictures as well as narrative.

The PTSD symptom of flashbacks can be considered to be an unintentional retrieval of information that was encoded during a period of intense trauma. Brewin (2001) describes PTSD flashbacks as an example of a 'situationally accessible' but not 'verbally accessible' memory system. He argues that this memory system does not use a verbal code, and that these memories contain mainly perceptual (mostly visuo-spatial) features.

Given this evidence it was reasoned that the emotionality of material should affect the consolidation of and memory for the ink colour that the material was presented in. Pictures would be more effective than words or other material in eliciting emotional effects on memory. The problem of the emotional and neutral materials differing systematically on other attributes (e.g. semantic cohesion) could be addressed by re-presenting the emotional / neutral materials at retrieval (i.e. a recognition memory task) and making the key to-be-remembered material the colour of the ink. Therefore the memory demands would be the same in both emotion conditions – recalling the ink colour. Thus the idea of testing source memory by memory for ink colour from Doerksen & Shimamura (2001) will be used in a recognition memory task with emotionally arousing pictures.

The analysis of recognition performance, using signal detection methods Macmillan & Creelman (1991) to calculate estimates of both bias and sensitivity on this task may allow further insight into the memory processes affected by the drugs. If more emotional material is recognised than neutral material it may partly be because the retrieval criteria are more liberal (Windmann & Kutas, 2001). Theoretically, it is possible that a drug might impair the extra consolidation that emotional material is thought to receive, but not affect the retrieval criterion. Alternatively a drug might cause emotional memories to be both retrieved and consolidated like neutral memories, and the recognition bias would be the same in emotional and neutral categories.

As memory performance is usually better for emotional pictures (e.g. Hamann et al, 1999) it is predicted that in the placebo group, recognition performance will be improved by emotional material compared to neutral material. If memory for ink colour is a peripheral detail, it will be impaired by emotionally arousing material in this group.

It is well documented that diazepam produces memory impairment. Therefore given the evidence in the literature, it is expected that both recognition memory (Curran 1999) and source memory (e.g. Mintzer and Grittiths, 1999) will be impaired by diazepam. However of more theoretical interest is whether either diazepam or propranolol will alter the *pattern* of memory performance across the three emotion categories.

If propranolol and/or diazepam impair a specific emotional memory system, then memory for emotional and neutral material would be similar both for picture recognition and source memory. If it is some other mnemonic process that is disrupted by the drug it could be expected that 'emotionally' enhanced recognition would disappear, but source memory would be unaffected. As benzodiazepines are thought to affect memory at the encoding stage rather than the retrieval stage (Curran 1999) it is expected that they should not affect the bias criterion. As no study to date has addressed the effect of propranolol on recognition memory biases there are no clear predictions on this exploratory part of the study.

3.1.2.2.Implicit memory task

The role of emotion in implicit memory has received most attention in the context of 'repressed' memories of trauma. Christianson and Nilsson (1989) describe a case study of CM, a woman who had been raped while jogging. CM had developed total amnesia for the assault and for her previous life. When accompanied to the location of the assault, and exposed to visual cues (bricks on a path) that had been present where the attack had begun she expressed great anxiety – although at this stage she was unaware this was the place where she had been attacked.

If perceptual priming is facilitated by emotional situations, especially if this facilitation remains intact in situations where explicit memories break down (e.g. drug rape, anaesthesia, amnesia associated with severe trauma) this would have far reaching therapeutic and legal implications. There is some experimental evidence that this may be the case. Johnson et al (1985) found Korsakoffs patients who had no explicit memory for the biographical information presented about various people still retained a sense of liking 'good guys' and disliking 'bad guys'. Further Gidron et al (2002) showed that reaction times for providing associates to word pairs that had been presented under anaesthesia (patients had no explicit memory for the pairs) were quicker for emotional word pairs than for neutral word pairs.

One way to study this phenomenon experimentally in healthy volunteers is by using diazepam, a benzodiazepine which has been shown experimentally to disrupt the formation of declarative memories and leave perceptual priming intact (Curran 1999). This should also produce a useful confirmation that benzodiazepines disrupt memory facilitation by emotion. Diazepam is not expected to alter priming, so if priming of words from emotional (and not neutral) sentences is impaired by diazepam, this would be good evidence that it is an *emotional memory* mechanism being disrupted by diazepam. With the explicit memory tests, it is more difficult to be sure that it is an emotional memory process being disrupted, because disruption of another mnemonic process could be altering the relative levels of neutral and emotional performance. Conversely, if priming effects remained intact under the influence of diazepam, a facilitating effect of emotion on priming may be observed in this group. This would suggest that in the explicit emotional memory tests in this

series of experiments, a non-emotional mnemonic process that was disrupted by diazepam, mediated any effect of diazepam on explicit emotional memories. In a typical priming experiment, words or pictures are studied. Later at the test stage reduced perceptual information (e.g. 3 letter word stems, tachistocopic presentation of pictures) is given about the studied information and participants are asked to complete, name or categorise them. The previously studied material will influence performance on the test by being produced more often or faster than unstudied objects.

Published studies of the effects of emotion on priming have tended to concentrate on patient groups. Mogg and colleagues have studied groups of anxious or depressed patients (Bradley, Mogg, & Millar, 1996; Bradley, Mogg, & Williams, 1994; Bradley, Mogg, & Williams, 1995;Mathews et al. 1995; Scott, Mogg, & Bradley 2001). This series of studies shows that the emotionality of previously studied words affects speed in a lexical decisions task when the words are re-presented. Depressed patients are particularly fast to recognise depression related words. However, the effects observed in these experiments were small, typically a speeding of response time for studied stimuli in the range 10 – 50 ms. compared to unstudied stimuli.

Cooley, Stringer, & Hodnett (1997) used a word stem completion task and showed both stroke patients and healthy controls showed greater priming effect for 'threatening' than 'non-threatening' words. This study did not measure how much explicit memory contributed to the observed priming effect.

As these studies use emotional words as the to-be-remembered material there is the problem that some other property of these words could be contributing to the 'emotion effect'. The sentences task used in the previous experiment avoids this problem, and also showed a very robust effect of memory facilitation for words presented in an emotional context in all drug groups. Therefore for the present experiment it was adapted to create an implicit memory task.

Volunteers will be presented with target words embedded in either emotional or neutral sentences. Instead of a free recall test, memory will be tested implicitly using a priming task.

Initially the method used for this was to be a 'process dissociation procedure (PDP)' based on the paradigm designed by Jacoby (1991) to dissociate the relative contributions of implicit and explicit memory. In this procedure

participants' retention of previously studied stimuli is tested in two conditions, (1) an inclusion condition in which the participant produces all the studied stimuli they can explicitly remember plus any items they think may have been on the studied list, and (2) an exclusion condition in which the participant excludes any stimuli they think were presented earlier. Jacoby, Toth, & Yonelinas (1993) theorise that this means that the probability of producing a studied item in the inclusion condition is the probability of the item automatically coming to mind, plus the probability of it being consciously recollected from the study list. The probability of producing a studied item in the exclusion condition is the probability of it automatically coming to mind, minus the probability of it being consciously remembered. The probability that an item will 'automatically come to mind' is the contribution of implicit memory plus the baseline probability of producing that item purely by chance – which can be estimated by measuring the probability of producing that item for participants who did not see it at study. The initial pilot test of this method in the current experiment found that participants did not produce enough studied words in the exclusion condition, to show evidence for implicit memory. Possible reasons for this are considered later in the discussion.

The procedure used in the second pilot study and followed in the main drug study (Experiment 2) was to ask volunteers to complete three letter word stems with 'the first word that comes into their head'. Half of these stems could be completed with the target words from the sentences, the other half began words from an unstudied 'distractor' list. The possible contribution of explicit memory was estimated later by asking volunteers which of the completed stems they recognised from the studied sentences.

The sentences and cue words were altered slightly from those used in Experiment 1. This is to allow equivalent target and distractor sets (to be counterbalanced across conditions) and to remove any words from the sentences that begin with the same three-letter word stems as the target words. The predicted pattern of results in the three conditions is that the placebo group should complete more stems with target words from emotional sentences than from neutral sentences, and more studied than non-studied words in each emotion category. They are expected to recognise many of the words they fill in. The propranolol group are also expected to complete more stems with studied

than unstudied words, but no more words from emotional sentences than from neutral sentences. They too should recognise most of the words they fill in. The diazepam group are also expected to complete more stems with studied words than unstudied words in each category. However, they are expected to recognise significantly less words than they were primed to complete. If diazepam disrupts emotional memory processes they should fill in the same number of words from emotional sentences as they do from neutral sentences; if diazepam does not disrupt emotional memory processes they should complete more words from emotional than neutral sentences.

3.1.2.3.Control Tasks

Several tests from the previous experiment will also be used. These are the physiological measures, tapping task, visual analogue mood rating scale and affect grid. This combination of tasks proved to be useful in comparing the change in various types of arousal in the different drug groups. The active drugs in the current experiment are expected to reduce rather than increase arousal on the various indices. In addition, the story task designed by Cahill and McGaugh (1995) will be used again. This was the only task to partially differentiate the effect of emotion on memory in the three drug groups in the previous experiment. Its use also allows comparison with many previous studies.

3.2.TASK CREATION

3.2.1.Creation of the Picture Colour Task

3.2.1.1.Pilot Test of the picture colour task: Introduction

As mentioned above (section 3.1.2.1.) the idea for this task originated in a verbal memory paradigm: Shimumura and Doerksen's (2001) source memory for emotional words. The main alterations were the substitution of pictures for words, the alteration of the colours, lengthening of study time, lengthening of time period between study and retrieval, and use of recognition rather than free recall.

The pictures were selected from the International Affective Picture System (IAPS) Lang et al (1999). Lang et al provide rating data (on a scale of 1-9) for

pleasure, arousal, and dominance of around 700 pictures, collected in 12 separate studies over the course of 10 years. Data are shown for men, women, men and women combined, and children. The valence ratings from the men and women combined were used to select the pictures for the present study. Neutral pictures had valence ratings in the range 4.25-5.75, negative pictures had valence ratings of <2.5, and positive pictures had valence ratings >7.5.
This initially led to the categorisation of some apparently emotional pictures as 'neutral'. It appeared this was because around half of the participants gave some pictures very high pleasure scores, and the other half of the participants rated the same pictures as very low valence. (e.g. pornographic pictures may have been rated very positive by men and very negative by women.) Therefore the average rating was around the 'neutral' centre. To remove these pictures standard deviations for neutral pictures were restricted to <2. In practice this eliminated mainly pictures with a sexual theme. Pictures were also rejected if they were likely to be familiar to participants because of their appearance in the media (e.g. the baby seal from the Greenpeace advert), or if the colour of presentation was important to the valence (e.g. chocolate brownies were much less appealing in green).
Two sets (version 1 and version 2) of pictures were then selected. Each set consisted of 32 neutral pictures, 16 negative pictures and 16 positive pictures. The two versions were matched, so that for each picture in version 1 there was a corresponding picture in version 2, matched as well as possible on the basis of physical appearance and emotion evoked. Some selected pictures were altered slightly to facilitate the matching process (e.g. mirror images, or enlargements of the main feature were used.)

Table 4: Mean (sd) ratings for pleasure, arousal and dominance of pictures in each of the three categories.

		Neutral	Negative	Positive
Pleasure	Version1	5.02 (0.35)	2.08 (0.31)	7.82 (0.28)
	Version2	4.90 (0.31)	1.99 (0.30)	7.72 (0.22)
Arousal	Version1	3.23 (0.88)	5.87 (0.67)	5.20 (0.95)
	Version2	3.23 (0.58)	6.20 (0.75)	5.08 (1.21)
Dominance	Version1	5.79 (0.59)	3.54 (0.56)	6.20 (0.66)
	Version2	5.80 (0.47)	3.30 (0.55)	6.27 (0.80)

ANOVA was used to test whether there were any differences between the versions on any of the published rated emotion dimensions. All Fs were >1, Valence p= 0.755, Arousal p= 0.833, Dominance p=0.869. Therefore the two versions were well matched for emotion.

The pictures were transformed into black and white images using Adobe PhotoDeluxe 2.0. These black and white images were then coloured either green or purple by altering the colour balance 'green' to either –100%(purple) or +100% (green).

The colours green and purple were selected as these are proposed to be the colours that have the least emotional significance. For example red and orange are associated with danger, yellow is seen as cheerful, and blue as sad or bored. Although green is sometimes equated with jealousy, green ink does not provoke jealousy in the same way as for example red provokes alerting and orienting.

Half of the emotional slides from version 1 were randomly selected to be presented as purple in "version 1A"; the remainder were presented as green in this version. The pictures were presented in the alternative colour in "version 1B". The matched pictures in version 2 were presented in the same colour as their matched pair in versions 2A and 2B.

The recognition test consisted of all 128 pictures presented as black and white images. All pictures were presented in a pseudo-random order[8] on Microsoft PowerPoint.

The study time for each stimulus was increased from the 2 seconds used by Shimumura et al to 3 seconds, as the pictures were more complex stimuli than single words. The inter-stimulus interval was kept at 1 second. To control for primacy and recency effects two buffer images were presented at the beginning and 1 buffer image at the end of the study session.

The free recall test used by Shimumura et al was rejected, as enhanced free recall of emotional items would cue enhanced recognition of the same items. In effect, recalled items would be presented twice and so the source recognition performance would be contaminated. Verbal recall of 64 pictures would also be very difficult to monitor in practice. A volunteer would have to describe some of the pictures in great detail before it became clear exactly which picture was being recalled for example the description 'an old man' might refer to several of the pictures in all of the categories.

3.2.1.2.Pilot Test of the picture colour task: Method

Thirty-seven student volunteers participated in the initial pilot run of the task. Twenty-eight were first year postgraduate students. These were shown version 1B of the test. The other 9 volunteers were American psychology students participating in an exchange programme. They saw version 2B of the test. These volunteers were told that they would see a set of pictures on the computer screen. They were warned that the set of pictures may contain scenes which some people might find disturbing, and advised that participation was optional and that they were free to withdraw at any time without having to give a reason for withdrawing. They were asked to look at each picture carefully and try and think about what was going on in the picture. They were also informed that the pictures would be presented in either green or purple and they should try to remember the colour in which each picture was printed.

After a break of approximately 10 minutes participants were told that they would see some more pictures on the computer screen. They were told that some of

[8] Maximum 3 neutral or 2 emotional pictures in succession, Maximum 2 pictures of either colour in succession.

the pictures were 'new' (they had not been shown them before). The 'old' pictures that they had seen before had been either green or purple. They were asked to tell the experimenter if the picture had been green or purple when they saw it before or if it was a new picture.

3.2.1.3.Pilot test of the Picture Task Pilot Test: Results

Recognition memory and source memory performance were equivalent on the two versions of the test, therefore data were collapsed over the two versions for analysis. Table 5 shows the mean (s.d.) corrected hit and false alarm rates for pictures in each emotion condition. There was statistical evidence for a difference in hit rates between emotion categories ($F_{2,72}=7.25$, $p=0.003$)^{GG}. Simple effects analyses show that there is a clear difference between the neutral and negative categories ($t_{36}=3.36$, $p=0.002$). A tendency to a difference between neutral and positive pictures ($t_{36} = 2.183$, $p=0.036$), and a trend to a difference between hit rates for neutral and positive pictures ($t_{36} = 2.005$, $p=0.053$), did not exceed the Bonferroni corrected critical probability for three comparisons of $p=0.017$.

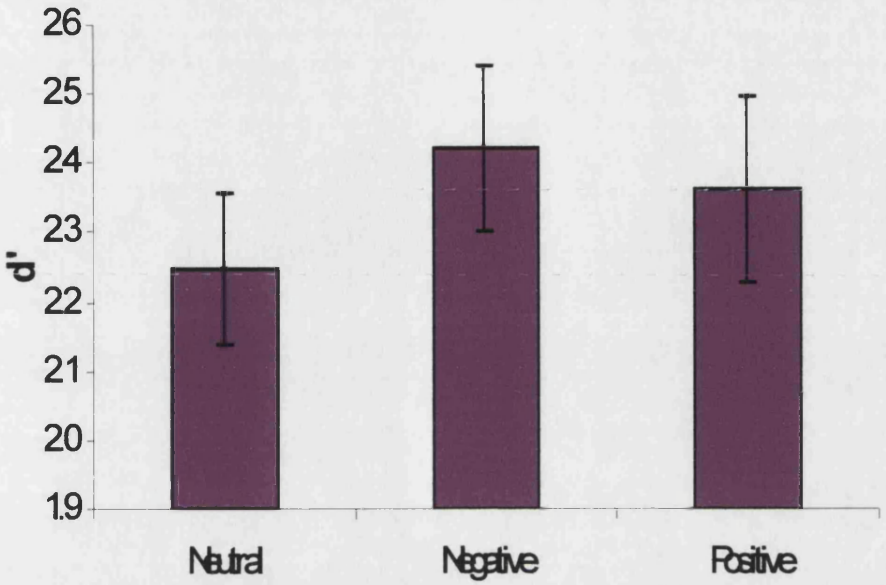
False alarm rates were low, but there was evidence for a difference between false alarm rates for the three different types of emotional material ($F_{2,72}=4.34$, $p=0.025$)^{GG}. Simple effects show this is mainly due to the difference in false alarm rates between the neutral and negative conditions ($t_{36} = 2.55$, $p=0.015$). The tendency to a difference between the negative and positive conditions did not exceed the critical probability of 0.017 ($t_{36} = 1.755$, $p=0.088$). There was no evidence for a difference between the neutral and positive conditions ($p=0.183$)

Table 5: Mean (s.d.) hits, false alarms, and proportion of correct colour identifications (source) in each emotion category.

	Hits	False Alarms
Neutral	0.78(0.13)	0.10(0.08)
Negative	0.88(0.11)	0.16(0.08)
Positive	0.82(0.12)	0.12(0.09)

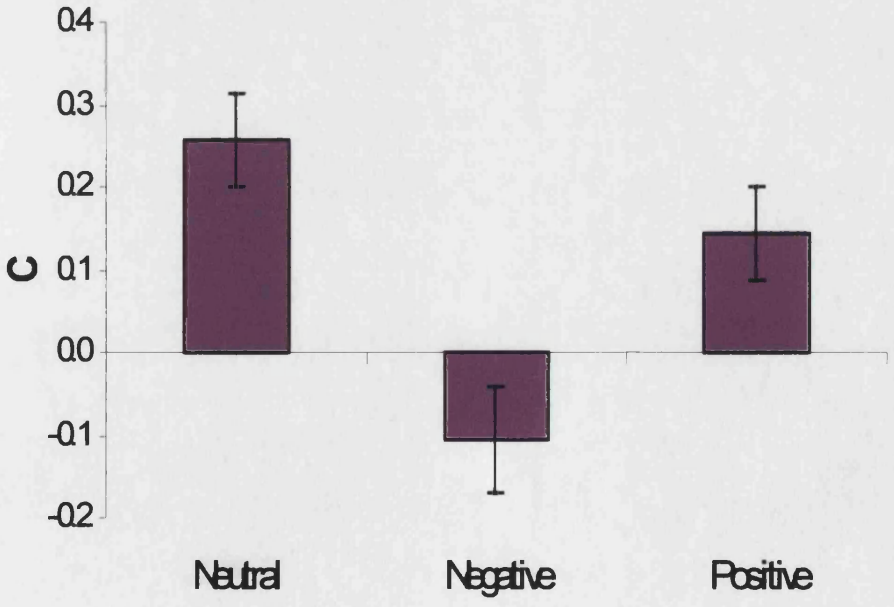
The signal detection parameters d' and C were calculated, mean values of d' are shown in Figure 23.

Figure 23: Mean (s.e.) of d' for each emotion category



There was no difference between d' for the three types of stimuli ($F_{2,72} < 1$)

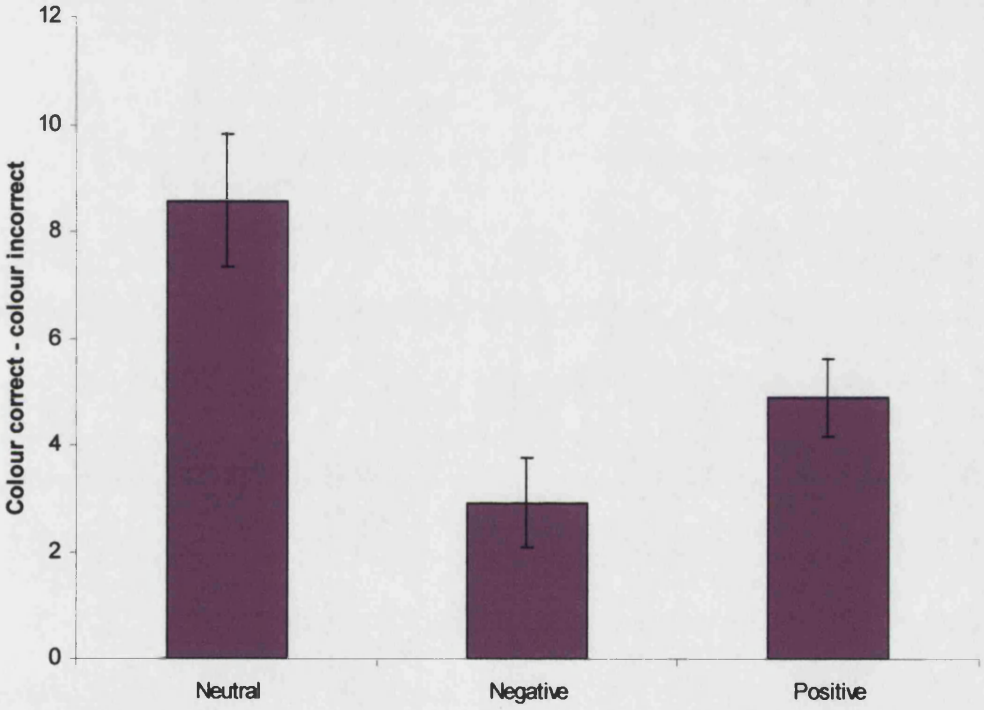
Figure 24: Mean (s.e.) of C for each emotion category



The ANOVA of the bias parameter C showed a significant difference between the three emotion categories. $F_{2,72} = 8.53$, $p < 0.002^{GG}$. As can be seen Figure

24, this is due to more a more liberal bias when negative pictures are being recognised compared to either of the other emotion categories. Simple effects analyses confirm this, with a significant difference between neutral and negative (t_{36} =3.63, p=0.001),and neutral and positive (t_{36} = 2.50, p=0.017). The difference between negative and positive (t_{36} =-2.22, p=0.033) did not quite exceed the Bonferroni corrected significance level for three comparisons (p = 0.05 / 3 = 0.017).

Figure 25: Source memory (colour correct - colour incorrect)



Source memory appears to be lowest for the negative pictures (Figure 25). ANOVA confirmed the difference between the three types of emotion material $F_{2,72}$ = 17.90, P<0.001 ^{GG}.

As can be seen in Figure 25 negative emotional content appears to cause the largest detriment to source memory. Source memory for positive pictures looks impaired compared to neutral pictures, but not as badly as that for negative pictures. The detriment to source memory caused by negative pictures was significant compared to neutral pictures (t_{36} =6.35, p<0.001), and for positive pictures compared to neutral pictures (t_{36} =3.50, p=0.001). However source memory performance for the two emotion categories was not significantly

different (t_{36} =2.135, p=0.040) if the Bonferroni corrected critical probability for 3 comparisons (p = 0.017) is considered.

3.2.1.4.Pilot test of the Picture Task Pilot Test: Discussion

The increased hit rate and reduced source memory observed for negative pictures are as predicted for emotional pictures. The positive pictures did not show this predicted pattern of effects quite so clearly. Although the hit rate for positive pictures is increased it is not as high as that for negative pictures. Similarly the source memory performance for positive pictures was not as impaired as the negative pictures. Therefore it seems the effect of the positive pictures on memory is not as strong as the effect of the negative pictures. There are three possible reasons why positive pictures did not produce strong memory effects (1) The positive pictures may not have provoked emotion. This is possible but as Lang et al (1999) carried out extensive validation of the emotionality of the pictures it is unlikely, unless the colour manipulation had a large effect on the emotionality – which is again thought to be unlikely.
(2) Perhaps the amygdala based emotional memory system only deals with negative emotions, or perhaps even just fear. LeDoux (1999) argues that there is no reason to generalise from his work to any emotion other than fear. However Hamann et al. (1999) used pictures from the IAPS in a PET study and found that increased amygdala activity was associated with enhanced long term (4 weeks) recognition memory for both negative *and positive* pictures.
(3) It may not be extremes of emotional valence so much as high arousal which activates the amygdala based emotional memory system. Balch, Myers, & Papotto (1999) argue that high arousal and extremes of valence are often confounded. The limitations of the possible sample of pictures made it impossible to match the three emotion conditions for all other variables. Examples of possible differences between the picture sets include complexity of stimuli, and the *arousal* and dominance dimensions of emotion. No data is available for complexity but the data from Lang et al (1999) give scores for dominance and arousal. Arousal was not matched in the two emotion groups Lang et al (1999) discuss the difficulty in obtaining low valence (positive), high arousal pictures. There were also few high valence (negative), high arousal pictures in the 'all subjects ' male and female ratings. Hence it would not be

possible to modify the task so that arousal was matched in the three valence groups. (Hamman et al 1999 were able to use all heterosexual male subjects and thus were able to use sexually arousing pictures to provoke high arousal positively valenced moods.) Investigation of whether the emotional memory system is activated by (1) extreme emotional valence or (2) high emotional arousal would be theoretically interesting. However it is proposed that for the purposes of the current study, (investigating the neurochemical basis of the emotional memory system) the distinction does not have to be made. As long as the 'emotional' stimuli used are activating the system, and the 'neutral' stimuli not activating the system the precise component of emotionality that causes the activation is unimportant. Thus the two categories of stimuli could be called negative and neutral, or high arousal and low arousal – the results would be interpreted in the same way.

In conclusion, the improved recognition memory performance and impaired source memory performance for the 'negative' emotional pictures in this task is good evidence that memory for these pictures utilises the theorised emotional memory system. Therefore this task will be used in the drug study. If either propranolol or diazepam disrupts this pattern of results relative to placebo, the drug can be concluded to be affecting the neurochemistry of the emotional memory system. The positive pictures do not appear to have as much utility in providing evidence about the emotional memory system. However it is proposed that they remain as part of the task. If the task were composed of just negative and neutral pictures it would be a rather harrowing experience for the subjects. The positive pictures may still produce theoretically interesting results. It is possible that drugs may differentially affect the processing of the different categories of emotion pictures.

3.2.2.Creation of the Implicit Memory Sentences Task

Stimulus words were taken from a set of high frequency neutral words provided by Maratos et al. (2001). These were the target words from the sentences task of the previous experiment. Criteria for selection of a word were that the first three letters of the word (the word stem) had to begin at least 5 other words in the Oxford English Minidictionary.

Fortuitously the set of available words included ten pairs of words where both members of the pair shared a suitable word stem. Half of each of these word pairs was included in version 1 and half in version 2. (Table 6, rows 1-10) The use of word stems which make a different word in version 1 and version 2 reduces the number of stems needed in the stem completion part of the task. If the seen word is completed it can be counted as priming, if the unseen word is completed it is counted as a baseline.

Because only ten pairs of words shared a stem, another 10 pairs of words had to be selected whose stems were matched for number of possible completions (Table 6, rows 11-30). Therefore in the stem completion task volunteers would be presented with 30 word stems in total (Table 6). Ten of these stems did not begin any word from their study list. If these stems were completed with a word from the unseen study list they would be counted as baseline completions. The other 20 stems could be completed with words that they had seen, although a subset of ten of these could also be completed with a 'baseline' word from the unseen study list.

Table 6: Stems and corresponding words.

	Stem	Version 1	Version 2	Appears emotional in version A/B	Total poss. words
1	con	concert	concrete	A	318
2	bri	bride	bridge	B	48
3	win	wind	winter	A	36
4	but	butter	butterfly	B	17
5	lad	ladder	lady	A	10
6	sta	starling	stairs	B	99
7	sto	stone	stomach	A	54
8	bre	breakfast	bread	B	45
9	bra	brain	branch	A	47
10	tra	train	traffic	B	114
11	cou	cousin		A	68
12	hil	hill		B	6
13	sca	scan		A	50
14	tem	temple		B	18
15	tea	teacher		A	21
16	bea	bear		B	33
17	boa	boat		A	14
18	ric	rice		B	10
19	uni	uniform		A	20
20	sti	stick		B	35
21	man		manager	A	68
22	gue		guest	B	6
23	cro		crowd	A	54
24	fle		flesh	B	18
25	unc		uncle	A	25
26	shi		ship	B	30(+7)*
27	din		dinner	A	15
28	fas		fashion	B	10
29	bon		bone	A	17
30	stu		studio	B	34

* The (+7) words were listed as separate words by the Oxford English minidictionary, but were extrapolations of the word ship. E.g. shipbuilding, shipyard, shipwreck

Thus two versions of the task version 1 and version 2 are needed to control for baseline completion of words. Version 1 and version 2 were well matched for number of total possible stem completions. 1063 words could be made from the stems in version 1 and 1065 words could be made from the stems in version 2.

To allow each word to appear in each emotional context, two alternative versions (version A and version B) were made from each of the versions 1 and 2. Therefore there were 4 versions of the task altogether 1A, 1B, 2A, 2B. Following Maratos et al (2001) emotional context was provided for each word by putting it into either an emotional or neutral sentence. Therefore if a word appeared in an emotional sentence in version A. (e.g. Ten thousand people died when the bomb exploded at the **concert**) it would appear in a neutral sentence in version B (e.g. Ten thousand people were at the **concert**). Versions A and B were matched as well as possible for number of possible stem completions. Total possible words from version A = 817, total possible words from version B = 523. (The 200 word discrepancy is due to version A containing con... with 318 possible completions, whereas the largest number of words from a single stem in version B is tra... with 114. All the other stems are well matched.)

To facilitate matching of emotional valence, imagability, and other extraneous variables between versions 1 and 2, each sentence in version 1 was matched semantically with a sentence in version 2. (E.g. Version 1: Ten thousand people died when the bomb exploded at the **concert**, Version2: Ten thousand people died when the bomb exploded in the **crowd**).

The sentences were created so that no words except the target list words began with the stems used in the stem completion task. The sentences can be found in Appendix 8.

3.2.2.1.Implicit Memory Sentences Task; Pilot 1: Method

Process Dissociation Procedure

The first method piloted was a process dissociation procedure (Jacoby, 1991; Jacoby, Toth, & Yonelinas, 1993). For the study phase of the experiment, eight

volunteers (two saw each of the four versions) saw stimuli sentences presented on a computer screen. Stimuli were presented in a pseudo random order using Microsoft Powerpoint. The sentence was presented for 4seconds in black ink on a white background with the keyword underlined and italicised in blue ink. This was followed by the keyword alone (underlined, blue italics) for 4s. Volunteers were asked to read the sentences out loud and try to remember the keywords.

After a gap of 5 minutes filled by conversation (no visual input) volunteers did the stem completion task. They were told they would see word stems appear on the computer screen and were asked if the stem was accompanied with the word 'old' to use it as a cue to recall a target word from the sentences (inclusion condition). If the stem was accompanied by the word 'new', they were to complete it to make any English word except proper nouns, or words from the previously presented sentences (exclusion condition). Volunteers gave their answers verbally and these were recorded by the experimenter.

Half of the volunteers who had seen each version saw version X of the stem completion task, the other half saw version Y. The inclusion condition stems in version X were exclusion condition stems in version Y and vice versa.

3.2.2.2.Implicit Memory Sentences Task; Pilot 1: Results

Table 7 shows the mean (s.d.) and minimum and maximum number of stems completed in each category. Very few (maximum 2) sentences words were filled in the exclusion task. Significantly more baseline words were filled in than sentence words in the exclusion task (t_7= 3.33 p=0.013). Therefore this method produced no evidence of priming. The number of words from emotional and neutral sentences was equivalent in both the implicit (t_7 = -0.683, p=0.516) and explicit (t_7= -0.704 p=0.504 conditions).

Table 7: Mean, SD, min, and max, stems completed in each condition.

	N	Minimum	Maximum	Mean	(S D)
Baseline	8	1	7	3.38	(1.92)
Explicit-emotional	8	1	4	2.38	(0.92)
Explicit-neutral	8	1	4	2.75	(1.28)
Implicit-emotional	8	0	1	0.50	(0.53)
Implicit-neutral	8	0	2	0.75	(0.71)

3.2.2.3.Implicit Memory Sentences Task; Pilot 1: Discussion

This first method piloted failed to show evidence of priming. Hardly any of the key sentence words were produced in the exclusion condition. There were two probable reasons for this (1) the other written words in the sentences may have caused interference (2) the component of explicit memory was too strong. The process dissociation procedure as designed by Jacoby et al, (1993) was used with many more words (128 at test) than were used in the present study (30 at test). In the present study explicit memory of the studied words was probably strong enough to prevent participants producing list words in the exclusion condition.

Therefore to promote priming in the second pilot task the process dissociation procedure was not used. Instead participants were asked to complete the stems with the first word that came to mind, with no mention of a memory test. The possible contribution of explicit memory was assessed by asking participants to look back through the stems they had completed and mark any that they recognised from the sentences. To prevent interference from the other sentence words the sentences were presented aurally, so that only the 'target' words appeared in print.

3.2.2.4.Implicit Memory Sentences Task; Pilot 2: Method

The second method piloted was designed to increase the size of the priming effect. The keywords were presented in the same ink colour, font etc. as before, but this time they were on flashcards. The sentences did not appear in print, but were recorded onto cassette tape. Sixty volunteers (15 for each version) were

asked to listen to the sentences and try to think of the printed word in the context of the sentence. The retention gap of 5 minutes, was filled with the distractor task of rating the Cahill and McGaugh (1995) slides for arousal and valence. The rating scales were carefully designed to use only pictures, so that no words could interfere with the implicit memory task. The word stems were presented in the identical font, ink size, colour etc on more flashcards and volunteers were asked to complete each one verbally with the 'first word that came into their head'.

After they had seen all the stems they were shown the list of words they had produced and asked to mark any that they recognised from the sentences.

3.2.2.5.Implicit Memory Sentences Task; Pilot 2: Results

The mean (s.d.) number of words completed and recognised from each type of sentence is shown in Table 8. The mean number of stems completed from the unseen (baseline) list was 4.38 (s.d. 2.37). Participants completed significantly more stems with studied than unstudied words ($t_{59} = 5.17$, $p < 0.001$). Participants had a tendency to complete more stems with words they had seen in emotional sentences, than with words they had seen in neutral sentences ($t_{59} = 1.94$, $p = 0.057$).

Table 8: Mean (SD) words

	Neutral	Emotional	Total
Stems completed	3.25 (1.74)	3.68 (2.17)	6.93 (3.54)
Complete words recognised	2.52 (1.69)	2.72 (1.86)	5.23 (2.99)

More stems were completed than marked as recognised from both emotional ($t_{59}=3.166$, $p=0.002$) and neutral ($t_{59}=2.59$, $p=0.012$) sentences.

3.2.2.6.Implicit Memory Sentences Task; Pilot 2: Discussion

One or both of these alterations had the desired effect. In the second pilot run of the task participants completed more stems with words from the sentences that they had seen, than from the sentences they had not and they did not recognise all the words they completed. There was a tendency to complete more words that had been presented in emotional sentences at encoding.

3.3.METHOD (DRUG STUDY)

3.3.1.Participants

Forty-eight participants completed the study, 24 males and 24 females. They ranged in age from 18-35 years. Volunteers were recruited from advertisements placed around the university. Prospective volunteers were informed that the study was part of a research programme investigating how drugs affect mood and information processing.

They were told the study consisted of one main session (during which they would swallow two capsules), a brief medical checkup, and a short follow up session. They were informed that the contents of these capsules could include either 15mg diazepam (valium) or 80mg propranolol (a blood pressure drug) or an inactive placebo, and no participant would receive two active drugs. The possible side effects of the drugs were described. Participants were warned that the tests contained some emotional material, which they might find disturbing.

A medical doctor screened volunteers for any possible health conditions that the drugs could exacerbate. He took a detailed medical history, measured lung capacity, and listened for evidence of cardiac or lung abnormalities. Potential participants who reported, or showed signs of asthma, medically significant low blood pressure, psychiatric history, any history of drug or alcohol abuse, pregnancy, risk of pregnancy due to inadequate contraception, diabetes, hypertension, hyperthyroidism, glaucoma or any other medical problem were excluded from the study.

Volunteers who met the inclusion criteria were sent or given an information sheet detailing all the above information and the standard information given to all volunteers for studies involving drugs at UCL. Thus student volunteers were instructed to inform their tutor of their participation and to ensure that taking part in the study would not interfere with their normal studies. All volunteers were informed that they must agree not to take any mood-altering drug (including alcohol) the night before and throughout the day of each test. They also agreed not to drive any vehicle or make any important decisions on the day of the first test session. On test days they were asked to consume only light, low fat meals and no more than their usual amounts of caffeine.

3.3.2.Design

Equal numbers of males and females were randomly allocated to one of three parallel groups (diazepam 15mg, propranolol 80mg, or lactose placebo). A double blind procedure was used utilising a double dummy procedure to allow for the different absorption rates of the two drugs. Where tests were repeated the 2 parallel versions were counterbalanced across subjects and conditions. Where four versions of the memory tasks were used (picture colour test and emotional sentences priming test) these were balanced across drug groups and gender. Three experimenters who all followed an identical procedure with scripted instructions administered the tasks.

Two tests included in the experiment 'the emotional voices task' and a variation on the (Calder & Young 1996) emotional expression recognition task, were mainly of interest to the other experimenters and so are not reported here, although they are found on the test order printed in Appendix 4

3.3.3.Procedure

The UCL/UCLH committee on the ethics of human research approved the study and all participants gave written informed consent. They then performed the pre-drug battery of tests (described below), which gave baseline measures of mood, motor arousal (tapping), heart rate, blood pressure, and prose recall performance.

Propranolol (80mg) or lactose placebo formulated in identical gelatine capsules was ingested immediately after the predrug test battery at T_0. Twenty minutes later (T_{0+20}) participants received either Diazepam (15mg) or lactose placebo also formulated in identical gelatine capsules. Thus treatments were defined as propranolol (propranolol T_0 + placebo T_{0+20}), diazepam (placebo T_0 + diazepam T_{0+20}), or placebo (placebo T_0 + placebo T_{0+20}).

Whist waiting to perform the post-drug test battery participants were given instructions for the emotional sounds and emotional facial expressions tasks. Forty minutes later (T_{0+60}) the post-drug battery (described below) was commenced. The tests were performed in the order in which they are described below. (Test order can be found in Appendix 4)

3.3.3.1.Predrug Test Battery

Participants listened to the prose passage on tape, completed a visual analogue mood rating scale, had their pulse and blood pressure taken, completed an affect grid, had their pulse and blood pressure taken again, did the tapping task and then recalled the prose passage.

- **Prose Recall Task**

A short prose passage taken from the Rivermead behavioural memory test battery was played to the participant. Participants were asked to recall the story after a short interval filled with other tasks. Two counterbalanced stories were used, one was presented at the beginning of the predrug battery and the other at the beginning of the post drug battery. At the end of the main test session participants were asked to recall both stories again. The stories were divided into 21 idea units and participants were scored 1 point for each idea unit or exact synonym and half a point for each partial unit, or partial synonym (Wilson et al 1985).

- **Mood Rating Scale (MRS) (Bond & Lader 1974)**

This same scale as used in Experiment 1, with the same instructions was used again. It was filled in pre-drug, post-drug, and at the end of the main test session.

- **Pulse and blood pressure**

Pulse and blood pressure were taken using an Omron M5-1 monitor. Two readings were taken and the mean of these was used. Pulse and blood pressure were recorded during the pretest battery, at the beginning of the post test battery, and towards the end of the post test battery.

- **Affect Grid (Russell, Weiss, & Mendelsohn 1989)**

Participants were presented with a grid as described in chapter 2. They were given the same instructions as in that previous experiment. Affect grids were completed pre drug and at 7 time points during the postdrug test battery.

- **Finger Tapping Speed (Frith, 1976)**

This was used again as a measure of manual motor arousal both pre and post drug

3.3.3.2.Postdrug Test Battery

The Predrug test battery was repeated. This was followed by the picture colour test study session, an affect grid (no. 3), the emotional tone recognition task, another affect grid (no. 4), and the picture recognition test. Another affect grid (no. 5), presentation of the sentences for the implicit priming task, a practise of the Calder facial recognition task, and then the word stem completion task followed this. Then participants completed affect grid (no. 6), the facial recognition task, and affect grid (no. 7), before watching, and rating the story slide presentation. The end of session tests were as the predrug tests and comprised of a third mood rating scale, a blood pressure and pulse reading, the final affect grid (no. 8), pulse and blood pressure once again, and finally recall of the two prose passages.

- **Picture Colour Test**

Participants were told they would be shown some pictures on the computer screen. They were asked to study each picture carefully, and think about what was going on in the picture, and how they felt about each picture. They were also told that each picture would be presented in either green or purple and they should try and remember the colour of presentation. They were then shown the 'study' set of 67 pictures.

Participants were distracted from rehearsing the pictures they had studied by the emotional tone recognition task and completing an affect grid. Then they were told that they would be shown some black and white pictures. Some of these pictures they had never seen before, and some of them had been presented a few minutes ago when they were coloured either green or purple. They were asked to tell the experimenter if each picture was a new picture or if it had been green or purple when they saw it previously, if they recognised a picture but weren't sure of its colour, they were asked to guess the colour. The timing of the test pictures was participant controlled.

- **Emotional sentences priming task**

This task took the same format as described for the second pilot run. However, instead of flashcards and cassette tapes the task was presented with Microsoft Powerpoint.

Participants were told that they would hear some sentences through the computer speakers, and see some printed words on the computer screen. They

were asked to listen to each sentence, think of the printed word in the context of the sentence, and to read the printed word out loud when the sentence finished. Sentences lasted for approximately 6seconds and the printed word remained on the screen for another second so each printed word was visible for a total of 7 seconds.

Each participant heard 20 sentences. Ten of these were emotional and 10 were neutral. The printed words appeared in the sentences, and all had neutral emotional valence (words taken from Maratos et al 2001). To control for emotional context and baseline completion rates the task had four parallel study versions balanced across experimental conditions. These were matched for number of possible stem completions and approximate content (see section 3.2.2)

After a 5 min break during which time the facial recognition task (a task with little verbal and no written input) was practised, participants performed the stem completion task. Three letter word stems were displayed on the computer screen in exactly the same font and position as the study words. Participants were instructed to add some letters to each stem to make an English word (avoiding proper nouns) as quickly as possible, using the first word that came into their heads. Thirty stems were shown. From these it was possible to make all 20 words from the study session. It was also possible to make the 20 distractor words from the alternative study version.

Once the thirty stems had been completed explicit recognition memory was tested by the experimenter showing the participant the completed list of words and asking them to mark any words that had appeared on the computer screen while they were listening to the sentences.

- **Emotional story task (Cahill & McGaugh 1995)**

The task was taken from Cahill & McGaugh (1995) the procedure used followed exactly the procedure in Experiment 1 reported in section 2.2.3.6

3.3.4.Statistics

Where Mauchley's W indicated the sphericity assumption had been violated significance levels were corrected using the Greenhouse Geisser method. Where post hoc tests were employed Dunnett's test was used. Where several comparisons are carried out actual probabilities (as given by SPSS) are

reported and the Bonferroni corrected critical probability is given for comparison.

The tests, which were administered at several time points (pulse, blood pressure, Tapping, Affect grid, MRS, prose recall,) were analysed using the GLM Repeated Measures procedure in SPSS. Drug group (3 levels) was used as a between subjects factor and within subjects factors were 'time' 3 levels (predrug postdrug and end of session) for physiological measures, 2 levels (predrug and postdrug) for tapping and prose recall, and 8 levels for the affect grid.

The GLM repeated measures programme was also used for the emotional memory tasks. Again drug group (3 levels) was used as the between subjects factor. Emotion was used as the within subjects factor (2 levels in the sentences task, and 3 levels in the Colour picture task and the Cahill and McGaugh story task). Planned comparisons were made to test the effect of emotion in each drug group separately in the Colour Picture Task and the Cahlill and Mc Gaugh task.

To compare number of list words produced with number of baseline words, and number of list words produced with number of list words recognised t- tests were used.

Before the picture test was analysed the signal detection statistics d' and C (Macmillan & Creelman, 1991) were calculated. Hits and false alarms were calculated using the correction suggested by Snodgrass and Corwin (1988) to remove the chance of hit rates of 1 or false alarms of 0. Snodgrass and Corwin (1988) recommend adding 0.5 to the frequency and dividing by N+1 to avoid situations where hits=1 or false alarms=0. As there were 32 pictures in the neutral condition and only 16 pictures in the positive and 16 in the negative condition the frequency in the positive and negative conditions was multiplied by 2 and divided by (16 * 2+1), in order to make this correction have an equal effect in the emotional and neutral conditions.

Source memory was defined as

Source = (green correct + purple correct) - (green incorrect + purple incorrect)

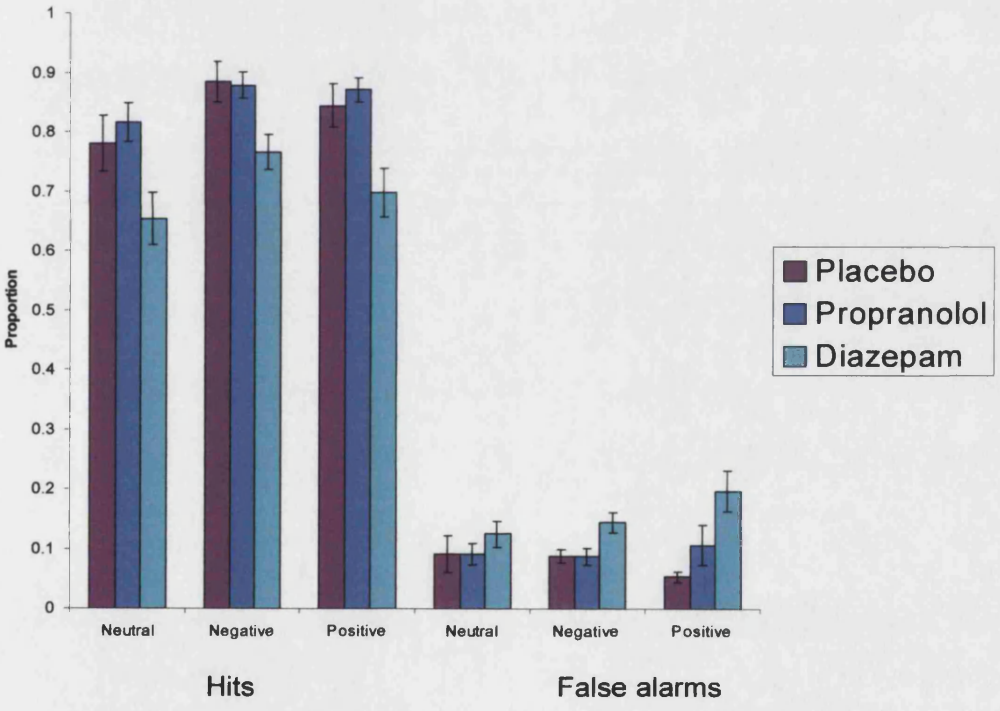
This translates as the number of times the source was correctly identified minus the number of times the source was incorrectly identified.

3.4.RESULTS

3.4.1.Picture Colour Task

Proportion of hits and false alarms for each drug group in each emotion category are shown in Figure 26. There was one missing data point, subject 6 (female, placebo) picture number 92. This picture was negative and green at presentation. For this case one was subtracted from the denominator for the calculation of negative hits and false alarms. Therefore the correction described in the method was applied as usual but allowance made for the possible number of hits being one less than for participants who saw all 16 pictures.

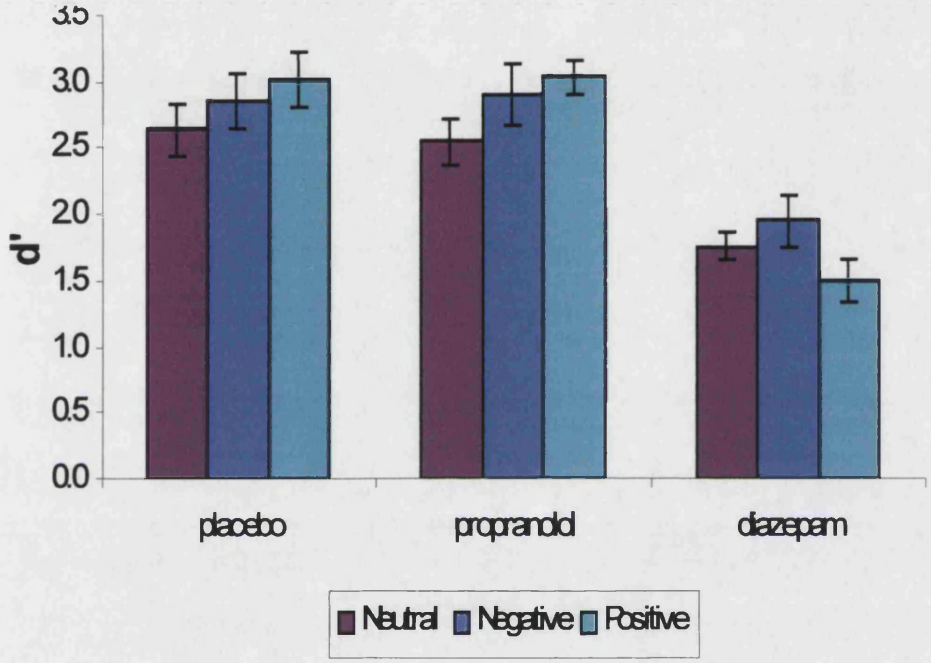
Figure 26: Mean (s.e.) hits and false alarms for each emotion category in each drug group



The ANOVA of the hits showed the drug X emotion interaction to be non-significant (p=0.69). There was a main effect of emotion ($F_{2,90}$ =12.668, p<0.001) whereby most hits were made to negative pictures, then positive, then neutral. The diazepam group made less hits than the other two groups, confirmed by a main effect of drug ($F_{2,45}$ =7.539, p=0.002).

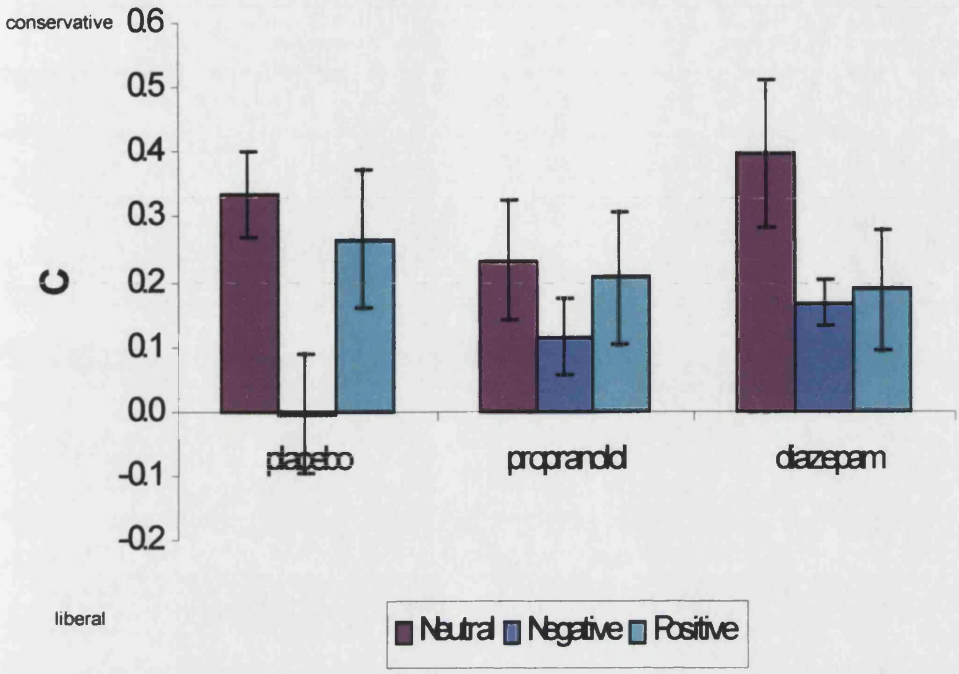
Most false alarms appear to be made by the diazepam group to positive stimuli, and a trend ($F_{4,90} = 2.40$, p=0.055) towards a drug x emotion interaction supports this. A main effect of drug ($F_{2,45} = 5.80$, p=0.006) reflects more false alarms being made by the diazepam group, and there was no main effect of emotion (p=0.54)

Figure 27: Mean (s.e.) sensitivity d' for each drug group and each emotion category



The signal detection statistic d' was calculated, and an initial 'health check' of the data revealed five outlying scores (subjects 27, 29, 33, 37, and 43). These were omitted from the ANOVA calculations and from Figure 27 which shows d' for each drug group for each emotion. There was a drug X emotion interaction ($F_{4,80} = 3.15$, p=0.018). The pattern of performance for the diazepam group (positive < neutral< negative) is different from the placebo group (neutral < negative & positive). A main effect of emotion ($F_{2,80} = 3.48$, p=0.035) reflects higher levels of d' for emotional than neutral pictures. A main effect of drug ($F_{2,40} = 17.73$, p<0.001) reflects lowered values of d' in the diazepam group. The maximum possible d' in the present study (32 hits, 0 false alarms) was 4.33.

Figure 28: Mean (s.e.) C for each emotion category in each drug group



The signal detection bias statistic C was calculated and outlying scores (subjects (3, 18, 35,36, & 47) were excluded. The ANOVA showed a clear main effect of emotion ($F_{2,80} = 6.71$, p=0.002). Bias was lower for negative pictures. The interaction and main effect of drug were not significant.

Means and standard deviations for proportion of times the colour was remembered correctly are presented in Table 9 (there were no extreme scores). The ANOVA showed a main effect of drug ($F_{2,45}$=6.37 p=0.004). The interaction and main effect of emotion did not reach significance. The diazepam group had poorer source memory than the other groups; however emotion category did not affect source memory.

Table 9: Mean (s.d.) proportion correct colour identifications for each emotion category by each drug group.

	Placebo	Propranolol	Diazepam
Neutral	3.75 (5.19)	4.53 (4.87)	1.22 (3.44)
Negative	3.63 (4.19)	3.31 (4.80)	-0.38 (4.35)
Positive	5.56 (5.02)	4.38 (5.43)	-1.00 (5.82)

3.4.2.Implicit Memory Task

As can be seen in the first two rows of Table 10 all drug groups completed more stems with words from the list they had seen, than with words from the baseline list they had not seen. Additionally all drug groups completed significantly more words they had seen in the sentences, than they recognised as sentence words.

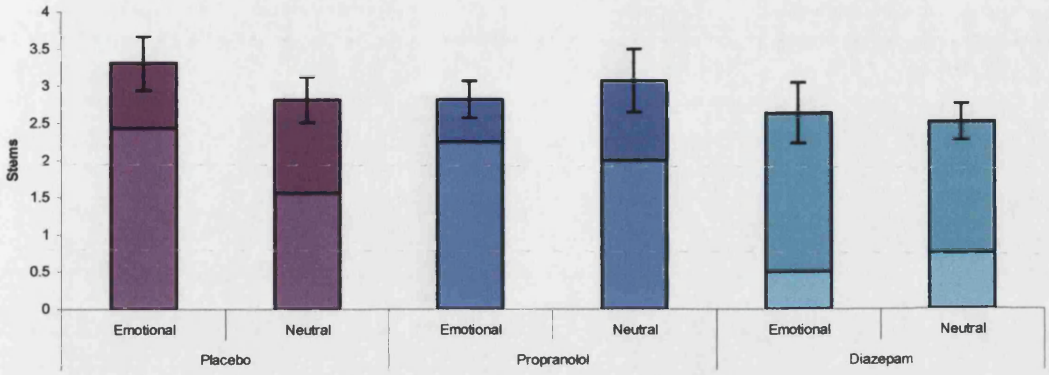
Table 10: Mean (s.d.): (a) Number of words completed from the seen list. (b) Number of words completed from the unseen list. (c) Number of completed words recognised. (d) t-test of the difference between stems completed and baseline. (e) t-test of the difference between stems completed and words recognised

	Placebo	Propranolol	Diazepam	All groups
a) Priming	6.13 (2.09)	5.88 (2.16)	5.13 (1.63)	5.71 (1.98)
b) Baseline	3.63 (2.25)	2.44 (1.55)	3.81 (1.60)	3.29 (1.89)
c) Recognition	4.00 (2.45)	4.25 (2.57)	1.25 (1.18)	3.17 (2.52)
d) a vs b (t_{15}=)	3.45**	5.44***	2.13*	6.14***
e) a vs c (t_{15}=)	4.41***	4.47***	9.29***	9.15***

* p=0.05, **P<0.01, ***P<0.001

Figure 29 shows the number of stem completions with words from sentences of each category, by each drug group. There was no statistical evidence for an effect of drug, emotion, or an interaction between the two in the number of stems completed with list words. Therefore priming was unaffected by the emotion and drug experimental manipulations.

Figure 29: Implicit memory task. Bar height is the number of stems completed. Pale portion is the number of completed stems recognised.



There was a tendency to an interaction between emotion and drug on number of completed words recognised ($F_{2,45}$=2.67, p=0.08). The placebo group recognised slightly more words from emotional sentences than from neutral sentences ($F_{1,15}$ =4.02, p=0.063); the propranolol ($F_{1,15}$ =0.056, p=0.468) and diazepam ($F_{1,15}$ =1.154, p=0.300) groups did not.

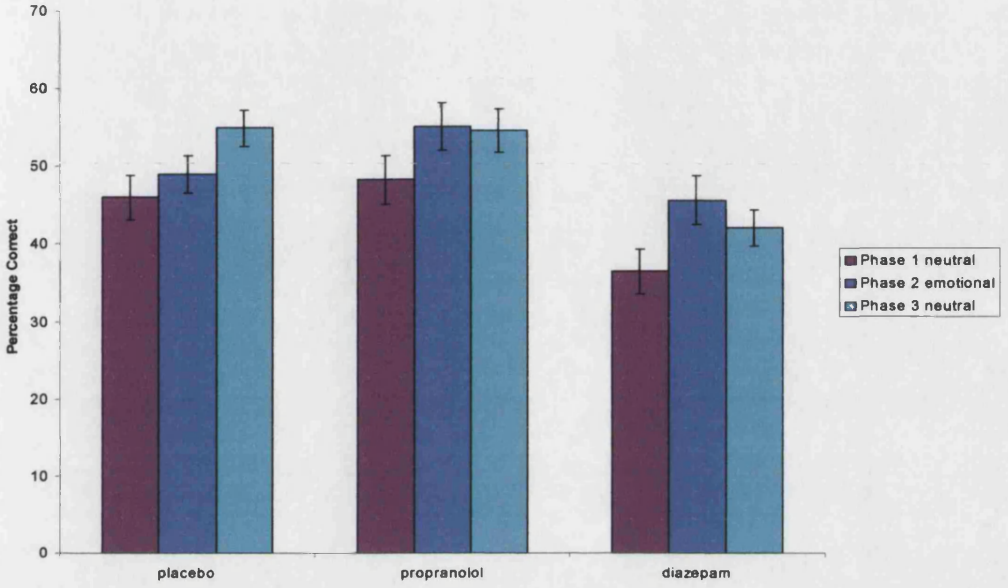
There was also a main effect of drug ($F_{2,45}$=9.50 p<0.001) on number of words recognised. The diazepam group recognised less words than either the placebo group or the propranolol group.

3.4.3.Story task (Cahill & McGaugh, 1995)

The mean (s.d.) subjective ratings of emotionality of the Cahill story in the respective groups were; (placebo 5.69 (2.50); propranolol 5.50 (1.59); and diazepam 4.56 (2.42)). There was no evidence for a group difference in subjective ratings ($F_{2,45}$ = 1.19 p=0.313)

One member of the diazepam group did not return for the memory test, meaning this group has one case of missing data (n= 15). The mean recognition scores for the three drug groups on each of the three phases are shown in Figure 30 .The ANOVA gave main effects of emotion ($F_{2,88}$ =8.76 p<0.001) and drug ($F_{2,44}$ = 10.84 p<0.001), but no interaction (p=0.403). It can be seen from Figure 30 that the phase where the placebo group showed their highest scores is phase 3.

Figure 30: Mean (s.e.) recognition memory for each of the three phases in each drug group



The slide-by-slide breakdown of memory performance (Figure 31) shows a 'slide 8 effect' most clearly in the propranolol group. Table 11 shows the difference between the drug groups on each slide. If the Bonferrroni corrected critical value for 11 comparisons p=0.0045 is considered none of these comparisons reach significance, however to reduce the probability of type 2 error all comparisons are presented.

Figure 31: Recogniton performance for each group on each slide

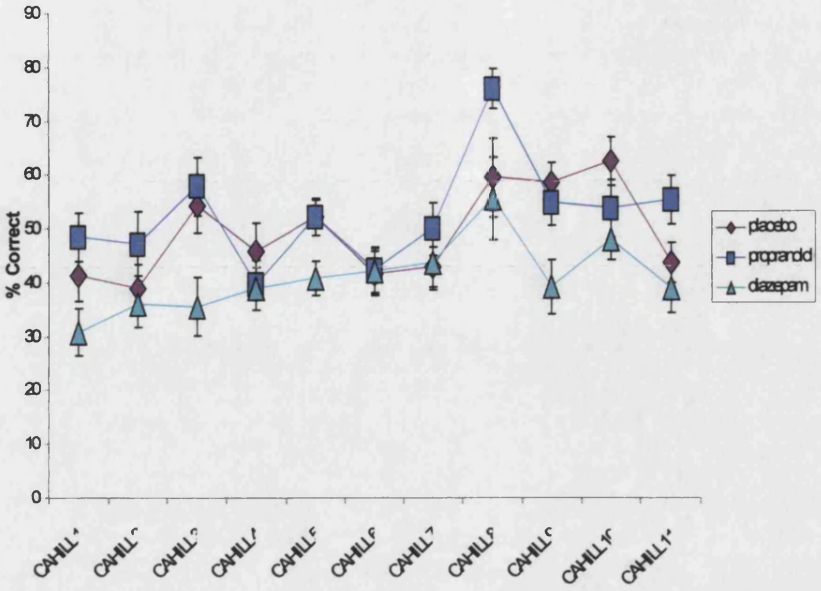


Table 11: Oneway ANOVAs testing the difference between drug groups on memory for each slide

Slide	$F_{2,46}$ =	Sig.
1	3.594	.036
2	1.370	.265
3	5.087	.010
4	.702	.501
5	3.764	.031
6	.007	.993
7	.727	.489
8	2.868	.067
9	5.638	.007
10	2.481	.095
11	3.906	.027

3.4.4.Control measures

3.4.4.1.Physiological Measures (Table 12)

The tendency towards a drug x time interaction ($F_{4,90}$=2.54, p=0.067) for pulse is due to heart rate being more constant in the diazepam group than either of the other 2 groups. The significant main effect of time ($F_{2,90}$=13.38, P<0.001) reflects how pulse dropped in all groups as the experiment progressed. Dunnett's test post hoc showed that the significant main effect of drug ($F_{2,45}$=3.18, p=0.05) was due to lower pulse rate in the propranolol group than the placebo group (p=0.015), although it should be noted that this was apparent even at the pre-drug stage.

Systolic blood pressure showed a similar pattern with a significant drug X time interaction ($F_{4,90}$=3.28, P<0.05) reflecting how systolic blood pressure dropped more in the diazepam group than the other two groups. The main effect of time ($F_{2,90}$=6.24, P<0.01) reflects how blood pressure decreased in all groups as the experiment progressed. There was no main effect of drug on systolic blood pressure. There were no significant effects of either drug on diastolic blood pressure.

Because of violations of sphericity the Greenhouse Geisser correction was applied when calculating the effects of time and interactions for the physiological measures.

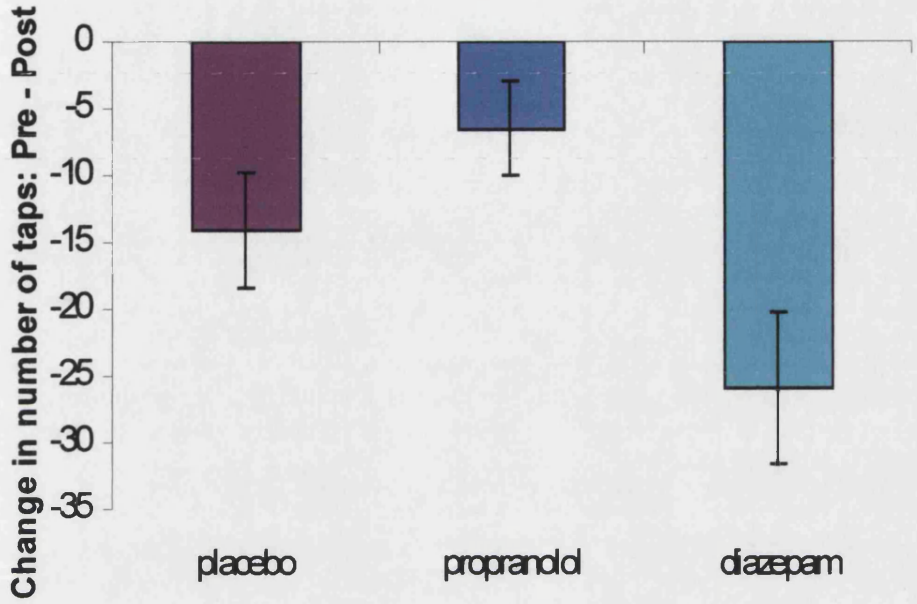
Table 12: Mean (s.d.) of cardiovascular measures

		Placebo	Propranolol	Diazepam
Pulse	Pre-drug	78.63 (12.11)	67.50 (7.91)	70.02 (8.70)
	Post-drug	69.25 (10.10)	60.53 (7.08)	69.91 (9.55)
	End of session	66.59 (10.80)	62.72 (17.60)	65.00 (9.88)
Systolic Blood Pressure	Pre-drug	114.75 (12.27)	112.63 (10.01)	125.10 (23.77)
	Post-drug	114.59 (10.48)	111.66 (10.26)	115.13 (16.23)
	End of session	114.44 (9.70)	109.19 (8.59)	111.44 (12.45)
Diastolic Blood Pressure	Pre-drug	72.38 (8.86)	71.19 (7.44)	73.27 (6.15)
	Post-drug	73.88 (7.19)	72.75 (8.23)	72.94 (8.74)
	End of session	71.00 (6.70)	74.53 (17.86)	69.34 (5.64)

3.4.4.2.Motor Arousal

A significant interaction ($F_{2,45}$=4.51 p=0.016) reflects a larger decrease in number of taps in the diazepam group compared to the other two drug groups (Figure 32). All groups made significantly less taps postdrug than they did predrug confirmed by a main effect of time ($F_{1,45}$ =34.14 p<0.001). There was no main effect of drug.

Figure 32: Change in Taps; post - pre in each drug group. As there was no group difference at the predrug stage, change scores are displayed for simplicity.



3.4.4.3.Mood Rating Scale

MRS factor1 **alert-drowsy** showed a significant drug X time interaction ($F_{4,90}$ =3.194, p=0.017) and main effect of drug ($F_{2,45}$ =6.24 p=0.004) confirming that the diazepam group felt less alert than the placebo group (Dunnett's test p=0.004) at the postdrug and end of session (EOS) time points (Figure 33). The propranolol group did not differ from the placebo group (p=0.677). A main effect of time ($F_{2,90}$ =21.64 p<0.001) shows groups became less alert as the experiment progressed.

Figure 33: Mean (s.e.) alertness in each drug group

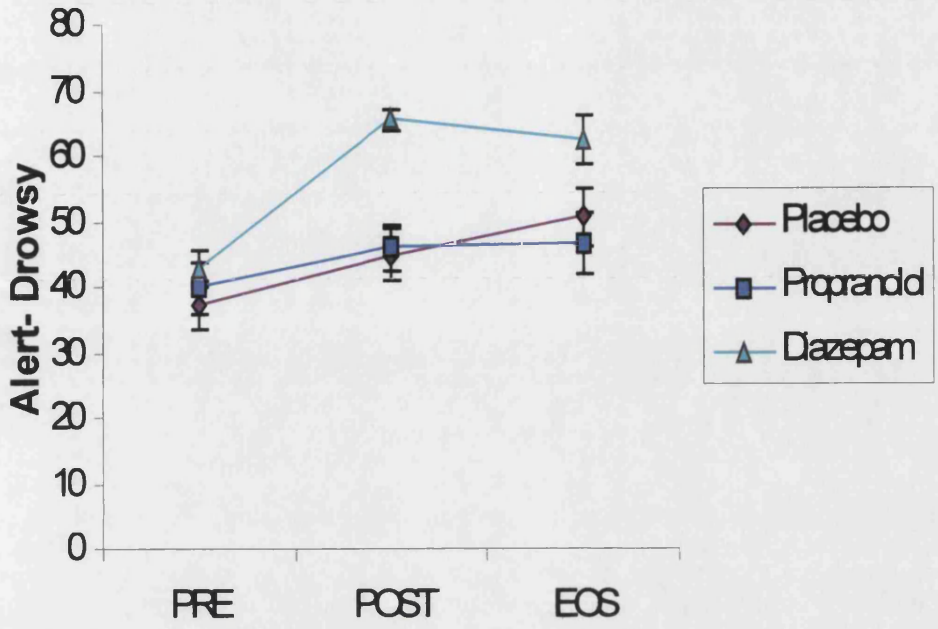


Table 13: Mean (s.d.) for each group on the contentedness and calmness factors

		Placebo	Propranolol	Diazepam
Contentedness	Pre-drug	36.96 (17.29)	37.40 (12.61)	40.40 (9.41)
	Post-drug	36.83 (17.58)	38.84 (10.92)	42.00 (10.80)
	End of session	48.64 (18.19)	40.30 (13.38)	43.06 (6.07)
Calmness	Pre-drug	42.84 (18.18)	35.41 (13.69)	38.38 (14.02)
	Postdrug	38.31 (14.98)	37.97 (11.65)	30.84 (12.36)
	End of session	36.28 (17.80)	37.41 (14.20)	29.75 (12.59)

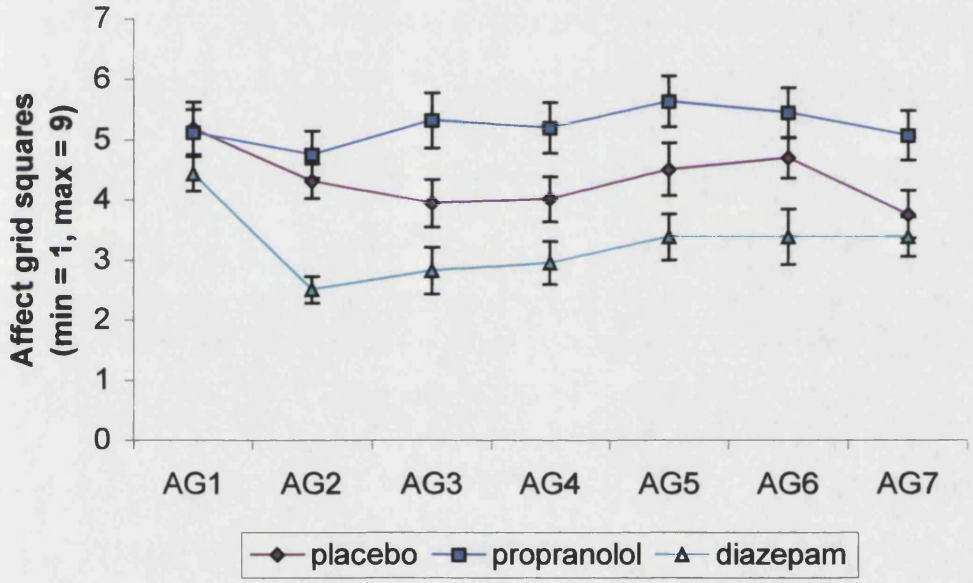
Participants also felt less **contented** as the experiment progressed, confirmed by a main effect of time $F_{2,90} = 5.245$ $p=0.011^{GG}$ on factor 2 irrespective of drug group, (there was no interaction or main effect of drug). The third factor **anxiety-calmness** showed no significant interaction or main effects (Table 13).

[GG] Greenhouse- Geisser correction applied to compensate for violation of sphericity

3.4.4.4.Affect Grid

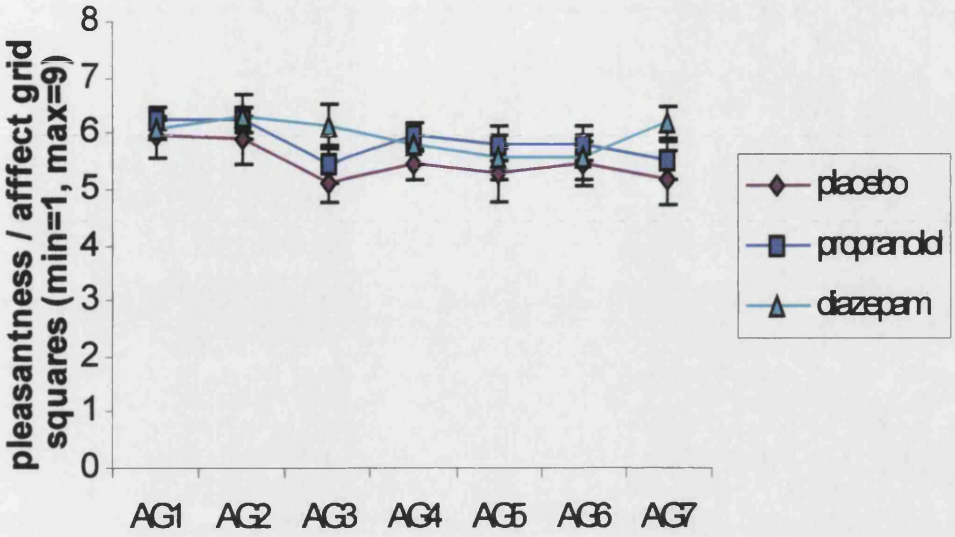
Figure 34 shows how propranolol appears to *increase* and diazepam to decrease arousal relative to placebo (drug X time interaction $F_{12,270} = 2.25$ $p=0.02^{GG}$, drug main effect $F_{2,45} = 10.23$, $p<0.001$) Dunnett's test post hoc showed arousal was lower in the diazepam group (p=0.031), and higher in the propranolol group (p=0.089) than the placebo group. This is a two-tailed test as an increase in arousal in the propranolol group was in the opposite direction to predicted. There was also a main effect of time on arousal ($F_{6,270} = 6.73$ $p<0.001^{GG}$).

Figure 34: Affect grid – Arousal



The affect grid dimension of pleasantness showed no significant interaction or effect of drug. A main effect of time ($F_{6,270} = 3.415$, $p=0.013^{GG}$) reflects how all groups reported feeling less pleasant as the experiment progressed, illustrated in Figure 35.

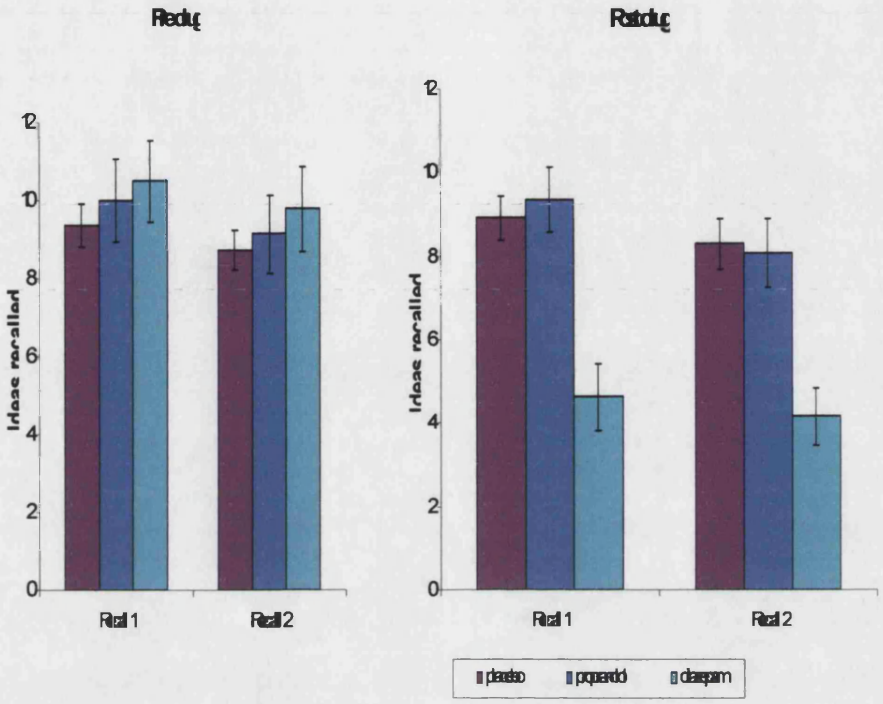
Figure 35: Affect grid – Pleasantness



3.4.4.5.Prose Recall

This was analysed by a 2x2x3 split plot ANOVA. The factors were study time (predrug vs postdrug), delay (1 vs 2) and drug. There was a significant encoding X drug interaction ($F_{2,44} = 11.22$ $p<0.001$) whereby the diazepam group performed worse when encoding occurred post drug. There was also a main effect of delay ($F_{1,44} = 23.36$ $p<0.001$), more was recalled after the short delay (1) than the longer delay (2) in all drug groups, for both pre and post drug encoding. A main effect of encoding ($F_{1,44} = 19.99$ $p<0.001$) reflected better memory for the prose passage encoded predrug compared with the passage studied postdrug. The main effect of drug, the interactions, retrieval x drug, and encoding x retrieval and the three-way interaction were non-significant. (Figure 36)

Figure 36: Prose recall



3.4.5. Summary of Results

- Picture Colour Test
    - Recognition memory hits
        - Negative > Positive > Neutral
        - Less hits and a tendency to more false alarms in the diazepam group
        - Neither drug altered *pattern* of hits
    - Recognition memory d'
        - Placebo: positive > negative > neutral
        - Propranolol: no different from placebo
        - Diazepam: Negative > positive > neutral. Overall d' lower than placebo
    - Recognition memory bias was less conservative for negative pictures in all drug groups
    - Source memory
        - Impaired by diazepam
        - Unaffected by emotion

- Implicit memory task
    - More stems were completed (primed) from the studied than the unstudied version in all drug groups
    - More words were primed than recognised
    - Neither drug nor emotion affected priming
    - Placebo group recognised more words from emotional than neutral sentences
    - No effect of emotion on recognition in either the propranolol or diazepam groups
    - Diazepam impaired recognition (but not priming)
- Story Task
    - Memory was best for the (non-emotional) phase 3
    - Diazepam impaired memory
    - Neither drug significantly affected the *pattern* of memory across the phases
    - The slide 8 effect was only apparent in the propranolol group
    - No evidence for a group difference in subjective ratings
- Control battery
    - In Table 14 a ✓ indicates the group did, and an X indicates the group did not show decreases in arousal relative to placebo

Table 14: Summary of control battery results

	Propranolol	Diazepam
Pulse	✓	X
Systolic blood pressure	X	✓
Diastolic blood pressure	X	X
Tapping	X	✓
MRS: alert – drowsy	X	✓
MRS: content – discontent	X	X
MRS: anxious –calm	X	X
AG: arousal	X	✓
AG: pleasant	X	X
Prose	X	✓

3.5.DISCUSSION

3.5.1.Picture Colour Task

As predicted, picture recognition (indexed by d') was better for emotional pictures than neutral pictures. Also as expected participants given diazepam recognised fewer pictures than participants given other treatments. However there were interesting differences between drug treatment groups in the pattern of recognising pictures of differing emotional valences. For both the placebo and propranolol groups positive and negative pictures were recognised more than neutral pictures. For the diazepam group, the pattern was towards better recognition of negative pictures than neutral pictures and recognition memory of positive pictures was impaired relative to neutral pictures. When hit and false alarm rates were considered separately, it could be seen that this impairment is due both to an elevated false alarm rate and reduced hit rate for positive pictures in these subjects. The increased false alarm rate is particularly interesting as the placebo group made their least number of false alarms to positive pictures.

This altered pattern of performance due to diazepam is interesting as it may reflect on the anxiolytic action of benzodiazepines. Perhaps the increased number of false alarms to positive pictures reflects participants under the

influence of benzodiazepines showing a cognitive bias toward positive emotions. The increase in d' sensitivity for emotional pictures in the placebo group fits with the broader literature describing memory facilitation by emotional material. This effect was not very highly significant and no difference was observed between positive and negative pictures, but conclusions are limited by a ceiling effect. With many participants scoring above 0.9 hits and below 0.1 false alarms, picture recognition in both the placebo and propranolol groups was at such a high level that there was no room for facilitation by the negative emotion pictures. It is speculated that had this part of the test been made more difficult, (e.g. by use of a longer delay, or by testing retention by free recall, or by using a greater number of stimulus pictures) the placebo group would have showed better memory performance for the negative pictures, whereas the propranolol group may not have done. Although the placebo group mean for negative pictures is not the highest, no participant had a low value of d' in this condition.

The factor that most clearly affected the bias parameter (C) was emotion. Participants used a much lower criterion when recognising emotionally negative pictures than either emotionally neutral or positive pictures. The observed mean value of C was lowest in the placebo group although the interaction was not significant.

This lowered value of C the retrieval criterion for emotional stimuli has been reported before, (e.g. Windmann & Kutas 2001). It also appears to be more easily detectable than the effect of emotion on sensitivity, as the small size of the d' effect in both the current pilot and main drug tests implies. The non-significant interaction between drug and time on the bias parameter C suggests that it is a robust effect, and one which is unaffected by propranolol and diazepam.

Considering the large amount of interest in recognition memory for emotional material, surprisingly little attention has been given to the question of a recognition memory bias for emotional material in non-clinical populations. Windmann and Kutas (2001) discussed the phenomenon and investigated ERPs associated with recognition memory bias for emotional words. They found that emotion affects word recognition at a very early (preattentive) stage and argue that the relaxation of retrieval criterion for emotional words may have

evolutionary advantage by ensuring that emotional events are not as easily missed or forgotten as neutral events.

One possible explanation of the bias effect could be that emotional arousal due to the pictures increased participant's propensity to respond, increasing both hit and false alarm rates as observed. This would explain why positive pictures (which are given lower arousal ratings by Lang et al, 1999) do not show this bias effect. However the effect was as strong in the two drug groups whose arousal levels were controlled by the active drugs, as it was in the placebo group.

Another possible explanation is that the lowered bias criterion could be a result of participants remembering more central (gist) information and less peripheral information from the emotional pictures. Perhaps on seeing a disturbing photograph of a car crash participants are just encoding 'car crash' rather than the actual scene. If so, on seeing a distractor car crash, they would be more likely to accept it was the one they saw.

A related explanation is that emotion pictures belong to a more coherent semantic category. Participants may have encoded the information ' lots of really bad things'. Therefore as the distractors also fell into the category of 'really bad things' they would be more easily confusable with the targets as observed. Therefore one would expect more false alarms, but no difference to hits, which was not observed in the data. Additionally the positive pictures, which also form a loose semantic category 'lots of nice things', did not show a bias effect.

Another way in which the semantic categorisation of the emotion category could have affected bias towards responding 'old' for negative pictures is that subjects may have false memories of seeing these pictures. A classic demonstration of false memory is Roediger's work. He gave subjects a list of words from a category with one item missing. The missing category item would then be falsely 'remembered' in a memory test of the word list. Could a similar mechanism be leading to the false memory of negatively emotional pictures? Freyd and Gleaves (1996) argue that false memory is less likely for highly emotional than neutral information. In a discussion of how they believe Roediger's work is not a good analogy to 'recovered' memories of child abuse they ask, " ...see how often the participant misidentifies the word *penis* as

being on the list..." Pesta et al (2001) show that it is the distinctiveness of emotional information that offers it some protection from it being falsely remembered in this situation. When they made emotional words less distinctive by adding further emotional words to the study list, they found emotional words such as 'penis' and 'rape' could be falsely remembered. Therefore it appears that false memories for emotional items are certainly possible. Nodel et al (2002) showed that high stress (due to simulated public speaking) led to increased level of false memory. As emotional items may lead to heightened arousal and, in the scenario of an emotional picture among a set of emotional pictures, are not particularly distinctive, perhaps false memories may be even more likely for them than for neutral items. It seems that this is a hypothesis that requires testing. However it may not be the explanation for altered recognition bias. Windmann and Kutas (2001) argue that the pattern of ERPs produced by emotionally altered recognition memory bias does not support an interpretation in terms of conventional explanations of false memory.

An explanation in terms of false memory does not quite match the theory behind the bias data. Theoretically an unbiased responder would score a C of zero. Scores below zero represent liberal bias and scores above zero represent conservative bias. In the current experiment scores were generally above zero, dipping only occasionally below zero for the negative stimuli. Theoretically, therefore, it is previously seen stimuli that are being rejected, rather than unseen stimuli that are being accepted.

If the memories for these emotional items were not 'true memories' but confabulations due to category membership this has implications for the interpretation of the slide colour memory data. The pattern of decreased 'source memory' for emotional slides that was demonstrated in the pilot run of the task, was predicted because it was thought that ink colour would be a peripheral detail. However it could also be caused by the memory of a particular picture being a false memory – whose colour had been confabulated along with the memory. Therefore source memory performance for these pictures would be lower than for the 'truly remembered' neutral pictures. There would be no need to propose an explanation for this impairment in terms of an emotional memory system and colour being a peripheral detail. The results could equally well be explained by enhanced recognition and bias towards negative pictures being

due to the category membership of those pictures, and the lowered source memory performance in terms of false memory. However this explanation does not account for the increased value of d' for emotional pictures found in the drug test, and the lack of a difference between source memory for the three emotion categories in the drug test where strong effects on bias were found.

3.5.2.Implicit memory task

This new task showed evidence for implicit memory. All drug groups showed priming, producing more words from the list that they had seen presented in sentences than from the baseline list that they had not seen. In all drug groups some of the words produced ('primed') were not recognised as sentence words, suggesting automatic influences. This was particularly clear in the diazepam group. The level of priming was unaffected by diazepam, and recognition memory was significantly impaired. In the placebo and propranolol groups chance (baseline) completion rates could account for many of the unrecognised words produced. In the diazepam group, there were many more unrecognised completed sentence words than baseline completions.

Therefore, as has been described in the literature (e.g. Vidailhet et al, 1996), diazepam did not impair priming, but did impair explicit memory. Priming was also unaffected by propranolol, also expected, as there are no reports of beta-blockade affecting priming. The emotionality of the sentence that the words were originally presented in had no effect on priming either. This was contrary to predictions, and an effect of emotion on priming was observed in the pilot study. However this effect had been a small, barely detectable in the pilot study with a large number (60) of participants. Therefore if emotion does affect implicit memory this new task is not a good method for detecting it.

Priming taps into a very shallow, modality specific level of encoding (the perceptual features of the printed words). The emotional part of the stimulus was presented in a different (auditory) modality, and requires a deeper semantic understanding of the stimulus.

Another reason that increased priming was not observed for words from emotional sentences, could be the effects of emotional stimuli on attention. For example participant 8 heard the sentence "the lady was raped on her wedding day" .The printed target word was 'lady' but the participant read 'raped'.

Therefore even if the emotionality of this sentence led to enhanced consolidation, it would have been the task-irrelevant sentence word 'raped' that would have been enhanced rather than the target word 'lady'.
Emotion did have an effect on the number of words recognised in the placebo group, but not in either of the other two active drug groups. Given the enhanced free recall for similar stimuli from emotional sentences in the previous experiment, this is as would be predicted. However the measure does have a problem as the participants were only able to recognise words that they had already completed in the priming task. Therefore as the placebo group did complete slightly (non-significantly) more words from emotional sentences there were more chances for them to recognise these words than words from non-emotional sentences. A preferable way of administering the recognition task (to make it independent of the priming task) would be to present participants with the complete list of sentence and baseline words and ask them to mark any that they recognised.

3.5.3.Story Task

The placebo group did not show the predicted memory improvements associated with the emotional section of the story. The most probable reason for this is that the story was presented at the end of the experiment, after the participants had already been exposed to a large amount of highly emotional material. Therefore it seems likely that the participants had become 'desensitised' to the emotional stimuli. Another possible explanation could be that the shocking slide 8 may gain much of its mnemonic strength from its distinctiveness. In the current experiment there were other pictures of badly injured bodies, therefore this slide may not have been distinctive and this could be why it was not as well remembered as in the previous experiment (chapter 2).
The clearest group difference was found in memory for slide 9. This was due to memory performance in the diazepam group being lower than the other two groups. Christianson & Nilsson (1984) showed participants a series of slides featuring pictures of faces, some disfigured. They showed that participants had impaired memory for information immediately succeeding these 'traumatic' pictures. As slide 9 (a picture of the mother leaving to make a phone call)

immediately follows the most traumatic slide (slide 8 – a picture of a toddler's severed feet), the effect reported by Christianson, could be operating in the diazepam group. If this is the case it is interesting that this effect does not appear in the placebo group.

Interestingly, and contrary to predictions the propranolol group showed the slide 8 effect more than the other two groups. As the peak concentration of propranolol is reached at 1.5 hours after drug and the half-life of propranolol is 3.9 hrs Hardman et al, 2002) the propranolol should have still been active when the story was presented at 2 hours post drug. The prediction that propranolol would reduce memory for the emotional parts of the story was based on reports by Cahill et al (1994), O'Carroll et al (1999b) van Stegeren et al (1998). However memory facilitation for the emotional section of this story was observed for participants under the influence of propranolol by (O'Carroll et al. 1999a). All these studies used a dose of propranolol of 40mg, lower than the 80mg dose used in the current study.

It was expected that the higher dose would have more effect. However another action of propranolol is as a serotonin antagonist. Propranolol is a 5HT-1A receptor blocker (Lane and Baldwin, 1997). Perhaps the increased dose of propranolol may have altered the relative balance of serotonin and noradrenaline action. There is a small amount of evidence that serotonin may have a role in emotional memory. Fear conditioning has similar neuroanatomical substrates to emotional memory (see section 5.1.2.1). Bond et al (2002) demonstrated reduced aversive conditioning in participants treated with buspirone (a 5HT-1A agonist).

If propranolol is somehow reducing the effect of desensitisation it has significant implications for the current trend of administering β-blockers to trauma victims to try and prevent PTSD (e.g. Taylor and Cahill, 2002; Pitman et al, 2002; Reist et al 2002).

3.5.4.Physiological and Control Measures

3.5.4.1.Physiological measures

All groups appeared to relax during the experiment, with both pulse and systolic blood pressure decreasing as the experiment progressed. Propranolol did not

cause much change in the cardiovascular measures; this is in line with Hardman et al (p.250) who state that propranolol has little effect on the heart of a normal individual at rest. All the volunteers were fit and healthy, and at the time of the physiological readings had just completed a mood rating scale, and listened to the prose passage. (Neither task is mentally or physically strenuous). The diazepam group showed greater blood pressure decreases than the other two groups. This could be attributed to the relaxing effects of diazepam, but it should be noted that the diazepam group had higher average blood pressure readings pre-drug and therefore may have been regressing to the mean.

3.5.4.2.Motor Arousal

The results of the tapping task were similar to the physiological measures in that all groups had reduced tapping rates on the postdrug test. Therefore motor arousal, like cardiovascular arousal, decreased in all groups over time. The diazepam group showed the greatest decrease in motor arousal, as they did in blood pressure. Again the propranolol group did not show evidence for a drop in arousal, showing a slightly smaller drop in number of taps pre-post than the placebo group.

3.5.4.3.Subjective ratings

As expected, and supporting the physiological and motor arousal findings diazepam reduced subjective arousal as measured on the affect grid, and subjective alertness on the MRS. The propranolol group did not differ from placebo on the MRS alertness factor, and if anything showed increased ratings of arousal on the affect grid. In Experiment 1 it was discussed that the MRS were designed to measured decreases in arousal and perhaps the factors do not pick up so clearly on arousal increases. Therefore it appears that the subjective experience of the propranolol group in the current experiment was actually of increased arousal, and this conclusion is not contradicted by the physiological and motor data. Therefore any effects of propranolol on emotional memory cannot be purely attributed to reduced arousal.

Contentedness on the MRS and pleasantness on the Affect grid only showed an effect of time, all subjects felt less contented / pleasant as the experiment

wore on. As these concepts have face similarity it is reassuring to find that they change in a similar way.

3.5.4.4.Prose Recall

As predicted, the diazepam group performed worse on recall of the 'post drug' prose passage that they heard under the influence of the drug. Diazepam impaired recall at both delay periods. Immediate recall is not usually greatly affected by diazepam (Curran, 1999). In the current experiment, between hearing the story and performing the "delay 1" recall test participants performed the other baseline measures. This delay of about 10mins was enough for recall to be affected by this dose of diazepam. All drug groups performed better on the recall test at 10mins than at the longer delayed test, as would be expected. The effect of all participants remembering more from the first story that they encoded pre-drug, than from the second story they encoded post-drug, may reflect effects of fatigue or proactive interference. As listening to the story was the first task participants performed (apart from the consent form and medical screening) their recall of the first story should have been relatively unaffected by these factors.

In summary there was some evidence that diazepam reduced arousal, and disrupted the memory facilitating effect of positive (but not negative) pictures. Diazepam did not impair priming, but did impair recognition of the primed words. There was no evidence for an effect of emotion on priming in any of the three groups, although there was some suggestion that the placebo group recognised more words from emotional sentences (which were a subset of the primed words). Propranolol reduced physiological, but not psychological arousal. Propranolol did not disrupt emotional memory.

CHAPTER 4: PICTURES AND PROFANITIES: The effects of diazepam and methylphenidate on recall memory for emotional and neutral pictures and taboo words (EXPERIMENT 3)

4.1.INTRODUCTION

Experiment 2 indicated that diazepam disrupted emotional facilitation of memory. In Experiment 1 there was some evidence that when arousal was both pharmacologically increased (by methylphenidate) and decreased (by lorazepam) the memory-facilitating effect of emotional material was marginally reduced. However the process that was disrupted to reduce the mnemonic advantage of emotional material was not tested in the first experiment.

This third experiment aims to partially replicate and extend the findings of Experiment 1 by using two emotional memory tasks that are designed to address the shortcomings of the tasks used in Experiment 2. These tasks are a 'picture recall task' adapted from the picture colour test used in Experiment 2 and the 'taboo words task' devised by LaBar & Phelps (1998).

Another aim of the current experiment is to explore the mechanisms that are disrupted by drugs to produce the observed effects on emotional memory. McGaugh hypothesises that noradrenaline modulates the consolidation of emotional memories. However experiments using pharmacological manipulations to alter noradrenaline levels after encoding (i.e. during consolidation) have had mixed success. Neither post-encoding administration of propranolol (van Stegeren, Everaerd, & Gooren 2002) nor injections of yohimbine (Southwick et al. 2002) alter the relative levels of emotional and neutral material in memory. However recently (Cahill & Alkire 2003) found that for the first few slides in a series (which caused autonomic arousal) memory could be enhanced by post-learning infusions of adrenaline. The influence of diazepam (15mg) and methylphenidate (40mg) on consolidation of emotional memories will be investigated in the present experiment, using a task with two test intervals to explore the time window of the drug effects (see below, section 4.1.2.).

In experiment 1 there was some suggestion that methylphenidate may have altered the perceived emotionality of the story task stimuli. Influencing emotion at encoding is another mechanism by which a drug might disrupt emotional memory. Therefore in the present experiment there is additional emphasis on the rating of stimuli for subjective emotionality during the encoding phase.

4.1.1.Picture Recall Task

In Chapter 3 (Experiment 2) the possibility that effects of emotion may have been obscured by a ceiling effect in the picture colour task was discussed. To overcome this problem, two possible ways of making the task more difficult were considered. The first of these was to increase the number of stimuli, making it less likely that participants would recognise all of them. This was rejected, as there was a possibility that participants became desensitised to emotion pictures even with the number used in experiment 2. Therefore it was decided to increase task difficulty by changing the picture colour task from a recognition task into a free recall task.

Testing memory by free recall not only has the advantage that there are less likely to be ceiling effects, it also means that a smaller number of pictures need to be presented. Therefore there is less likelihood that participants will become desensitised to the emotionality of the pictures.

In a free recall test participants may use various strategies to cue retrieval. This means that facilitation of memory by emotional material may potentially be confounded with other properties that make these pictures easier to retrieve. For example, participants may use category membership to cue picture retrieval. Therefore the part of the task where participants report the ink colour of their recalled pictures is particularly important. This is the only part of the task where memory demands are similar for all three categories of pictures. The to-be-remembered material is constant - the ability to retrieve the colour of the ink regardless of whether the emotional valence of the pictures is positive negative or neutral.

Whether participants can remember the colour of the picture is also interesting as it provides insight into the nature of emotional memory in the three groups. Emotional memories in some circumstances (e.g. flashbulb memory) are thought to have more of the qualities of episodic memory than neutral

memories. For example flashbulb memories have been argued to contain more contextual details. Whether or not these memories actually have more of this information remains open for debate (rev. Christianson 1992). It is also interesting to consider whether increases in arousal following methylphenidate have similar effects to increases in arousal due to the emotional valence of stimuli, on the relative number of pictures for which there is episodic (colour) information.

If either drug altered participants' perception of the emotional valence of pictures, as was suggested by the subjective ratings of the (Cahill & McGaugh 1995) story in experiment 1, this would limit the conclusions that could be drawn about the influence of the drug on emotional memory. Therefore another way in which the present task differs from the picture task used in the previous experiment is that at encoding participants will rate the pictures for both valence and arousal using the first two scales (arousal and valence) of the self assessment manikin (SAM) provided by Lang, Bradley, & Cuthbert (1999). This scale has the advantages of being user-friendly and distinguishing between arousal and valence. Further it disguises the fact that this is the encoding part of a memory test and therefore reduces the likelihood that participants will intentionally rehearse the pictures. Participants will also be asked to report the colour of the pictures during the study session, to ensure that neither of the drugs, or the emotional arousal induced by the pictures impair perception and registration of this information.

It is predicted that, as in Experiment 2, because emotional arousal increases memory for central information to the expense of peripheral information:

i) The placebo group will *recall* more emotional than neutral pictures, but identify the ink colour of more neutral than emotional pictures.

ii) Because diazepam impairs memory, and because benzodiazepines are thought to impair the enhanced consolidation of emotional material (McGaugh & Cahill 1997) the diazepam group will recall less pictures overall than the placebo group, but emotion will not differentially affect memory.

If methylphenidate enhances consolidation of neutral stimuli

iii) the methylphenidate group will recall the same number of emotional as neutral pictures, but they will recall more neutral pictures than the placebo group.

If these predictions are supported, the effects can only be attributed to disruption of the emotional memory system, if the corresponding drug does not alter the emotion ratings given to the pictures at encoding.

4.1.2.Taboo words

An important distinguishing feature of emotional memory is that arousal modulates memory over time. This was first described by Kleinsmith & Kaplan (1963) who found that paired associates of words learned under high arousal were remembered worse at immediate test and better at delayed test than those associated with low arousal. LaBar & Phelps (1998) modernised this paradigm, using taboo words (profanities, sexually explicit words and words depicting social taboos), and testing memory for the actual words themselves, (not paired associates). They found that although taboo words were recalled better than neutral words when tested immediately after encoding, the mnemonic advantage of this highly arousing material increased even more over a one hour delay filled with other tests. However patients with damage to the medial temporal lobes (including the amygdala) did not show differential forgetting rates for taboo and neutral words.

The relative increase of memory over time can be explained as being due to arousal mediated memory consolidation. This is the process hypothesised by McGaugh to be altered by noradrenaline. Isolating the time window where the drug groups differ from placebo in their relative retention of emotional and neutral material will allow conclusions to be drawn about whether they impair or facilitate emotional memory by similar alterations of consolidation. This will be done with LaBar & Phelps' (1998) taboo words task, which is designed as a dual interval task where memory is tested both immediately and after a delay. If either drug group shows the same pattern of performance as placebo at immediate test, and then shows differentially impaired memory for emotional material at the delayed test, emotional memory must be being disrupted at the consolidation stage. If however, a drug group already differs from placebo at immediate test, the action of this drug could be on encoding processes.

The participants will be asked to rate the words for arousal at encoding using the four point rating scale designed by LaBar and Phelps. If either drug group differs from placebo on these subjective ratings, conclusions relating to

emotional memory will be limited. Due to the profane nature of the arousing stimuli all groups are expected to remember more taboo words than low arousal words at immediate test. If the drugs disrupt emotionally mediated consolidation, only the placebo group are expected to show a different pattern of recall of taboo and non-arousing words at immediate than at delayed testing.

4.1.3.Baseline Measures

The same assessments of arousal were used as in Experiments 1 and 2. As previously it was predicted that methylphenidate would increase and diazepam decrease arousal, relative to placebo.

The prose recall test was again used, and diazepam was predicted to impair recall, and methylphenidate to slightly enhance delayed recall. A 'serial sevens' task, a test of working memory, was also included because it may be sensitive to improvement by methylphenidate. Therefore improvements were expected after methylphenidate (Elliot et al, 1997) and impairments after diazepam.

4.2.METHOD

4.2.1.Participants

48 healthy volunteers took part in the study. They ranged in age from 18 – 35 years; there were an equal number of males and females in each drug group. The study was approved by the UCL/UCLH committee on the ethics of human research.

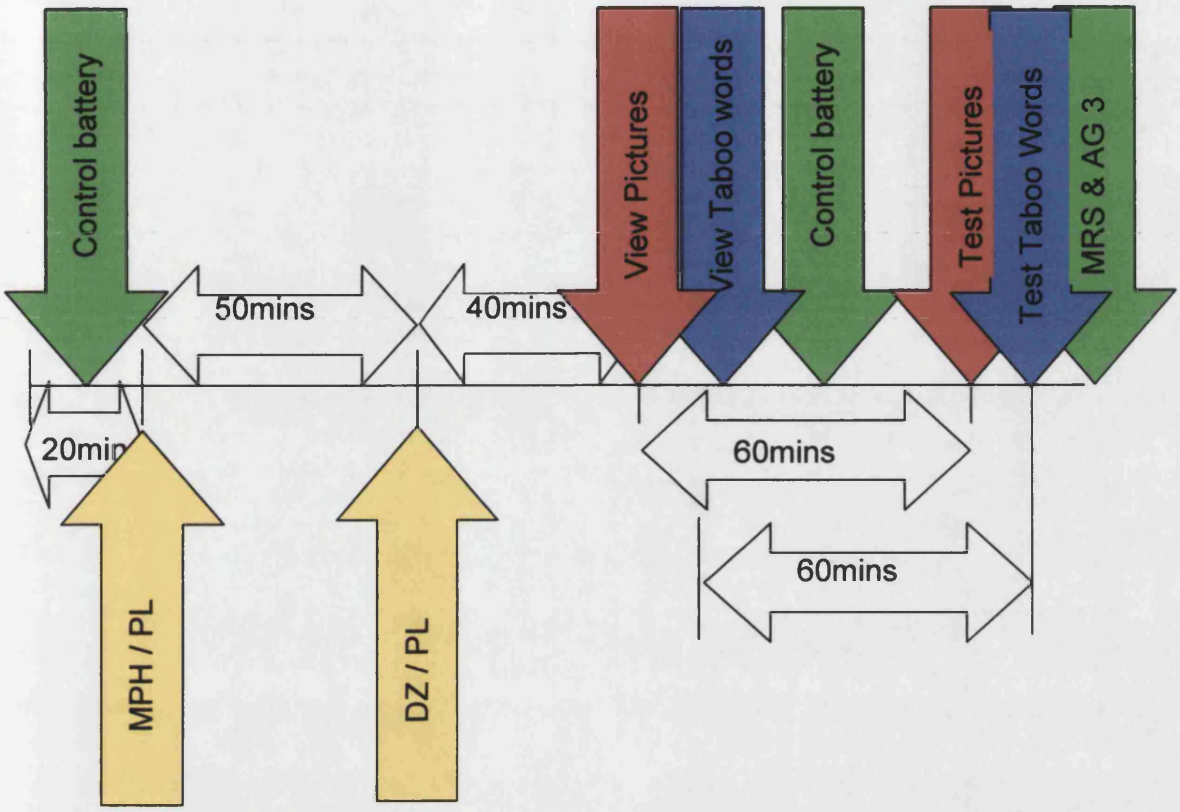
4.2.2.Design

Subjects were randomly allocated to one of three parallel groups (methylphenidate, diazepam, or placebo). The experiment was double blind, with a double dummy procedure concealing the identity of the capsules while allowing for the different absorption rates of the two drugs. There were two parallel versions of the 'control battery' tests which were administered both pre and post drug. These were counterbalanced across subjects and conditions.

4.2.3.Procedure

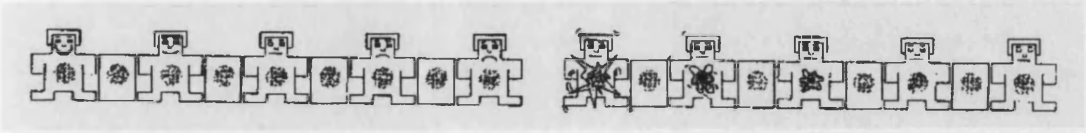
On arrival participants gave written informed consent and completed the screening interview. The pre-drug battery of tests was then completed in the following order: (1) the mood rating scales, (2)pulse and blood pressure readings, (3) the affect grid, (4) the tapping task, (5) the prose recall test from the Rivermead behavioural memory battery, and (6) the serial sevens task. Participants were administered a capsule containing 40mg methylphenidate or placebo, then 20 minutes later another capsule containing either 15mg diazepam or placebo (Figure 37). Forty minutes after that (i.e. 60mins after capsule 1) the post drug test session was started. A double dummy procedure was used.

Figure 37: Representation of test timings



Immediately after receiving the first capsule (i.e. before the drugs would have taken effect), participants learned how to mark the SAM rating scale using the instructions printed in the manual provided with the IAPS (Lang et al, 1999). An example of the scale appears in Figure 38. It was explained to participants that SAM showed two different kinds of feelings, 'happy versus unhappy' and 'excited versus calm'. It was pointed out that the midpoint of each scale represented a completely neutral mood, and the types of feelings represented by the extremes of the scale were described. Participants were told that they could mark an X on the SAM figure, or between two figures, that best represented how they felt.

Figure 38: The SAM rating scale dimensions of pleasantness (on the left) and arousal (on the right).



The post-drug test battery started with the study section of the picture test followed by the study and immediate recall of the taboo words. Test order can be found in Appendix 5.

This was followed by a repeat of the tests that appeared in the pre drug battery. These were performed in the same order as in the pre drug battery. This 'control battery' was followed by two filler tests. These were a story task test of aggression, and an emotional voices task. This was followed by delayed prose recall.

Memory for the pictures was then tested by free recall, and participants were then asked for delayed free recall of the taboo words. At the end of the experiment participants filled in a final Mood rating scale and affect grid. Participants were not allowed to leave until they were considered 'street ready' and refreshments were provided while they were waiting.

4.2.3.1.Picture Test Free Recall

The materials used were taken from the picture colour test described in Experiment 2. There were thirty pictures, ten from each category (positive, negative and netural). These were carefully chosen so that verbal descriptions given for each picture could only apply to one picture in the set. Five pictures from each emotion category were presented in green ink, the other five were presented in purple ink. There were two versions of the task so that pictures appeared in the other colour in the alternate version.

The pictures were presented on the computer screen in a pseudo random order. Each picture remained on the screen for 3 seconds, and after it disappeared the participant had 10 seconds to fill in the arousal and valence rating scales from the SAM. They were also asked to report the ink colour of the picture.

The pictures were viewed and rated at the beginning of the main test session, and picture recall was tested towards the end of the main test session –

approximately one hour later. Participants were asked to report as many pictures as they could remember, and these were recorded by the experimenter. For each picture the participant recalled they were asked if they could remember the ink colour at presentation.

4.2.3.2.Taboo words task

The 20 taboo words were kindly provided by Liz Phelps (LaBar & Phelps, 1998). As they were unable to provide the matched non-arousing words, 20 low arousal words were selected from the Affective Norms for English Words (ANEW) (Bradley & Lang 1999). Therefore in the same way as the taboo words form a loose category, the non-arousing words also formed a loose category. Low arousal words were selected to match the taboo words in terms of number of syllables and word frequency. As frequency estimates for expletives do not appear in the conventional lexicons (e.g. Kucera and Francis) following Blair, Urland, & Ma (2002) estimates of word frequency were taken from the internet search engine Altavista. Three additional taboo and three non-arousing words were used as primacy and recency controls. The word stimuli used appear in the Appendix 10, along with frequency data, and number of syllables.
The words were presented in large font, in a fixed pseudo random order using the program PowerPoint. After each word disappeared from the screen participants rated it on an arousal scale ranging from 1 (not at all arousing) to 4 (very arousing). Participants gave their arousal ratings verbally, and the experimenter recorded these. The scale was printed on a card, which was in front of the participant throughout the rating task.
Immediately following the encoding phase, participants were asked to write down all the words they could remember. Responses were written on paper to try and reduce the risk of participants not producing the taboo words because they were embarrassed to say them. The delayed recall test was approximately one hour after the immediate recall and the intervening time was filled with other tasks.

4.2.4.Statistics

The picture colour task data was analysed with a 3 x 3 (emotion x drug) split plot ANOVA. Separate analyses of variance were calculated for the free recall,

source memory, and subjective ratings data. Where simple effects analyses were carried out the actual probabilities are presented and an appropriate Bonferroni corrected critical probability is presented for comparison. Source memory was defined as the proportion of pictures recalled whose colour was correctly identified. This source memory measure differs from the measure used in the other experiments in the series where source memory was derived from recognition memory data by subtraction. The method of calculating proportions used here was selected for the current experiment to prevent the source memory measure from becoming confounded with the number of pictures correctly recalled.

The taboo words task was analysed with a 2 x 2 x 3 (emotion x delay x drug) split plot ANOVA. A 2 x 3 (emotion x drug) ANOVA was used to analyse the arousal ratings.

The tests performed at 2 time points (pulse, blood pressure, tapping task, serial sevens) were analysed with a 2 x 3 (time x drug) split plot ANOVA.

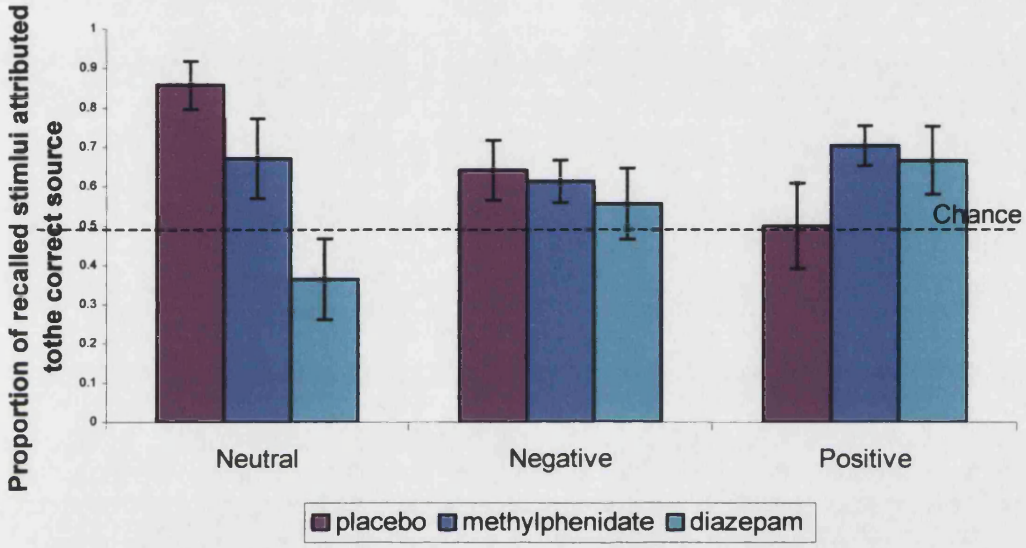
For the affect grid, which was completed at three time points, a similar ANOVA was calculated with 3 levels of time. The prose recall task had an additional factor 'delay' which had two levels. Therefore this was a 2 x 2 x 3 ANOVA.

4.3.RESULTS

4.3.1. Picture Recall Task

4.3.1.1. Source memory data

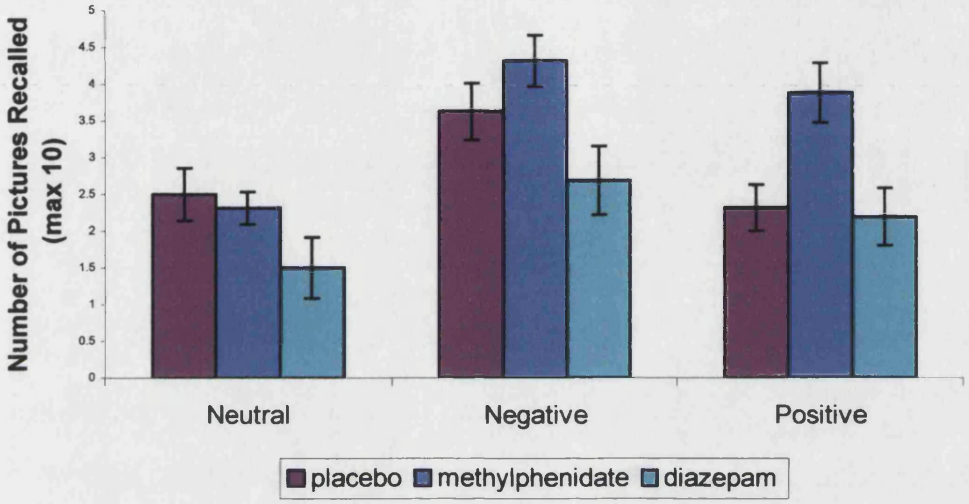
Figure 39: Mean (s.e.) proportion of pictures recalled, correctly attributed to source



The source memory results produce an interesting drug x emotion interaction ($F_{4,90}$ = 4.46, p=0.003)(Figure 39). The placebo group show the predicted pattern of poorer source memory for the emotional than for the neutral pictures. (There was a significant difference in this group between performance on the three emotion categories $F_{2,30}$ = 4.77 p=0.022^{GG}). The methylphenidate group show relatively similar levels of source memory for all types of pictures (p=0.625). The diazepam group show better source memory for positive pictures, (the difference between emotion categories was marginal $F_{2,30}$ = 3.18, p=0.056). Source memory for the negative and neutral pictures was at or below chance levels in the diazepam group.

4.3.1.2. Recall memory Data

Figure 40: Mean (s.e.) number of pictures recalled from each category, by each drug group



The 3 x 3 (emotion x drug) ANOVA showed a drug x emotion interaction, ($F_{4,90}$ = 2.52, p=0.047). As seen in Figure 40 the pattern of recall differed between groups whereby a similar number of neutral and positive pictures were recalled after placebo, but active drug groups recalled more positive than neutral pictures. The interaction is investigated further by the simple effects analyses in section (4.3.1.2.1.)

A main effect of emotion $F_{2,90}$ = 18.85, p<0.001 confirmed that more negative pictures were recalled than positive pictures and more of both emotional categories than neutral (Figure 40). There was a main effect of drug, $F_{2,45}$ =5.63 p=0.007, which Dunnett's post hoc test showed was due to both (i) a trend for the diazepam group to remember less pictures than placebo (p=0.088, one-tailed) and (ii)a trend for the methylphenidate group to recall more pictures than placebo (p=0.088, one-tailed).

4.3.1.2.1. Simple Effects Analyses

A suitable critical probability for these comparisons might be 0.0125. This allows for four possible comparisons, comparing each drug with placebo and comparing each emotion with neutral (0.0125 = 0.05 / 4).

Two 2x3 ANOVAS were calculated (comparing each drug with placebo across the three emotions) to determine the cause of the interaction.

The placebo vs diazepam ANOVA showed no interaction ($p=0.242^{GG}$). There was a main effect of emotion ($p<0.001^{GG}$) and a trend towards a main effect of drug (p=0.081)(i.e. this is the same as the Dunnett's test, just the probability is corrected in Dunnetts test, and here the correction was applied to the critical probability.)

The placebo vs methylphenidate ANOVA showed a significant interaction $F_{2,60}$ = 4.85, $p=0.011^{GG}$ and main effects of drug and emotion. Therefore the interaction was due to the pattern of results in the methylphenidate group being different to the placebo group.

To investigate further how the patterns differed, two 2x2 ANOVAS were used to compare (placebo vs methylphenidate) groups' memories for (neutral vs negative) and (neutral vs positive).

For (methylphenidate vs placebo) x (neutral vs negative) there was no interaction (p=0.125), for (methylphenidate vs placebo) x (neutral vs positive) there was a significant drug x emotion interaction $F_{1,30}$=10.16, p=0.003. Therefore the main statistical difference causing the interaction in the omnibus ANOVA was a difference between methylphenidate and placebo on relative levels of memory for positive emotional pictures.

4.3.1.3 Emotion Ratings

Participants rated the pictures for valence as expected, giving the lowest ratings for the positive pictures, then neutral, then negative (Table 15). The categories received significantly different emotion ratings. Evidence for this is the main effect of emotion $F_{2,90}$ = 110.19, $p<0.001^{GG}$. The hypothesis that valence ratings were unaffected by the drugs was supported by the non-significant interaction ($P=0.433^{GG}$) and no main effect of drug (P=0.349)

Arousal ratings were also different for the different emotion categories $F_{2,90}$ = 44.93 $P<0.001^{GG}$: Participants found the neutral pictures to be neutral in arousal as well as valence, positive pictures were thought to be slightly more arousing, and negative pictures were found the most arousing. These ratings were unaffected by drug (Interaction $p=0.516^{GG}$: Drug p=0.410).

Table 15: Mean (s.d.) valence and arousal ratings (valence: 1= positive extreme, 5= neutral, 9=negative extreme) (arousal: 1= arousing extreme, 5=neutral, 9=relaxing extreme)

		Placebo	Methylphenidate	Diazepam
Valence	Neutral	5.29 (0.44)	5.15 (0.83)	5.48 (0.66)
	Negative	7.77 (0.73)	7.29 (1.62)	7.22 (1.43)
	Positive	3.31 (1.42)	3.56 (1.23)	2.89 (1.25)
Arousal	Neutral	5.78 (0.87)	5.25 (0.90)	5.62 (0.74)
	Negative	3.89 (1.25)	3.83 (1.13)	3.41 (1.18)
	Positive	4.29 (0.50)	4.27 (0.80)	4.22 (1.08)

Participants correctly identified the colour of most pictures (Table 16) and there was no evidence that either the drug (p=0.353) or the emotionality (p=0.455) of pictures or an interaction of both (p=0.602) affected participants' ability to identify the ink colour immediately after viewing the pictures.

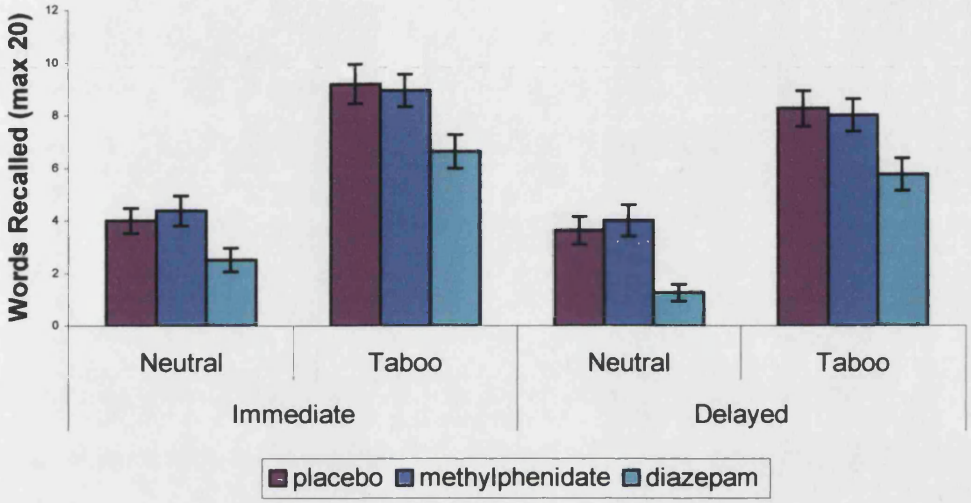
Table 16: Number of pictures (max 10) whose colour was correctly identified.

	Placebo	Methylphenidate	Diazepam
Neutral	9.44 (0.89)	9.00 (1.26)	8.63 (2.09)
Negative	9.50 (1.03)	9.00 (1.93)	8.69 (1.82)
Positive	9.56 (0.63)	8.94 (1.65)	9.13 (1.71)

4.3.2.Taboo Words

4.3.2.1 Memory Data

Figure 41:Mean (s.e.) number of taboo and neutral words recalled by each drug group at each testing time



The 2 x 2 x 3 (time x emotion x drug) ANOVA on the taboo words task produced none of the predicted interactions. There was a main effect of emotion $F_{1,45}$ = 163.50, P<0.001, whereby more taboo words were recalled than low arousal words (Figure 41). There was a main effect of time $F_{1,45}$ = 25.71, p<0.001, whereby more words were recalled at immediate test than delayed test. A main effect of drug $F_{2,45}$ = 109.57, p=0.001 was shown by Dunnett's test to be due to the difference between diazepam and placebo (p=0.002), as there was no difference between methylphenidate and placebo (p=0.993). Diazepam reduced recall of both taboo and neutral words relative to other treatments.

4.3.2.2 Subjective Ratings

The taboo words received higher arousal ratings than the neutral words $F_{1, 45}$= 528.64, p<0.001 (Table 17). There was no evidence that either drug affected this, as both the interaction (p=0.291) and the drug main effect (p=0.429) were non-significant.

Table 17: Mean (s.d.) arousal ratings (min=1, max = 4)

	Placebo	Methylphenidate	Diazepam	Total
Taboo Words	3.11	2.93	3.24	3.09
	(0.43)	(0.60)	(0.63)	(0.56)
Neutral Words	1.39	1.37	1.39	1.38
	(0.30)	(0.38)	(0.23)	(0.30)

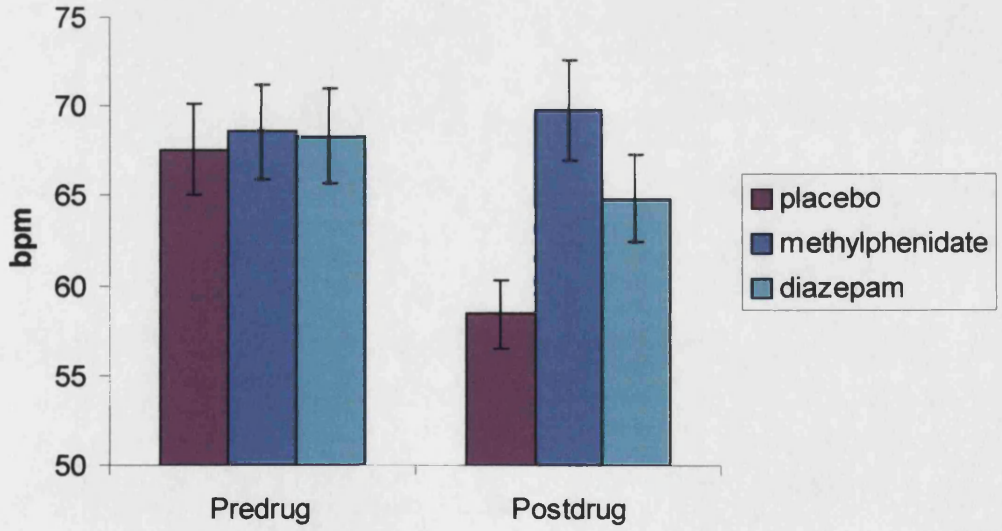
4.3.3.Control measures

4.3.3.1Physiological Measures

4.3.3.1.1Pulse

The pulse rate data showed a significant drug x time interaction $F_{2,45} = 8.66$, $p=0.01$, and a main effect of time $F_{1,45} = 13.67$, $p=0.001$. As seen in Figure 42 change in pulse rate was greatest after placebo, slight after diazepam and negligible after methylphenidate. There was no main effect of drug.

Figure 42: Mean (s.e.) Pulse Rate

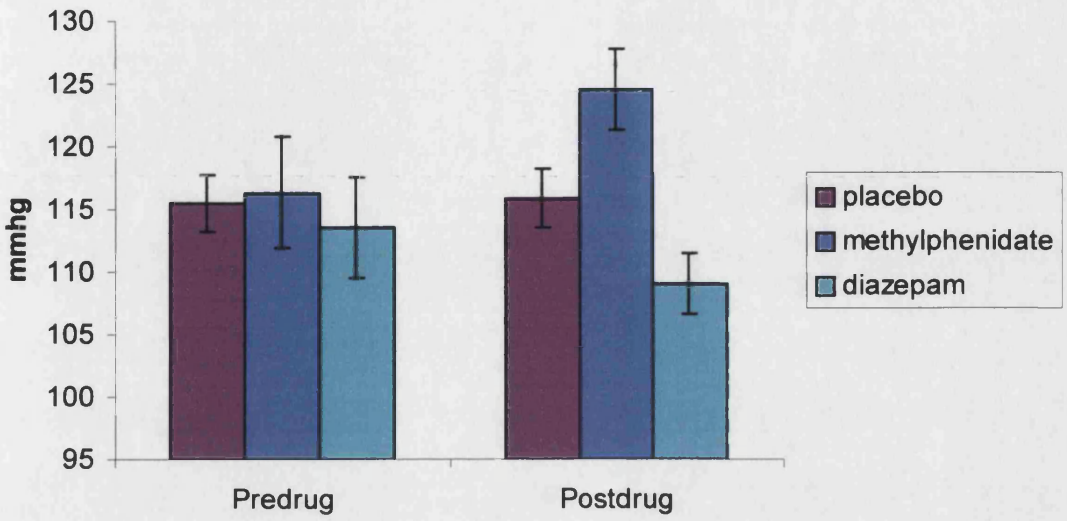


4.3.3.1.2 Blood pressure

For systolic blood pressure there was a significant drug x time interaction $F_{2,45} = 5.473$, $p=0.007$. As predicted after methylphenidate there was a marked increase, and after diazepam a slight decrease in systolic blood pressure. The

main effects were not significant. For diastolic blood pressure there were no significant main effects or interactions.

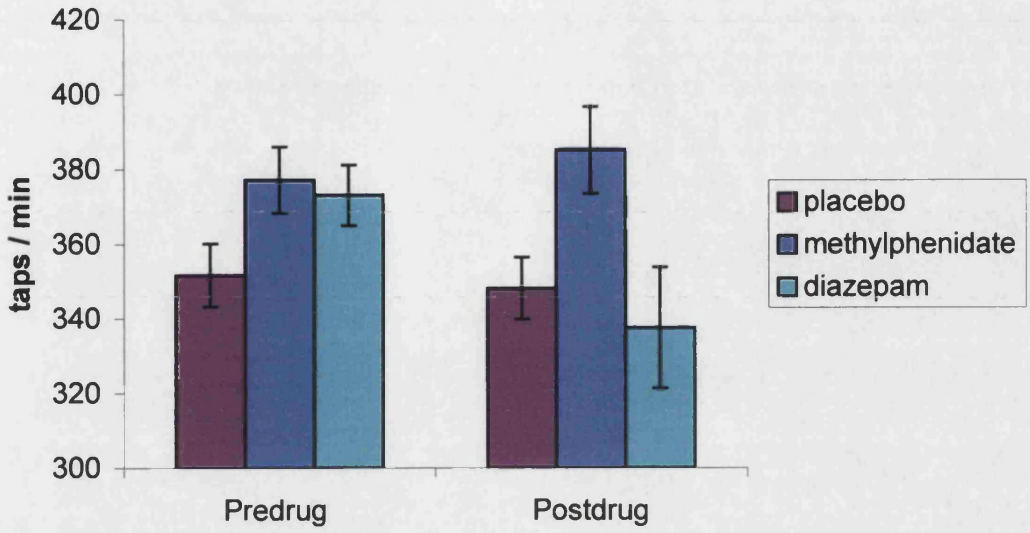
Figure 43: Mean S.E. Systolic Blood Pressure



4.3.2. Tapping Task

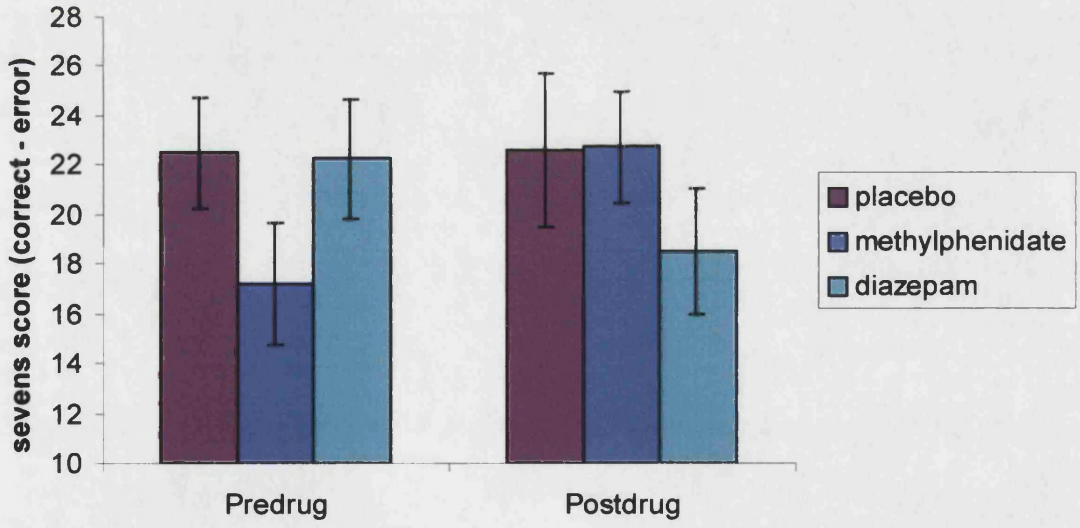
This showed a drug x time interaction $F_{2,45} = 8.002$, p=0.001. As expected tapping rate stayed constant in the placebo group, decreased in the diazepam group and increased in the methylphenidate group (Figure 44). A main effect of time $F_{1,45} = 5.05$ p=0.030 reflects average decreases as the experiment progressed, and a trend towards a main effect of drug. $F_{2,45} = 2.84$, p=0.069 reflects a lower tapping rate in the placebo group that was apparent even before the drug was given.

Figure 44: Mean (s.e)) taps / minute



4.3.3. Serial Sevens Task

Figure 45: Mean (s.e.) Sevens score (correct subtractions - errors)



An overall sevens score was calculated

Score = correct subtractions – errors

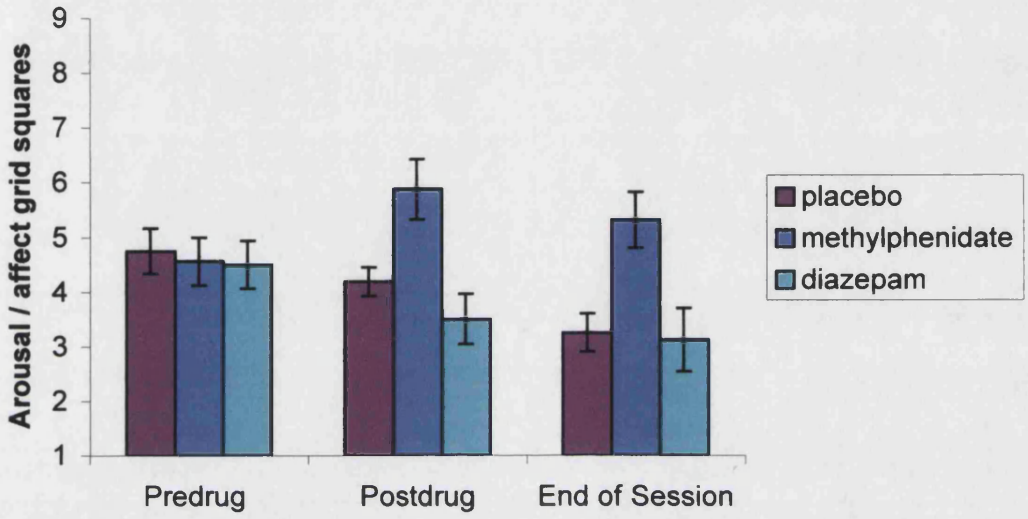
The ANOVA on this statistic showed a drug x time interaction $F_{2,45} = 7.06$, p=0.002, but no main effects. As can be seen in Figure 45 performance improved in the methylphenidate group, deteriorated in the diazepam group and

remained constant in the placebo group. The same pattern emerged when correct subtractions and errors were considered separately.

4.3.4. Subjective Effects

4.3.4.1 Affect grid

Figure 46: Affect grid measure of arousal (neutral = 5, 1 = lowest, 9=highest)

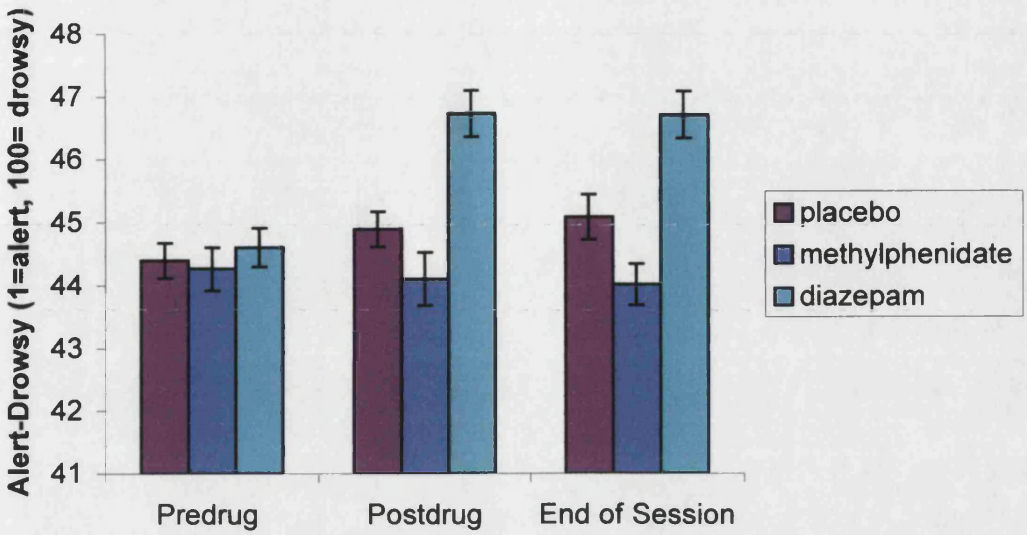


The affect grid measure of arousal showed a significant drug x time interaction $F_{4,90} = 5.28$, p=0.001. Arousal decreased during the experiment most notably in the diazepam, but also in the placebo group, and increased in the methylphenidate group (Figure 46). There was also a main effect of time $F_{2, 90} = 4.47$, p=0.017, and a main effect of drug $F_{2,45} = 4.69$, p=0.014.
For the measure of pleasantness there were no main effects or interactions.

4.3.4.2 Mood Rating Scale

The **alert- drowsy** factor showed a significant drug x time interaction $F_{4,90} = 7.91$, p<0.001(Figure 47). The diazepam group showed reductions in subjective alertness as the experiment progressed, the placebo and methylphenidate groups showed a fairly constant level of subjective alertness.

Figure 47: Mean (s.e.)Subjective alertness

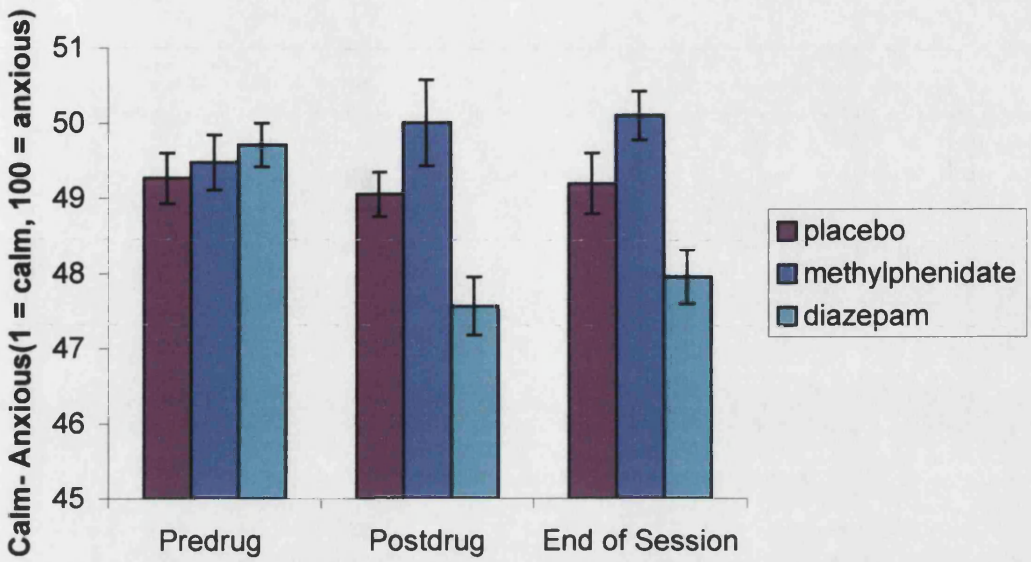


A main effect of drug $F_{2,45}$ = 11.77 p<0.001, and a main effect of time $F_{2,90}$ = 11.65 P<0.001 (due to the large alertness decreases in the diazepam group), were observed. Dunnetts test showed the drug effect was due to diazepam treated volunteers feeling less alert than the placebo group p=0.003, and a trend towards the methylphenidate group feeling more alert than placebo p=0.086.

The **content - discontent** factor showed no main effects or interactions.

The **calm - anxiety** subscale showed a drug x time interaction $F_{4,90}$ =4.77, p=0.002 (Figure 48). Relative to placebo the diazepam group felt calmer and the methylphenidate group more 'anxious/excited' as the experiment progressed. There were also main effects of drug $F_{2,45}$ = 8.21,p=0.001 and marginally time $F_{2,90}$=2.45, p=0.092. Dunnets posthoc test confirmed diazepam had rated increased calmness (p=0.035) and methylphenidate marginally lower calmness (p=0.055) than placebo.

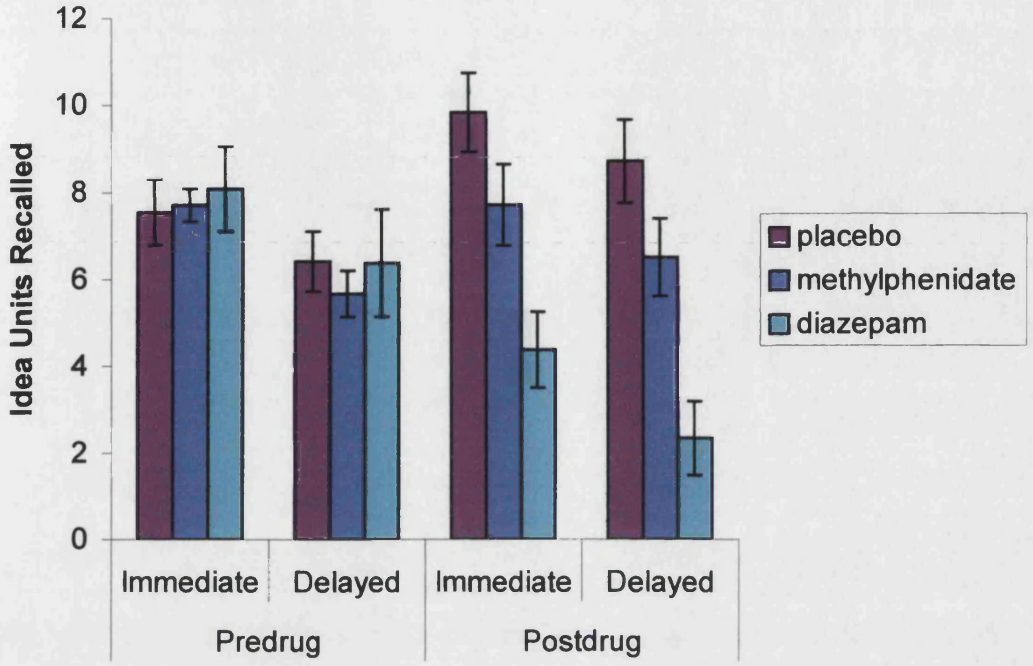
Figure 48: Mean (s.e.) MRS Calmness



4.3.5 Prose Recall

Prose recall scores showed a time x drug interaction $F_{2,45} = 11.90$, $p<0.001$ (Figure 49). The diazepam group were impaired by the drug whereas the placebo group improved pre to post drug. A main effect of delay $F_{1,45} = 40.72$, $p<0.001$ reflects all participants forgetting some of the story over time. There was a trend to a main effect of drug $F_{2,45} = 2.83$, $p=0.069$, which the post hoc Dunnett's test showed was due to a difference between the placebo and diazepam groups ($p=0.044$), and not between methylphenidate and placebo ($p=0.222$)

Figure 49: Mean (s.e.) immediate and delayed prose recall scores for the stories learned both pre and post drug in all drug groups.



4.3.4.Summary of results

- Picture Recall Task
  - Placebo group showed
    - Increased recall of negative emotional pictures
    - Decreased source memory for negative emotional pictures
  - Methylphenidate group showed
    - Increases in the number of positive pictures recalled
    - No effect of emotion on source memory
  - Diazepam group showed
    - Reduced overall level of recall
    - The same pattern of recall as the placebo group
    - The opposite pattern of source memory performance to the placebo group
  - Neither active drug affected emotion ratings
- Taboo words task
  - More taboo words than non-arousing words were recalled
    - In all drug groups

- At both time points
- Diazepam impaired recall of both categories of words
- Recall was poorer at delayed than immediate test
- Neither drug affected arousal ratings of words at encoding

- Control battery
  - Table X shows a ✓ if the measure did, or an X if it did not, show the predicted
    - Pre to post drug increases *relative to placebo* in the methylphenidate group
    - Pre to post drug decreases *relative to placebo* in the diazepam group

Table 18: Control battery summary of results

	Methylphenidate ↑	**Diazepam ↓**
Pulse	✓	X
Systolic BP	✓	✓
Diastolic BP	X	X
Serial Sevens (score)	✓	✓
Tapping Task	✓	✓
Affect grid: Arousal	✓	X
MRS: Alertness	X	✓
MRS: Calmness	✓	✓
Prose Recall	X	✓

4.4.DISCUSSION

4.4.1.Picture Recall task

This discussion concentrates first on the pattern of results observed in the placebo group, and then on how each of the active drug groups deviated from this pattern of behaviour.

The placebo group performed as predicted, showing a pattern of increased recall of emotionally arousing stimuli but reduced memory for the associated ink colour. Therefore in healthy participants the central information about the subject of the picture was retained better for emotional pictures, but the

peripheral information was less likely to be retained. This was particularly true for the negative emotional stimuli. This supports the suggestion made in the discussion of the previous experiment (section 3.2.1.4) that it is the *high arousal* induced by the pictures in the negative emotion category that causes the memory effects rather than the *negative valence*. Pictures in the positive category tend to receive intermediate arousal ratings, hence the intermediate levels of source memory and recall.

The most interesting result from the methylphenidate group was that their ability to correctly remember source (ink colour) was independent of emotional valence. This is in contrast to the placebo and diazepam groups and supports the finding of experiment 1 that methylphenidate reduces the effects of emotion on memory.

For the picture recall data, methylphenidate altered the *pattern* of results across the emotion categories. Although the methylphenidate group showed generally higher levels of recall than the placebo group, recall of the positive pictures was disproportionately increased by methylphenidate. The explanation for this may lie in the intermediate subjective arousal ratings that the positive pictures receive. The slightly raised arousal due to the pictures combined with the raised arousal due to the drug may possibly have led to higher recall levels for these pictures. Inverted U shape theories of the action of arousal (i.e. low arousal leads to poor performance, intermediate arousal leads to optimum performance and high arousal leads to poor performance) would explain why similar increases are not observed for the negative pictures. Pharmacologically increasing arousal further when arousal due to the stimuli is very high may not facilitate memory performance.

Although Diazepam reduced the level of recall overall, the pattern of recall across the three different emotion categories was similar to the pattern in the placebo group. Free recall was facilitated by the negative (highly arousing) emotional pictures. Interestingly however the pattern of source memory in the diazepam group was completely the opposite to that in the placebo group. The diazepam group showed poor (chance level) source memory for neutral and negative pictures, and their highest level of source memory was for positive pictures. In contrast to this, positive valence was the only emotion category where the placebo group showed source memory at chance level. This could be

evidence for participants under the influence of diazepam showing a cognitive bias towards positive stimuli, as was suggested in Experiment 2 (section 3.5.1). Perhaps more weight should be given to the effects of the drugs on the colour remembering part of the task, (i.e. the methylphenidate group showed little effect of emotion and the diazepam group showed bias towards positive pictures) given the methodological consideration that other features of the pictures will covary with emotion (e.g. distinctiveness, category membership). As false alarms are low (and hard to categorise emotionally) in free recall tasks, it is impossible to quantify the effect that emotion may have had on retrieval bias in the current experiment. However it is still possible that bias may have affected the free recall data. For example participants may have had more confidence in highly arousing negative memories and therefore been more likely to report them. However this problem is not unique to the present experiment as much of the literature about emotional memory uses free recall.

The rating data showed that neither drug affected the subjective arousal or valence of pictures at encoding. Therefore the reported effects must be due to the drugs altering memory processes. It is not possible to argue that diazepam just makes positive stimuli seem more positive, or methylphenidate just reduces emotional reactivity to external stimuli, because participants on the active drugs gave the same ratings as the placebo group.

4.4.2.Taboo Words Task

Diazepam globally impaired memory for both the taboo and neutral words. This is in line with the reports that benzodiazepines impair episodic memory (e.g. Curran 2000). However of greater theoretical interest to the research question of the current thesis is the effect of diazepam on the rate of forgetting of the two types of material over time.

The taboo words task showed a clear effect of emotion category on memory. The taboo words were better recalled than the neutral words by all drug groups at both immediate and delayed testing times. Participants forgot some words from each category over the hour, but contrary to predictions, a similar number of words were forgotten from each emotion category.

Therefore it is unlikely that the main mechanism operating to promote memory for the taboo words was enhanced consolidation, as this would have increased

the advantage of the taboo words over time. The taboo words had a memory advantage, but this was probably due to some other property of these words, perhaps their distinctiveness, or receiving increased attention at encoding. The mnemonic benefits of distinctiveness would not be affected by the pharmacological manipulations. Neither of the drug groups showed a different pattern of results to the placebo group.

One possible reason why the effect of arousal enhanced consolidation may not have been observable is the use of the free recall method. When memory for the same set of stimuli is tested more than once by free recall, a subsection of the stimuli (the words recalled at the immediate test) receive more rehearsal than the other stimuli. It was noticeable that words produced in the delayed test tended to have been produced in the immediate test. This effect of increased rehearsal may possibly have masked any effect of arousal enhanced consolidation.

Another explanation lies in the small size of the enhanced consolidation effect compared to the massive effects the taboo words would have had on other processes known to affect memory. In LaBar & Phelps (1998) approximately 0.5 more taboo words were recalled at delayed than at immediate testing. In comparison, at immediate testing (before consolidation), approximately 6.5 more taboo than neutral words were recalled. Taboo words would have been attention grabbing, and distinctive from participants schemata of 'words they expect to see in a psychology experiment'. Both these features would have increased the number of words recalled at both testings, so much so that an additional word recalled due to enhanced consolidation would not make a significant difference.

Another possible reason could be that there may not have been enough time between immediate and delayed testings to show the effects of arousal on consolidation. In a test of the effects of amphetamine on consolidation Soetens et al. (1995) found a delay of one hour barely distinguished their groups. Differences became clearer at least 24hours later. Therefore perhaps a longer interval should have been left between immediate and delayed test. However this could present a problem. LaBar & Phelps (1998) argue that the possibility of participants rehearsing the words between testings was minimal, because the intervening time was filled with other tasks (as was the case in the present

experiment). It would not be possible to ask participants to concentrate fully on other things for much more than an hour. It is possible that despite performing the other tasks, participants may still have thought more about the taboo than the neutral words during this time.

The current experiment differs from the classic paradigm of (Kleinsmith & Kaplan, 1964; Kleinsmith & Kaplan, 1963; Bradley & Baddeley, 1990). These studies asked participants to remember paired associates of the emotional stimuli, whereas the actual emotional words themselves were the to–be-remembered items in the present and LaBar & Phelps' (1998) study.

It is possible that the use of paired associates may be more likely to produce the emotion x delay interaction. The reasoning behind this is that emotional arousal may act in two opposing ways on the memory of paired associates. As peripheral details, paired associates of emotional words are less likely to enter working memory (and therefore be passed to longer term memory). Therefore at immediate test memory may appear impaired for these stimuli (as the memory for the associated ink colour in the picture colour test was impaired in the present experiment). However once in long term memory paired associates of emotional items are more likely to receive enhanced consolidation. Therefore at delayed testing memory is facilitated by these items. When using emotional items themselves the emotion acts in the same way, facilitating memory, at both the immediate and delayed tests. In other words, the emotional items are more likely to enter working memory and more likely to receive enhanced consolidation.

However like the present study, LaBar & Phelps (1998) used the free recall method with a 1hour delay between testings, and the taboo words themselves as the to-be-remembered stimuli and they found evidence for the predicted interaction between the amount of emotional and neutral material retained at immediate and delayed test. The major difference between the current experiment and that study was the neutral words. Although LaBar's set of neutral words was unavailable for comparison, they do mention in their discussion that their emotional words formed more of a cohesive semantic category than their neutral words. In the current experiment, the non-arousing words were chosen to be as cohesive a semantic category as the taboo words.

Therefore because the non-arousing words fit into a category, perhaps they would be less likely to be forgotten than LaBar & Phelps' (1998) words. Another possible difference between the present experiments and LaBar & Phelps (1998) was the nationality of the participants. Words gain ability to arouse through cultural learning. It could be that some taboo words are more taboo in New York than in London. Perhaps the cultural difference would not matter as much if the stimuli were pictures. Another difference between the participants in the two experiments was that the present experiment used students and LaBar & Phelps (1998) tested patients and age matched controls. As with the picture colour task there was no suggestion that either of the active drugs affected subjective arousal at encoding. However no conclusions can be made about the effects of the drugs on emotional cognition as the results show the same pattern of performance on taboo and neutral words in all three drug groups.

4.4.3.Control Battery

The control battery showed a very clear pattern of increases in arousal due to methylphenidate and decreases in arousal due to diazepam relative to placebo. This was clear across the range of tasks and therefore supports the range of tasks selected and the drug doses used.

Although pulse rate did not change pre-post drug in the methylphenidate group, they showed increased arousal relative to placebo as pulse rate decreased in the placebo group. Presumably the placebo group relaxed, as the experiment progressed. The diazepam group also showed decreases in pulse rate pre-post drug, but they did not show as much of a decrease as placebo. For systolic blood pressure, there was no change in the placebo group, however the active drug groups showed clear changes in the predicted direction. Diastolic blood pressure did not show statistical evidence for drug effects, but the means changed in the expected direction. Diastolic blood pressure would not usually be expected to change as much as systolic. The number of taps made in 60 seconds decreased after diazepam, remained constant after placebo and increased slightly after methylphenidate. Therefore both the physiological and motor indices of arousal showed the predicted effects.

The affect grid measure of arousal showed the placebo group decreasing in arousal throughout the experiment, this is similar to the observation made about pulse rate, reinforcing the idea that arousal really did reduce in this group. The affect grid measure of arousal also reduced after the drug and at the end of the session in the diazepam group, although this was not very different from placebo. The methylphenidate group showed clear increases in arousal pre-post drug, and at the end of the session arousal was still higher than it had been predrug.

On the Bond & Lader (1974) mood rating scale there are two subscales that may be related to arousal. These are alert-drowsy and calm-anxious. The diazepam group showed a clear move towards drowsiness as the experiment progressed. Although the placebo group did not change much they also showed a slight move in this direction, supporting that this scale is measuring something similar to the other scales. The methylphenidate group did not change on this scale. In the discussion of experiment 1 (chapter2 section 2.4.1) it was considered that this might be because the mood rating scale was designed to measure decreases in arousal rather than increases. The calmness subscale also showed the predicted pattern of change in arousal. The diazepam group reported feeling calmer after the drug, whereas the placebo group did not change, and the methylphenidate group became slightly more anxious as the experiment progressed. It is interesting that the methylphenidate was felt by participants in the present experiment as anxiety, whereas participants in the previous experiment did not interpret it this way.

The serial sevens task was selected for the current experiment because it is a demanding task and was therefore thought to be likely to be sensitive to improvements due to methylphenidate. As predicted the methylphenidate group did perform better post drug than they did predrug. However they made less correct subtractions predrug than either of the other two drug groups. The placebo group performed similarly pre and post drug and as predicted the diazepam group showed poorer performance post drug than they did predrug. The prose recall task also showed memory detriments after diazepam, but no improvements relative to placebo after methylphenidate.

Overall the control battery showed the predicted increases in arousal due to methylphenidate and decreases due to diazepam very clearly. As the tasks

were administered in the middle of the main post drug test battery, this supports the time frame chosen for the experiments. The previous experiments did not show the range of methylphenidate increases and diazepam decreases quite so comprehensively across the range of control tasks. Possibly this may have been due to individual differences in drug absorption times.

In conclusion the present experiment showed that the active drugs had the predicted effects of arousal. There was no evidence that either drug had the predicted effect on memory consolidation from the taboo words task. This was because no emotion effect on consolidation was observed. In the picture colour test the evidence that was arguably most valid showed diazepam increased relative levels of source memory associated with positive pictures and methylphenidate reduced the effect of emotion on memory.

CHAPTER 5: DRUGS, SWEAT, AND FEARS. The effects of diazepam and methylphenidate on fear conditioning, and explicit memory effects over time (EXPERIMENT 4)

5.1.INTRODUCTION

Experiment 3 found further evidence that methylphenidate reduces the effect of emotion on memory for the source of emotional pictures. There was also some suggestion that diazepam disrupted memory for the associated source of emotional pictures. Although there was evidence that free recall is impaired by diazepam, the pattern of free recall across emotion categories was similar to the placebo group. There was some indication that free recall of positive (intermediately arousing) emotional pictures was enhanced by methylphenidate. The dual interval taboo words task did not provide any evidence that the effects of these drugs were due to alterations in arousal mediated consolidation, the mechanism hypothesised by McGaugh.

Therefore this fourth experiment has two main aims.

- The first is to test whether or not the emotional memory modulating effects of diazepam or methylphenidate occur during consolidation.
- The second aim is to investigate whether aversive conditioning, which has been shown to have similar neuroanatomical substrates as episodic memory for emotionally arousing material, also has similar neurochemical substrates.

A 40mg dose of methylphenidate and a lactose placebo will be employed, as in the previous experiments. A 10mg diazepam dose will be used. This is lower than the 15mg dose of the previous experiments, and has been chosen i) because of concerns that the higher dose may disrupt skin conductance (see below) and ii) to reduce the probability of floor effects in the memory task.

5.1.1.Dual Interval Picture Task

The enhancing effect of emotional arousal on memory has often been found to increase over time (e.g. Kleinsmith & Kaplan, 1964; Kleinsmith & Kaplan, 1963; Bradley and Baddeley, 1990; LaBar & Phelps 1998). When tested *immediately*

after encoding, emotionally arousing stimuli have been found to be remembered only slightly better (LaBar & Phelps 1998) or sometimes worse (Kleinsmith & Kaplan 1964) than neutral stimuli. Over a period of time memory is modulated by arousal, and the difference between the amount of emotional and neutral material retained becomes larger. This is an important feature of emotional memory, as it distinguishes arousal mediated memory consolidation (which can be expected to be altered by pharmacological manipulations of arousal) from other non-neurochemical advantages (e.g. distinctiveness, depth of processing) that emotionally arousing material may also receive.

Isolating the time window where the drug groups differ from placebo in their relative retention of emotional and neutral material will also allow conclusions to be drawn about the mechanism by which they impair or facilitate emotional memory. This will be done with a dual interval task where memory is tested both immediately and after a one week delay. If either drug group shows the same pattern of performance as placebo at immediate test, but then shows impaired memory for emotional material at the delayed test, emotional memory must be being disrupted at the consolidation stage. If however, a drug group already differs from placebo at immediate test, the action of this drug could be on encoding processes.

A dual interval task (the taboo words task) was used in the previous experiment (chapter 4). No evidence was found for the predicted interaction between the amount of emotional and neutral material retained at immediate and delayed testing. Therefore it was not possible to tell whether either drug would have altered this effect of emotion. The present task is designed to increase the strength of the predicted emotion x time interaction effect by addressing the points raised in the discussion of chapter 4.

- Retention of the stimuli will be tested using a recognition task. Half the studied stimuli will be presented at an immediate recognition test and half will be presented at a delayed test. This prevents the immediate test acting as selective rehearsal of the subsection of pictures retrieved.
- The delay between testings will be seven days, a much longer delay than the 1 hour used in experiment 3. Subtle differences in consolidation are more likely to show after this longer time period. In an investigation of the effect of amphetamine on human memory consolidation in a word list

learning task, Soetens et al. (1995) found a delay of 1 hour barely distinguished their groups. Differences were most apparent after 24hrs. Tests of the effects of emotion on memory typically find effects using a one week delay (e.g. Cahill et al. 1994).

- The picture stimuli from experiments 2 and 3, originally taken from the IAPS (Lang, Bradley, & Cuthbert 1999) will be used, instead of taboo words. Taboo words have the disadvantage that they form quite a clear category, and are also distinctive as they are an atypical example of stimuli that participants expect to see in a psychology experiment. Therefore they can be expected to have mnemonic advantages unrelated to emotional arousal that might mask their effects on consolidation. As discussed in the introduction of Experiment 2, pictures are expected to be more likely than words to activate the emotional memory system. The information from pictures may reach the system by a more direct 'quick and dirty' route than a complex verbal code that needs to be decoded (LeDoux 1999).
- As well as testing memory for the stimuli themselves, memory for the colour of the stimuli will be tested. Testing of memory for the ink colour of the pictures is analogous to Kleinsmith and Kaplan's testing of memory for the *associates* of arousing words. This is expected to produce a clearer interaction of emotional and neutral stimuli over the times of testing, than memory for the actual stimuli, which is increased even at immediate recall. As the ink colour associated with emotional material is a peripheral detail, memory for it will appear impaired at immediate recall. However the ink colour associated with neutral material will receive less consolidation than the colour associated with emotional / arousing pictures, and is therefore more likely to be forgotten before the delayed test seven days later. Thus memory for ink colour should be impaired by emotion at immediate test and facilitated by emotion at delayed test.
- Testing ink colour has the additional advantage that it is not likely to be subject to the ceiling effects that were observed in the recognition memory part of the test in Experiment 2. Further as colour was encoded more elaborately in this experiment (following Wilding and Rugg 1996) floor effects on source memory should be minimised.

Therefore it is predicted for the placebo group that although recognition memory will be superior for emotional pictures at immediate testing, this difference will increase by day 7 as these pictures will receive increased consolidation. In both drug groups emotional pictures may have a memory advantage at immediate test, due to non-specific mnemonic advantages that tend to covary with emotion. However in the diazepam group the advantage will not increase over time, as the emotional pictures will not receive extra consolidation. The advantage of emotional material will not increase over time in the methylphenidate group either, as the neutral material will also receive extra consolidation in this drug group. As remembering the colour of pictures may be the picture equivalent of the paired associate learning investigated by (Kleinsmith & Kaplan 1963) it is expected that this will show the same pattern of impairments on the immediate test and facilitation on the delayed test. As with recognition memory, both drugs are expected to disrupt this pattern.

5.1.2.Fear conditioning

5.1.2.1.The amygdala and fear conditioning

Maren (2001) describes fear conditioning as *"squarely seated at the interface of memory and emotion."* Classical (Pavlovian) conditioning of a fear response to a CS+ (conditioned stimulus - an innocuous stimulus previously paired with an aversive unconditioned stimulus (US)) is often presumed to be a very basic, non-declarative, amygdala based form of memory. Le Doux (1998) (2000) and Fendt & Fanselow (1999) describe in great detail how amygdala lesions in the rat brain prevent the expression of conditioned fear responses. Research into the neuroanatomy of human emotional memory, has tended to show that the patients with amygdala lesions who show disrupted episodic memory for arousing stimuli are also impaired at fear conditioning.

Bechara et al. (1995) demonstrated that an Urbach-Wiethe patient, with bilateral amygdala damage, did not acquire a conditioned skin conductance response (SCR) to either auditory or verbal stimuli paired with a 100db boat horn. This was despite being able to consciously identify the stimulus which coincided with the aversive noise. A second patient with intact amygdalae but bilateral hippocampal damage was unable to form this declarative knowledge of the

relationship, but gained the conditioned response (increased skin conductance) to the stimuli paired with the boat horn. A third patient with damage to both amygdala and hippocampus was unable to acquire either explicit knowledge of the relationship, or the conditioned response.

LaBar et al (1995) demonstrated fear conditioning impairments in patients who had received unilateral amygdala lesions in treatment for epilepsy. Phelps et al (1998) reported another patient with amygdala damage who was impaired in fear conditioning. This patient was also impaired on an episodic memory task where performance is usually enhanced by emotional arousal. Further Hamann et al (2002) found impaired conditioning of SCRs to a visual stimulus paired with loud noise in patients with Alzheimer's disease. This was attributed to early onset of atrophy in the amygdala. It is also difficult to condition the eyeblink response in elderly Alzheimer's patients but not non-demented elderly patients (Woodruff et al, 1990, 96).

In a review of the neuroimaging data of aversive classical conditioning, Buchel and Dolan (2000) present evidence for amygdala activation during early stages of acquisition of US /CS+ pairing which decreases over time. Hippocampal activation was only apparent in studies where the CS+ and US were separated by time. Taken together these studies present good evidence that fear conditioning requires neuroanatomical structures implicated in arousal modulated episodic memory, although the debate over whether the amygdala is the locus of storage, or a modulator of other systems remains unresolved (e.g. Cahill et al 1999, Fanselow and LeDoux 1999, Vazdarjanova 2000, Maren 2000).

5.1.2.2.Drugs and fear conditioning

The neurochemistry of fear conditioning is less well defined. Explicit emotional memories are thought to be modulated during consolidation by raised catecholamine levels in the amygdala (e.g McGaugh, 2000). Whether catecholamines have a similar role in fear conditioning was investigated in rats by (Lee et al. 2001). They found no effect of either ephedrine (peripheral levels up), amphetamine (CNS up), sotalol (peripheral down),or propranolol (CNS down) on fear conditioning when injected systemically *after* acquisition. An early study found some evidence that stimulant drugs similar to methylphenidate may

increase fear conditioning in humans (Lobb 1968) and Alpern et al, 1943 investigated the effects in dogs. However there is no more recent work, as investigations of the effects of methylphenidate in classical conditioning have tended to use the drug as the unconditioned stimulus (e.g. Hsu, Schroeder, & Packard, 2002), or have concentrated on positive reinforcements in children with ADHD e.g. (Christensen & Sprague 1973)

There is a larger body of work on the effects of benzodiazepines on fear conditioning in animals. In general benzodiazepines have been found to impair the acquisition of fear responses to aversive conditioned stimuli, (e.g. Harris & Westbrook, 2001; Guscott, Cook, & Bristow, 2000; Sanger & Joly, 1985; Westbrook et al, 1991), although there are exceptions (e.g. Davis, 1979).

Hellewell et al (1999) tested the effect of diazepam on conditioning of a SCR to an aural US in healthy human volunteers, using the procedure described by Guimaraes et al (1991). They used a very small (2mg) dose of diazepam, and found that this reduced conditioning in women but not men. In fact none of their active drug treatments (fluvoxamine, diazepam, buspirone) had a significant effect on conditioning in men. Possible reasons for this might be the low dose, (women weigh less) and the men not showing a very significant ($p=0.098$) main effect of conditioning. This could be because they only paired the CS+ with the US once. However this single trial conditioning procedure has been used many times by Guimaraes, and men do usually show evidence of conditioning, but generally less than women. Hellewell et al's (1999) results suggest that a larger dose of DZ, and a conditioning procedure with more US / CS+ pairs is more likely to find evidence for DZ disruption of SCR conditioning.

In a test of state dependant learning Jensen et al (1989) gave 15mg diazepam to one group of volunteers and placebo to a second group, before they learned a conditioned SCR to a 1000hz tone on day 1. The groups were given alternate drug / placebo on days 4, 7, &10. The group who received diazepam on day1 and placebo on day 4 did not make responses to the CS+ that were discriminably larger than their responses to the CS- on day 4. Additionally, inspection of the amplitude and number of their skin conductance responses implies that this group did not show evidence for conditioning on day 4. However this is not conclusive evidence of impairment of fear conditioning by diazepam, as the group who learned on placebo on day 1 were given diazepam

on day 4. They did not show evidence for conditioning either. However, as they were medicated with diazepam during the day 4 test, they do not act as a control in the sense of showing if a healthy undrugged participant would have shown the conditioned response on day 4.

Molander (1982) found that (10mg) diazepam reduced the 'anticipatory response' during a conditioning experiment. Their experiment had two phases: habituation and partial reinforcement. During the partial reinforcement phase diazepam reduced both the level of skin conductance immediately before responses, and the number of responses. This is to be expected, as there is some evidence (see below) that diazepam may reduce skin conductance through non-specific mechanisms. Molander did not have a control CS- condition (innocuous stimulus similar to the CS+ but that has never been paired with the US) where the response to a stimulus that has never been paired with the aversive stimulus is compared with the response to the CS+ for that same drug group. They did report data for the skin conductance level and number of responses, for the habituation phase, before conditioning had occurred. In the diazepam group, both of these measures seem to be higher after conditioning, although these particular comparisons were not made by Molander (1982). However this study suggests that diazepam will impair skin conductance conditioning.

5.1.2.3. Possible effects of the drugs on unconditioned responses?

An important point illustrated by the previous paragraph is that if a reduction in SCR conditioning is found in participants given diazepam, there may be a question of whether, as hypothesised, they have impaired ability to form the necessary association between the CS+ and US or whether they just have less skin conductance responses to the CS+ because of a non-specific effect of diazepam.

In the amygdala and fear conditioning literature discussed above there is some evidence that diazepam may disrupt the unconditioned SCR. Hellewell et al (1999) found a trend in their females volunteers towards diazepam reducing skin conductance response to the US. However Jensen et al (1989) found no

deficits in SCR (if anything the mean amplitude was slightly higher than in the placebo group) to a 98db US in a group of subjects given 15mg diazepam.
The following studies did *not* involve forming an association between a fear response and another stimulus. They will be discussed briefly because they provide good accounts of how benzodiazepines and or methylphenidate have been observed to affect skin conductance in human subjects. Geddes, Gray, & Asbury (1994) tested SCRs to innocuous tone stimuli in preoperative patients given 0.06mg/kg midazolam. They did show SCR to these tones, although they showed fewer SCRs than placebo or propofol treated patients before they habituated. A novel stimulus (a different innocuous tone) elicited a dishabituation response in 4/15 patients given diazepam, a smaller proportion than the 13/15 given propfol or 11/15 who had placebo. Geddes et al. (1993) did a similar experiment with diazepam (10mg oral), morphine (10mg i-m), and a no-drug control. They found that patients who received 10mg of diazepam showed less non-specific SCRs than the morphine or placebo groups both during the main experiment and after warning of the catheter insertion. Responses to the innocuous auditory stimuli decreased progressively throughout the experiment only in the diazepam group. However there were no group differences in habituation or dishabituation, and all groups showed increases in SCL when they were told the catheter would soon be inserted. In the discussion they mention that barbiturates are also known to depress skin conductance and suggest that skin conductance may be more sensitive to drugs facilitating GABA transmission than drugs producing anxiolysis or sedation by other means.
However, Iacono, Boisvenu, & Fleming (1984) found that neither a 10mg dose of diazepam nor a 20mg dose of methylphenidate disrupted skin conductance responses enough to allow their volunteers to escape detection on a 'lie detector' test where their skin conductance response to answering questions untruthfully was measured. Therefore it is likely that in the present experiment enough unconditioned responses will be produced to make it feasible to carry out a test of fear conditioning where some participants have been given 10mg diazepam. However diazepam may reduce the number and or size of responses. A similar question can be asked about the effects of methylphenidate. Methylphenidate is more likely to increase skin conductance

through non-specific mechanisms. For example, Iacono et al (1992) reported more spontaneous fluctuations after methylphenidate. Therefore it is important to distinguish between increased response to the CS+ and increased responses generally.

This makes the use of a CS- vital. It is not sufficient to compare the drug groups' responses to the CS+ with the placebo group's responses to the CS+. The important comparison is how much larger responses to the CS+ are compared to responses to the CS-. The difference between these responses is what should be compared across groups.

Finally, non-specific effects on response to the US should be taken into consideration. Hamann, Monarch, & Goldstein (2002) use evidence from Skinner's (1938) work to argue that size of response to an unconditioned stimulus is associated with acquisition of a conditioned response. Therefore the data will be analysed using response to the unconditioned stimulus as a covariate.

In summary, the literature suggests that expression of the unconditioned response is not impaired by diazepam, but the forming of an association – an 'emotional memory' - between the CS+ and the UR might be impaired. It also suggests that baseline skin conductance levels will be reduced by diazepam. Therefore it is predicted that there will be no difference between responses to the CS+ and CS- in the diazepam group. As less work has looked at the effect of methylphenidate on skin conductance conditioning, the hypotheses for methylphenidate are less defined. Given the evidence of Iacono et al (1984) it can be predicted that methylphenidate will not reduce the unconditioned response. As Benzedrine has been found to increase levels of conditioning (Lobb 1968) methylphenidate might be predicted to do the same. This would be consistent with the theory that methylphenidate increases the effect of arousal on memory. However the results of the Cahill & McGaugh (1995) story task in Experiment 1, and the picture colour memory task in Experiment 3 suggested that methylphenidate reduces emotional memory. If this is the case, then it would be expected to reduce fear conditioning.

5.1.3.Control Battery

The control battery of tests used in the previous experiments will be repeated. Increases in arousal due to methylphenidate and decreases due to diazepam are predicted, and these will be measured on various indices as before.

5.2. METHOD

5.2.1.Participants

Forty-eight healthy volunteers participated in the study. They ranged in age from 18-35 years (mean 23.5 years). Exclusion criteria were the same as the previous experiments. In practice this only excluded one participant (prescribed the antidepressant paroxetine), In addition volunteers were excluded if they showed no skin conductance responses while preparing for the aversive conditioning task.

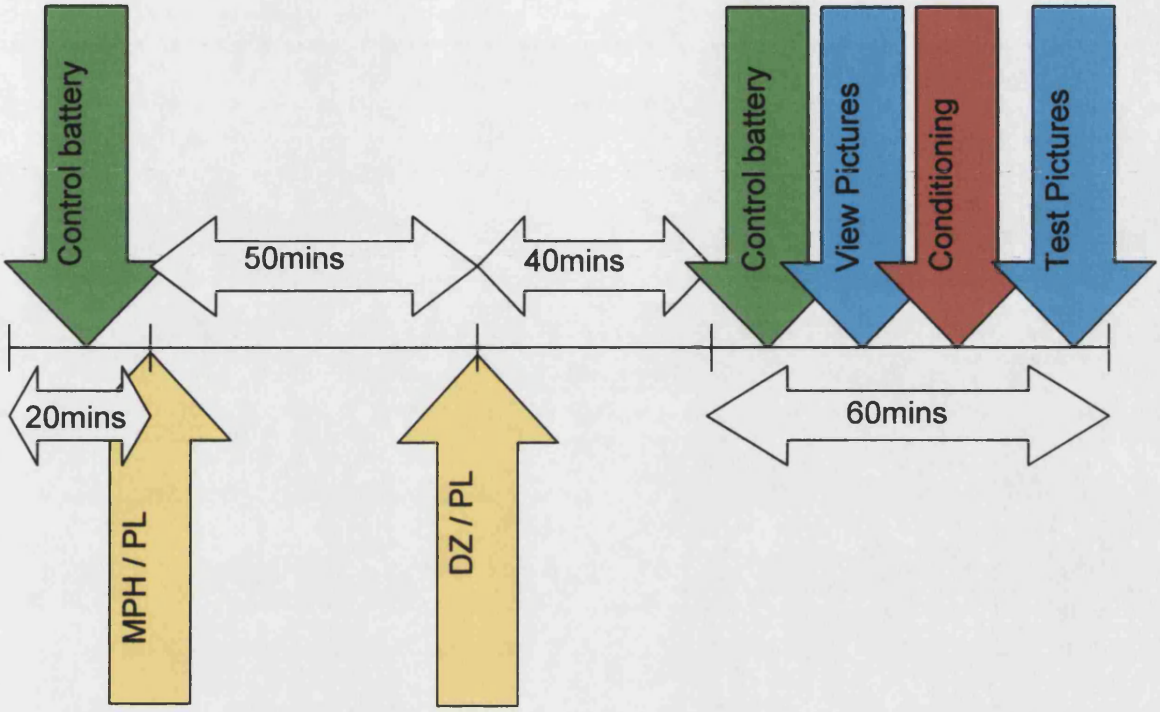
5.2.2.Design

As in the previous experiments, a double blind placebo controlled design was used. Participants were randomly allocated to one of three drug groups, the only constraint was each drug group contained the same number of each gender, as gender may influence emotional processing (e.g. Cahill et al, 2001). The four equivalent versions of the picture test (1A, 1B, 2A, 2B) and colour of the CS+ and CS- were equally dispersed across drug groups and genders. Where two versions of a task were used (prose, serial sevens) these were counterbalanced across drug groups.

5.2.3.Procedure

The UCL/UCLH committee on the ethics of human research approved the study and all participants gave written informed consent. On arrival participants were screened by asking them to fill in a medical questionnaire and then discussing any positive responses with the experimenter. Their height and weight were recorded and their blood pressure taken. They gave written informed consent and then started the pre-drug test battery.

Figure 50: Representation of day 1 test timings



5.2.3.1.Predrug Test Battery

The pre drug test battery consisted of the control measures used in the previous experiments. These were (in order of administration)

- Prose recall
- Pulse and blood pressure
- Affect grid
- Tapper
- Mood Rating scale
- Serial Sevens

After the predrug test battery the drugs were administered following a double dummy procedure. They received either methylphenidate 40mg or placebo immediately after the serial sevens task. Fifty minutes later they were given either diazepam 10mg or placebo and forty minutes after that (90 minutes after methylphenidate) the postdrug test battery was commenced. All drugs were administered orally as tablets swallowed with water.

5.2.3.2.Postdrug test Battery

Tasks were administered in the order given in Appendix 6. After the testing participants were given refreshments and allowed to relax until they were fit to leave.

5.2.3.2.1.Dual Interval Picture Colour Task

The same picture stimuli were used for the picture test as had been used in Experiment 2. At encoding each participant saw a set of 64 pictures (plus 3 primacy and recency controls): 32 pictures were neutral, 16 were negative and 16 were positive. These were presented in a pseudo random order. To reduce the probability of floor effects in the source memory part of the task, the colour manipulation was correlated with encoding task following Wilding and Rugg (1996). The encoding tasks used were making a pleasant/ unpleasant judgement or an active/ passive judgement.

If the pictures appeared in purple ink participants were asked to make a pleasant / unpleasant judgement. They were told *"If your instant reaction was to like the picture you would call it pleasant, if your instant reaction was to dislike the picture call it unpleasant."*
If the pictures appeared in green ink participants were asked to make an active / passive judgement. The instruction was *"You can interpret active / passive in several ways. An active picture might show movement, or something that is dominant or forceful. A passive picture might show no movement, or something submissive, or weak. Again I would like you to tell me about your first reaction to the picture. There are no right or wrong answers."*
The mapping between colour and task was constant. Counterbalanced versions of the task meant that 50% of the volunteers saw each picture in each colour. After a period of about 30mins filled with the conditioning experiment, the participants did the first part of the recognition test. They saw a set of 64 pictures (32 neutral, 16 negative, 16 positive). Half of each category were the pictures that had been previously studied, half were pictures from the unstudied version. The pictures were presented in a fixed pseudo random order, and participants were asked to tell the experimenter whether they had seen the picture before and if so the ink colour. The recognition test on day 7 followed

the same format, showing the previously untested half of the studied and unstudied sets of pictures. The two recognition sets were matched as well as possible on the measures given by Lang et al (1999) (Table 19).

Table 19: Mean (SD) Valence, arousal and dominance ratings of the pictures in the counterbalanced halves (X, Y) of the recognition test..

	Recognition X	Recognition Y
	Mean(SD)	Mean(SD)
Valence	4.94(2.11)	4.93(2.03)
Arousal	4.94(2.11)	4.93(2.03)
Dominance	5.27(1.22)	5.36(1.29)

5.2.3.2.2.Skin Conductance Conditioning

5.2.3.2.2.1.Materials

Skin conductance responses were recorded via silver/ silver chloride (Ag/AgCl) electrodes (EL5 999 collars for SC: Psylab) attached to the middle phalanges of the index and middle finger of the non-dominant hand. KY jelly was used as an electrolytic conductor. Physiological responses were transformed using a SC5 24 bit digital skin conductance amplifier (Contact Precision instruments, Psylab, London) and recorded by a computer running PSYLAB software

The visual stimuli were displayed using PSYLAB software on a 14" computer monitor - separate from the monitor used by the experimenter controlling the equipment, which faced away from the volunteer. The auditory US was presented on stereo headphones (Technics RP-FT30). The CS+ and CS- in this experiment were a blue circle and a green circle, counterbalanced across conditions. The US was a 100db white noise.

The test consisted of four phases which were

(1) **Habituation**: [4CS+], [4CS-] in this phase four of each type of coloured circle were displayed without reinforcement. This should familiarise the volunteers with the circles so that the SCRs to the circles alone approach zero, and any reaction to the circles in the following phases can be attributed to the conditioning procedure.

(2) **Acquisition (continuous reinforcement)**: [4CS-], [4CS+ immediately followed by US] The acquisition period started on a continuous

reinforcement schedule as Hamann, Monarch, & Goldstein (2002) report that this produces conditioning more quickly than starting with variable reinforcement.

(3) **Acquisition (partial reinforcement):** [16 CS-], [8CS+ (alone)], [8CS+ immediately followed by US] The partial reinforcement phase contains the critical trials for assessing conditioning. SCR Amplitude for these unpaired CS+ trials compared to the CS- trials in this phase, is the main measure of conditioning.

(4) **Extinction:** [16CS+alone], [16 CS-] during this phase the CS+ is never followed by the US. Therefore the response to the CS+ should extinguish, becoming no bigger than the response to the CS-. The trials and interstimulus intervals were presented in a fixed pseudo-random order.

5.2.3.2.2.2.Procedure

Participants were told that their skin conductance would be measured, and the electrodes were attached to their hands, which had been washed with soap immediately prior to the post drug test battery. (They were already sat in a comfortable chair facing the computer screen). They were then given the following instruction. *"Pay close attention to the coloured circles that appear on the screen, and the sounds that you hear over the headphones, and be attentive to any relationship you might detect between the colour and sound events."*

They were asked if they understood and when they confirmed this, they were told that it was very important that they sit still throughout this part of the experiment as the electrodes were measuring their reaction to coloured circles, which was a very small reaction that would be masked by any larger reactions caused by their moving or talking during the test. They were asked to sit comfortably, so they would not have to move during the test. When the participant felt they were ready the test was started.

The first trials 1-8 were habituation, trials 9-16 acquisition (continuous reinforcement), trials 17-48 acquisition (partial reinforcement), and the final 49-80 trials extinction.

A response was defined as the largest increase in skin conductance occurring within a window of 0.5 and 4.5 seconds after the onset of the stimulus. If the

response was outside this time window it received a value of 0, it also received a value of 0 if no response was detected.
After the final trial the electrodes were removed, and participants were given a paper towel to clean the gel from their fingers. They were then asked *"Did you notice any relationship between the colour and the sound".*

5.2.3.3.Day 7 Test Battery

The unseen half of the picture recognition task was performed, followed by the spot the word test, and the digit span test from the WAIS. Following this, participants were debriefed and paid £25 for their participation.

5.2.4.Statistics

5.2.4.1.Control Battery

The tests that were carried out both pre and post drug were analysed using a 2 x 3 (time x drug) split plot ANOVA. Where a main effect of drug was found that needed further clarification Dunnetts test was used to compare each of the active drug groups to the placebo group. The affect grid differed from the other tasks in the control battery as the 'time' factor had three levels. The ANOVA for the prose recall task had an additional factor 'delay' (immediate vs delayed recall) making a 2 x 2 x 3 split plot ANOVA.

5.2.4.2.Dual interval Picture task

A 3 x 3 x 2 (drug x emotion x time) split plot ANOVA was used to analyse the number of hits and false alarms, and the derived statistics on the picture test. The signal detection statistics d' and C were calculated. To avoid undefined values where hits = 1 or false alarms = 0 the correction of adding 0.5 to the numerator and 1 to the denominator was used. Source memory was defined as (correct source detections - wrong source detections)

5.2.4.3.Aversive conditioning

In order to normalise the distributions of responses a log transformation was performed on all the individual responses, as suggested by Venables & Christie (1980). Graphs were drawn to illustrate the mean response magnitude in each drug group to each trial. These means included trials where participants did not

respond, and therefore represent response magnitude in the sense defined by Venables & Christie (1980).

Amplitude was calculated for each stimulus in each phase. The amplitude was defined as the mean size of response, on all occasions on which a response was given, (Venables and Christie, 1980; Proskasy and Kumpfer, 1973). This method was selected to avoid confounding size of response with frequency of response. Trials where participants did not respond were not included in the calculation of amplitude. If for example a participant only responded on two of the four CS+ trials in the habituation phase, this participant's "habituation CS+" amplitude score would be a mean of the two responses that s/he did give. The ANCOVAs and ANOVAs were calculated from these amplitude statistics.

A (3 x 2 x 3) ANCOVA was used to compare response amplitude in the three phases (habituation, partial reinforcement, and extinction), 2 stimuli (CS+ and CS-), and three drug groups (placebo, methylphenidate, diazepam). The covariate was the response amplitude to the CS+US combination in the partial reinforcement phase.

Following this, three (2x3) ANCOVAs were carried out to compare stimulus (2) and drug (3) in each of the three phases. To confirm that conditioning occurred, the critical comparison is that responses to the CS+ should be bigger than those to the CS- in the *partial* reinforcement phase. Therefore three planned comparisons were carried out to investigate this in each drug group individually.

5.3.RESULTS

5.3.1 Fear Conditioning

The results of this part of the experiment are first presented in a descriptive fashion. The drug group means of response magnitude for each individual trial are graphed out. This allows the reader to see how the following amplitude data are composed. The inferential statistics are carried out with mean amplitude data for each type of trial in each phase. This reduces the complications that would be involved in calculating ANOVAs on the noisy individual trials, and avoids confounding size of response with frequency of response. Finally inferential statistics on response frequency are presented briefly in order to confirm the conclusions derived from the previous analyses are not an artefact

of the method of calculating amplitude. The report of the fear conditioning results is presented in the following sections:

5.3.1.1. Mean group magnitude of responses to individual trials
5.3.1.2. Amplitude
5.3.1.2.1 Habituation phase
5.3.1.2.2 Partial reinforcement phase
5.3.1.2.3 Extinction phase
5.3.1.3. Amplitude of response to the CS+US
5.3.1.4. Frequency
5.3.1.5. Explicit identification of the CS+

5.3.1.1. Mean group magnitude of responses to individual trials

A constant value of 0.01 was added to each participants response to each individual trial, and the $\log_{10}$ was taken. Thus the value for no response became (-2 $\log_{10}$microsiemens). In the calculation of magnitude these non-responses were included. As the data for the 80th trial (CS-) contained noise, this trial was ignored. The 79th trial (CS+) was also ignored so that there would be the same number of each type of CS. The mean magnitude of response in each drug group to individual stimuli is shown in Figure 51, Figure 52, Figure 53 and Figure 54.

Figure 51: Mean response magnitude to stimuli in the habituation phase

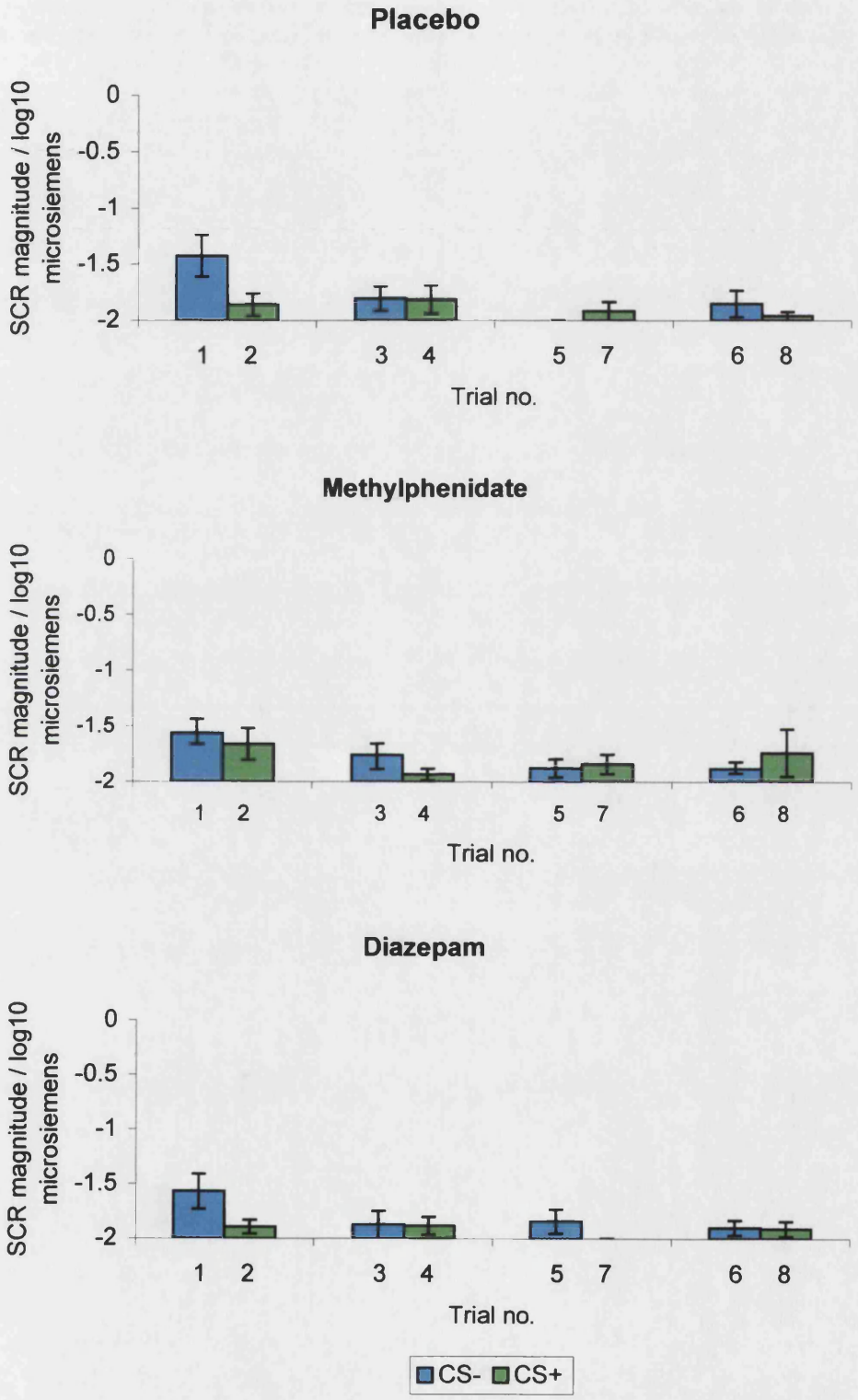


Figure 52: Mean response magnitude to stimuli in the continuous reinforcement phase

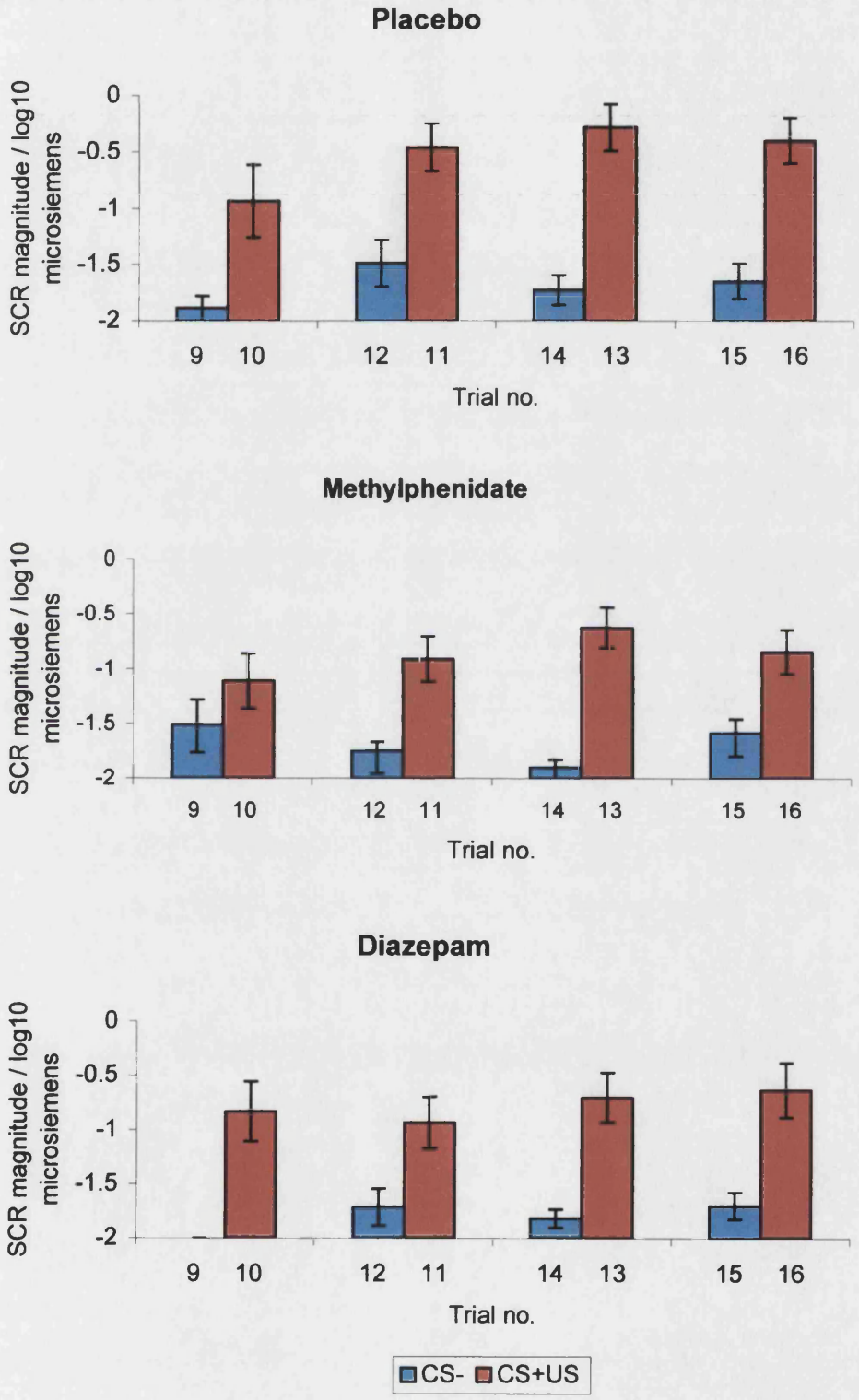
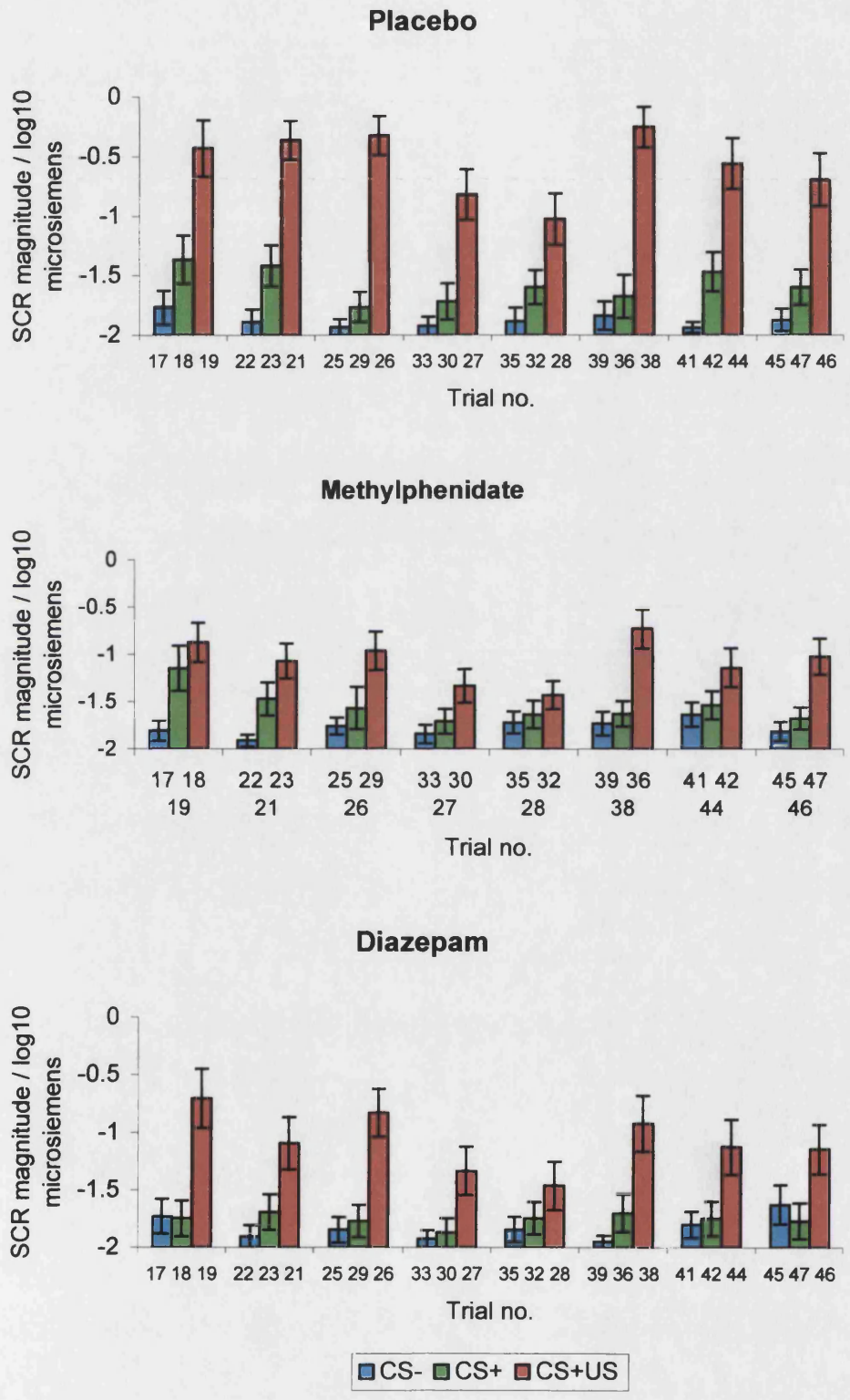


Figure 53: Mean response magnitude to stimuli in the partial reinforcement stage



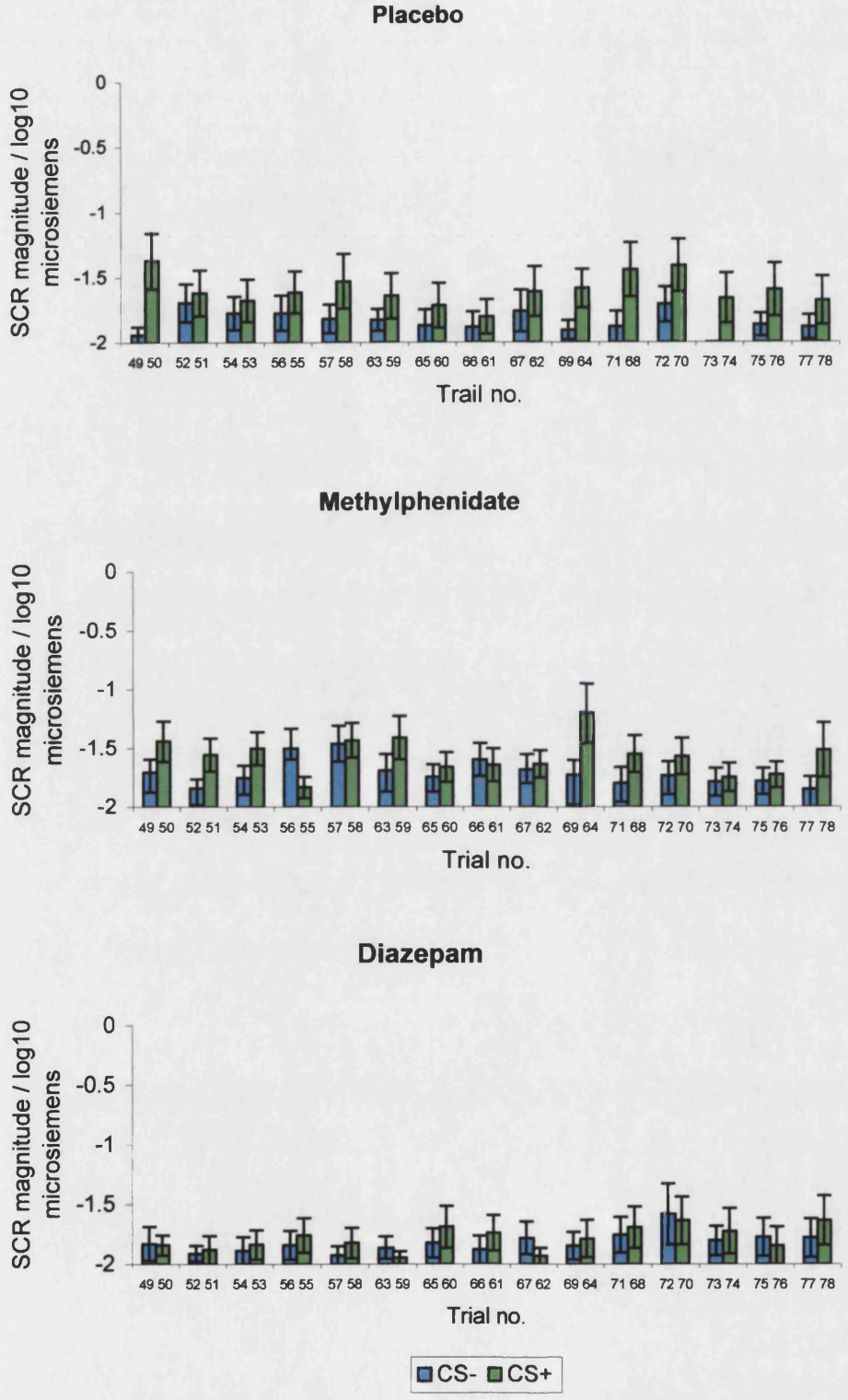
The first three graphs (one for each drug group) which make up Figure 51 show the mean skin conductance response magnitude to the CS- and CS+ in the first phase of the experiment (habituation). Most of the responses appear to be very close to -2 (the value for no response), the main exception is apparently a slightly larger response by all drug groups to the first CS-, which was the very first trial.

The next set of graphs (Figure 52) show the magnitude of responses in the second (continuous reinforcement) phase. This is the first part of the acquisition phase, and every CS+ was immediately followed by the US, (i.e. the CS+ never appeared alone in this phase). As would be expected, the responses to the CS+US appear much larger than the responses to the CS- in all three drug groups. The responses to the CS+US combination appear to get larger as the phase progresses, especially in the placebo group.

Figure 53 shows the second part of the acquisition phase, where only a proportion of the CS+ trials were reinforced. As there were twice as many CS- trials than either of the other type of trial, only every other CS- trial is displayed. The difference between the size of responses to the unreinforced CS+ trials and the size of responses to the CS- trials (which had never been reinforced) is considered to be an index of conditioning. For the placebo and methylphenidate groups responses to the CS+ appear to be larger than to the CS- (blue lines). For the diazepam group the bars are more similar in height.

The responses to the CS+US trials are larger than to either type of unreinforced trial. Interestingly although the responses to the CS+ are larger than those to the CS- throughout the phase in the placebo and methylphenidate groups there does seem to be some habituation as the largest CS+ responses occur on the first two trials of the phase.

Figure 54: Mean response to the trials in the extinction phase



In this final phase (Figure 54) none of the trials were reinforced. Responses to the CS+ seem larger than the CS- in the placebo and methylphenidate groups. The responses to the two types of stimuli seem closer together and sometimes the response to the CS- is slightly bigger in the methylphenidate group, but the responses are closest in size and most jumbled in the diazepam group.

5.3.1.2. Amplitude

This section begins with a description of the results of the omnibus 3 x 2 x 3 (phase x stimulus x drug) ANCOVA, followed by a short section about each of the three 2 x 3 ANCOVAs (one for each phase) that the larger ANCOVA was split into. The continuous reinforcement phase is not included as there were no unreinforced CS+ trials during this phase.

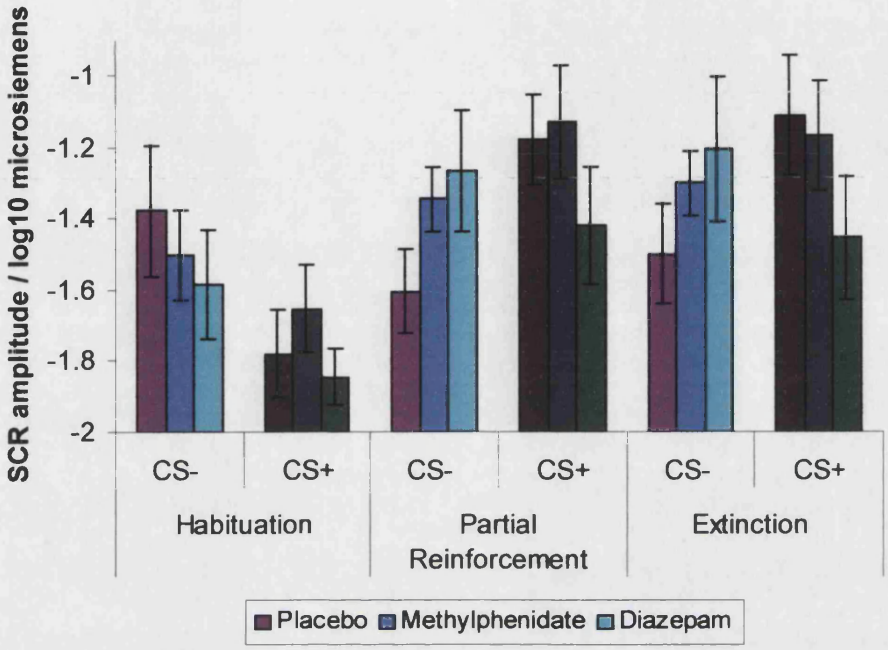
Three participants did not show a response with amplitude over-2 log10microsiemens to any of the stimuli in the partial reinforcement phase. They were excluded from the following analyses, leaving a total of 14 placebo, 16 methylphenidate and 15 diazepam participants.

Figure 55 shows group mean response amplitude for the CS- and CS+ in the habituation, partial reinforcement, and extinction phases. In the partial reinforcement and extinction phases, responses were bigger to the CS+ than CS- in the methylphenidate and placebo groups, therefore it appears conditioning occurred in these groups.

It appears that responses tended to be bigger for the CS- in the habituation phase. This was probably an artefact of the very first trial being a CS-.

The omnibus (3 x 2 x 3) ANCOVA showed a stimulus x drug interaction $F_{2,41}$ = 6.69, p=0.003^{GG}, whereby methylphenidate and placebo groups showed more response to the CS+ than the CS-, but the diazepam group did not. Thus there appears to be conditioning in the methylphenidate, and placebo groups but *not* the diazepam group.

Figure 55: Mean response amplitude to CS+ and CS-in the habituation phase (before conditioning), and partial reinforcement and extinction phases (after conditioning)



There was also a phase x stimulus interaction $F_{2,82} = 10.57$, $p<0.001^{GG}$. After conditioning occurred, responses became bigger to the CS+. There was a main effect of phase $F_{2,82} = 6.822$, $p=0.002^{GG}$, reflecting larger responses generally after conditioning. There was a phase x stimulus x covariate interaction $F_{2,82} = 5.148$ $p=0.008^{GG}$. There was no main effect of drug (p=0.52).

5.3.1.2.1. Habituation Phase

In the (2 x 3) ANCOVA comparing the two levels of stimulus and the three levels of drug in the habituation phase, there was a main effect of stimulus $F_{1,41} = 14.40$, $p<0.001$ Responses were larger to the CS- than CS+. This is because the very first stimulus presented to the volunteers was a CS- (see magnitude data presented above). There was no main effect of drug or drug x stimulus interaction. The active drugs did not affect the amplitude of unlearned responses.

Response to the CS+US in the continuous reinforcement phase (the covariate) was a predictor of responses in the habituation phase both on its own $F_{1,41} = 4.5$ $p=0.04$ and in interaction with the effect of stimulus $F_{1,41} = 4.49$ $p=0.040$. People

who showed a large reaction to the CS+US showed larger responses in the prior habituation phase.

5.3.1.2.2. Partial Reinforcement Phase

The 2 x 3 ANCOVA found there was a stimulus x drug interaction $F_{2,41} = 3.99$, p=0.026. The CS+ received a bigger response than the CS- in the placebo and methylphenidate groups, *but not the diazepam group.* A main effect of stimulus $F_{1,41} = 12.08$ p=0.001 reflects that participants gave bigger responses to the CS+ than CS-, showing that conditioning had occurred by this stage. There was no main effect of drug.

Three planned comparisons were carried out to investigate whether conditioning had occurred in each drug group individually. Significant differences in amplitude of responses to the CS+ compared to the CS- were found in the placebo ($F_{1,13}$, =16.26, p=0.002) and methylphenidate groups ($F_{1,14}$ = 9.65, p=0.008), but not the diazepam group (F<1 p=0.957)

Interestingly the covariate was only clearly a significant predictor in the methylphenidate group $F_{1,14}$=6.74, p=0.021, another possible reflection of individual differences in response to methylphenidate.

5.3.1.2.3. Extinction phase

The 2x3 ANCOVA found only a trend towards a stimulus x drug interaction, $F_{2,41}$ = 3.07, p=0.057 (without the covariate p=0.048). It seems that the placebo and methylphenidate groups continued to show slightly more of a response to the CS+ than CS-, whereas the diazepam group if anything were showing more response to the CS-. However when this was investigated further by comparing amplitude of responses to the CS+ with the CS- post hoc (Bonferroni corrected) in each drug group, none of the comparisons reached significance: [Placebo p=0.255, diazepam p=0.942, methylphenidate p=0.144].

To confirm that the conditioned response to the CS+ really did not extinguish, the magnitude[9] of responses to all the individual trials in the extinction phase were considered in a (2 x 15 x 3) (stimulus x trial x drug) ANCOVA (these

[9] i.e. On a trial were a participant gave no response, their response was counted as –2 $\log_{10}$microsiemens. This is the descriptive data presented above in 5.3.1.1. Mean group magnitude of responses to individual trials

means are depicted in Figure 54.) One diazepam participant and one placebo participant did not have data for the last few trials therefore there are 13 placebo, 16 methylphenidate, and 14 diazepam participants included in this analysis. There was a main effect of stimulus $F_{1,40} = 8.80$, p=0.005, but no stimulus x drug interaction (p=0.198) and no other significant main effects or interactions. Thus responses were fairly consistent from trial to trial and they did not decrease during extinction.

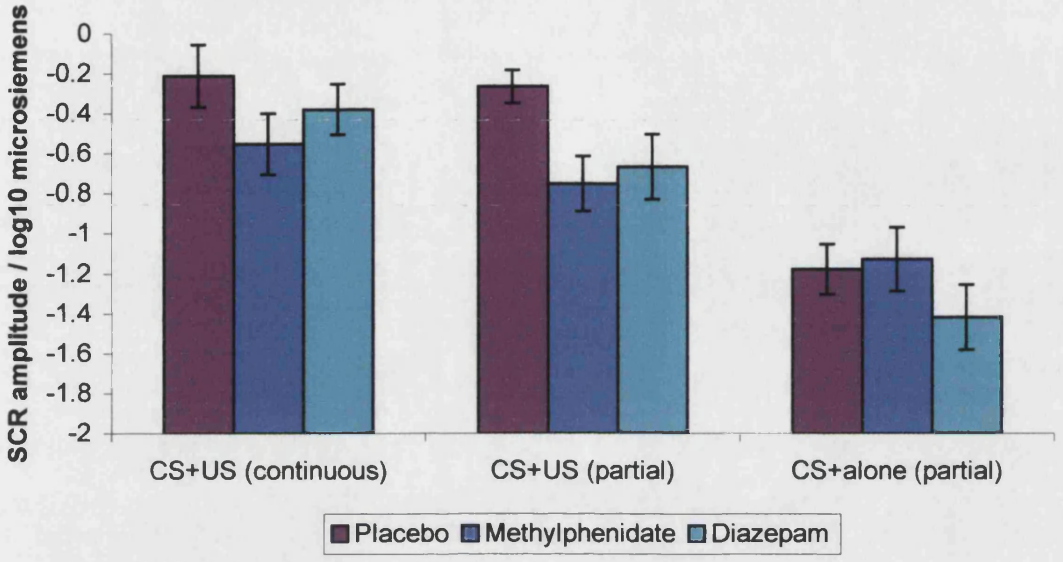
5.3.1.3. Amplitude of response to the CS+US

In the present experiment the US never appeared alone - it was always immediately preceded by the CS+. However, as argued by Hamann, Monarch, & Goldstein (2002), skin conductance responses to the US are so big in comparison to the CS+(alone) that the response to the CS+US combination can be used to accurately estimate amplitude of response to the US. Figure 56 shows the amplitude of these responses compared to the amplitude of the unreinforced CS+ trials

No covariate was used in the following analyses, as the covariate from the previous analyses (sections 2, 2.1, 2.2, & 2.3) was the response to the CS+US. This is being used as the dependant variable in this analysis.

To assess group differences in response to the US, and examine habituation to the US, a 2 x 3 split plot ANOVA (phase (continuous vs. partial reinforcement) X drug) was used. The dependent variable was amplitude of response to the CS+US. This revealed a main effect of phase $F_{1,42} = 6.13$, p=0.017, showing that participants habituated to the unconditioned stimulus- (their responses were significantly smaller in the partial reinforcement phase than the prior continuous reinforcement phase).

Figure 56: Mean (s.e.) log10 (amplitude+0.01) of responses to the reinforced and unreinforced CS+ in the continuous and partial reinforcement phases by each drug group.



No interaction between drug and phase was observed, therefore none of the drugs affected the rate of habituation, but there was a tendency to a main effect of drug $F_{2,42} = 2.78$, p=0.073. Post hoc Dunnett's test showed that this was due to a difference between placebo and methylphenidate (p=0.046) rather than any difference between placebo and diazepam (p=0.211). Therefore methylphenidate did, but diazepam did not significantly reduce response to the CS+US combination.

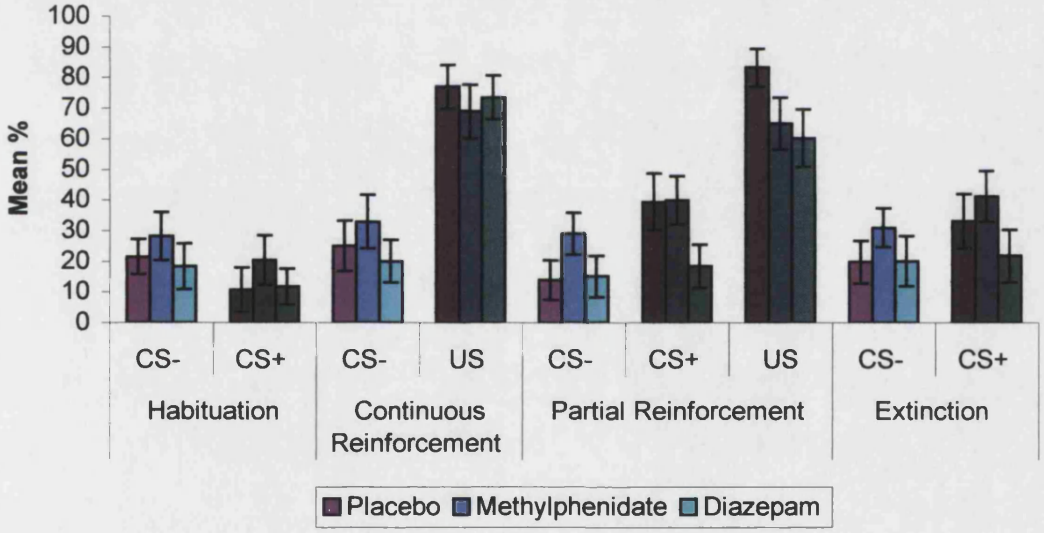
For the partial reinforcement phase a 2 x 3 (stimulus x drug) split plot ANOVA was used to compare the response to the CS+US with the response to the CS+ alone. This revealed a stimulus x drug interaction $F_{2,42} = 3.54$, p=0.038. Although the placebo group gave bigger unconditioned responses than the other two drug groups, the methylphenidate group gave larger conditioned responses. The difference between the methylphenidate group's conditioned and unconditioned responses was much smaller than either of the other two groups'. There was also a main effect of stimulus $F_{1,42} = 64.20$, p<0.001, whereby unconditioned responses were bigger than conditioned responses. Again, there was no main effect of drug.

5.3.1.4. Frequency

To confirm that the amplitude results were not an artefact of ignoring non-responses, the *number* of non-zero responses to each type of stimulus in each phase was counted for each subject. Because there were different numbers of possible responses for some kinds of stimuli (e.g. partial reinforcement was 8CS+, 16 CS-, and 8CS+US) these counts were converted to percentages. The analysis of number of responses showed a similar pattern of results to the analysis of amplitude (Figure 57).

As seen in Figure 57 volunteers responded the majority of times the CS+US was presented.

Figure 57: Mean (s.e.) percentage of possible responses made to each type of stimulus, in each phase, by each drug group.



For the omnibus 3 x 2 x 3 (phase x stimulus x drug) split plot ANOVA the stimulus x drug interaction was not significant $F_{2,42} = 1.94$, $p=0.156^{GG}$ There was a phase x stimulus interaction $F_{2,84} = 12.67$, $p<0.001^{GG}$, a main effect of phase $F_{2,84} = 4.80$, $p=0.011^{GG}$, and a main effect of stimulus $F_{1,42} = 4.53$, $p=0.039$. More responses were made to the CS+ than the CS- after conditioning. There was no main effect of drug ($p=0.264$)

The habituation phase showed a main effect of stimulus $F_{1,42} = 6.69$, $p=0.013$ whereby more of the responses to the CS- reached criterion. This was similar in all groups, and there was no effect of drug or interaction.

The partial reinforcement phase showed a stimulus x drug interaction $F_{2,42}$ = 4.03, p=0.025, a main effect of stimulus $F_{1,42}$ =17.41 p<0.001,and no main effect of drug. The planned comparisons for each drug group showed: Placebo $F_{1,13}$ = 13.41 p=0.003, Methylphenidate $F_{1,15}$ = 4.30 p=0.056, Diazepam NS F<1 p=0.428. Notably there is no evidence of significant conditioning in the methylphenidate group here. This is probably because they made a lot of very small responses to the CS-.

In the extinction phase there were significantly more responses to the CS+ than CS- $F_{1,42}$ = 5.55, p=0.023. Again there was no main effect of drug (p= 0.319) or interaction (p=0.358) and therefore no evidence for extinction.

5.3.1.5. Identification of CS+

Table 20 shows the number of people in each group who correctly identified the colour of the stimulus associated with the unconditioned stimulus at the first questioning. The numbers in brackets include participants who were not included in the analysis of skin conductance data. All participants were able to identify the stimulus when given a forced choice between the two colours.

Table 20: Number of participants correctly identifying CS+ on first questioning

	Placebo	**Methylphenidate**	**Diazepam**
Correct	14 (16)	12	12 (13)
Incorrect	0	4	3

5.3.2. Dual Interval Picture Task

The ink colour (source) memory data from the picture task will be presented first as it is thought that this is the least likely to be contaminated by non-emotional memorable properties of the material.

For the recognition memory data, both the number of hits and false alarms and the signal detection statistics derived from these measures were analysed. The reason for analysing the data in both forms is that the hit rate data is more comparable to most of the literature (e.g. LaBar & Phelps 1998) where number of items recalled is analysed. However considering false alarms and discriminability and willingness to respond should provide a clearer picture of

the content and accuracy of participants' memories for the various categories of information.

Therefore the results of the dual interval picture task are divided into four sections

5.3.2.1. Source memory

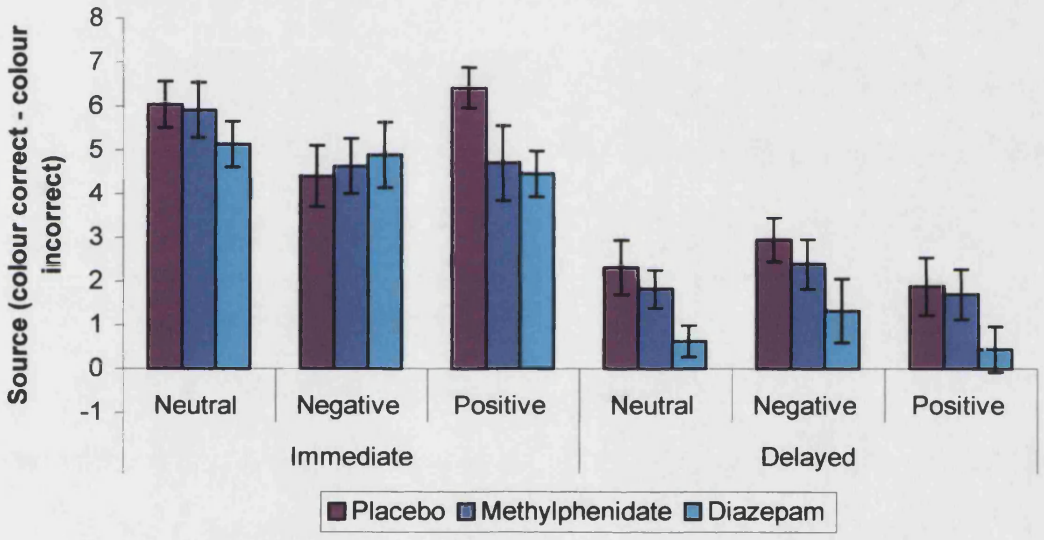
5.3.2.2. Number of hits

5.3.2.3. Number of false alarms

5.3.2.4. Signal detection

5.3.2.1. Source memory

Figure 58: Picture Test Source Memory



One participant (placebo) was excluded from this analysis because of poor colour vision. Source memory was defined as (correct source detections - wrong source detections). The ANOVA showed an interaction of delay with emotion $F_{2,88} = 5.81$, $p=0.005^{GG}$. As seen in Figure 58 source memory for negative pictures was worse than the other emotion categories at immediate recall and better than the other categories at delayed recall on day 7. There was also a main effect of time, $F_{1,44} = 121.13$ $p<0.001$. There were more correct source detections at immediate test than at delayed test. There was a trend towards a main effect of drug $F_{2,44}=2.27$, $p=0.077$ reflecting poorer source memory following diazepam (Dunnetts test, $p=0.024$) but this did not show an

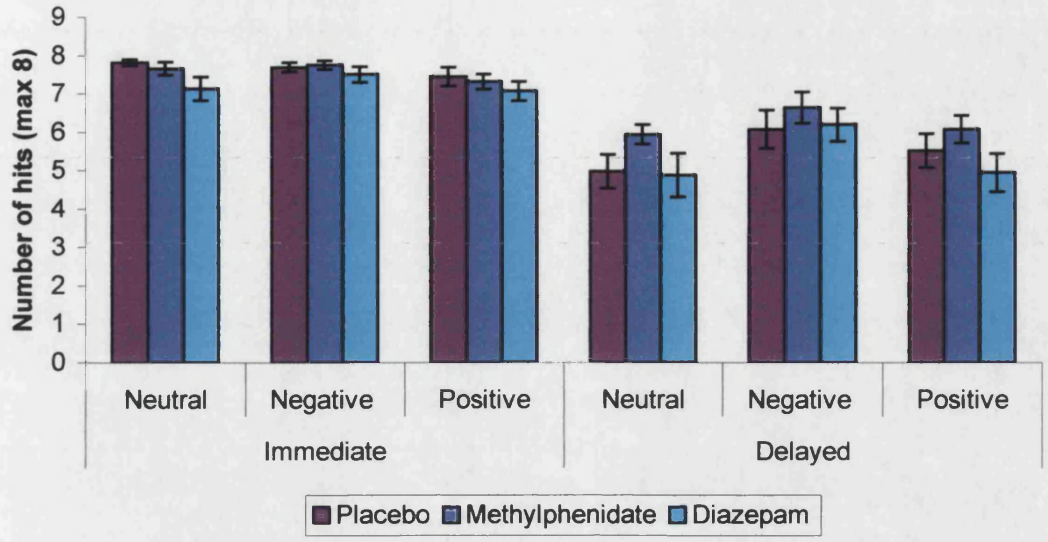
interaction with either emotion (p=0.535) or time (p=0.446). There was also no evidence for a three-way interaction (p=0.261) and no main effect of emotion. At immediate testing there was a tendency for an interaction between emotion and drug $F_{4,88}$ =2.21, p=0.074, a main effect of emotion $F_{2,88}$=3.98, p=0.022, but no main effect of drug. The placebo group showed slightly more of an impairment of source memory by negative emotion, than either active drug group.

At the seven day testing there was a main effect of drug $F_{2,44}$ = 4.53, p=0.016, and a tendency to a main effect of emotion $F_{2,88}$ =2.51, p=0.087, but no interaction between these. Diazepam impaired source memory after a delay, and all drug groups showed a similar pattern of slightly facilitated source memory after the delay.

5.3.2.2Number of hits

A (3 x 3 x 2) (drug x emotion x time) split plot ANOVA found a significant emotion x time interaction $F_{2,90}$ = 4.67, p=0.016 ^{GG}. As predicted, the forgetting rate (the difference between immediate and delayed recognition) is lower for the negative pictures. The time main effect $F_{1,45}$ = 104.35 p<0.001 and emotion main effect $F_{2,90}$ = 10.24, p<0.001 were both significant. There were more hits at immediate than delayed recall, and more hits for negative than positive or neutral pictures (Figure 59).
The time x drug interaction was not significant (p=0.199) although inspection of the means suggests less forgetting in the methylphenidate group. The drug main effect was not significant either (p=0.161), although the means are ordered in the expected way (methylphenidate > placebo> diazepam).
The three-way interaction and the drug x emotion interaction were not significant.

Figure 59: Mean (s.e.) number of hits on the picture test in each drug group to each emotion category.

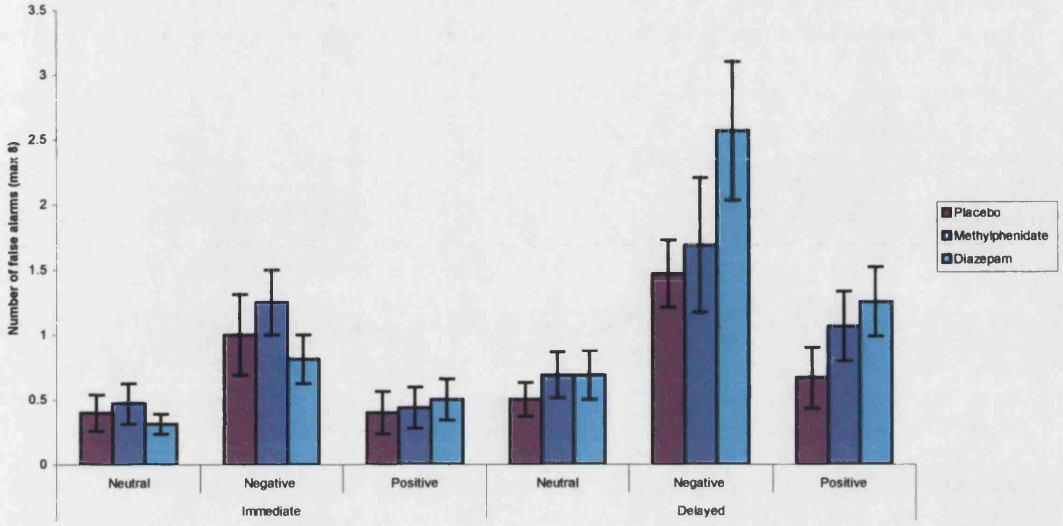


5.3.2.3. Number of False Alarms

There was a tendency to a time x drug interaction $F_{2,45} = 3.05$, $p=0.057$, and a time main effect $F_{1,45} = 20.73$, $p<0.001$. All groups made more false alarms at delayed than immediate recognition, but the diazepam group showed the greatest increase over time (Figure 11).

The main effect of emotion was significant $F_{2,90} = 37.92$, $p<0.001$. More false alarms were made to negative than to other pictures. The emotion x time interaction ($p=0.118$), emotion x drug, drug main effect, and the three way interaction were all non-significant.

Figure 60: Mean (s.e.) number of false alarms on the picture test in each drug group to each emotion category.

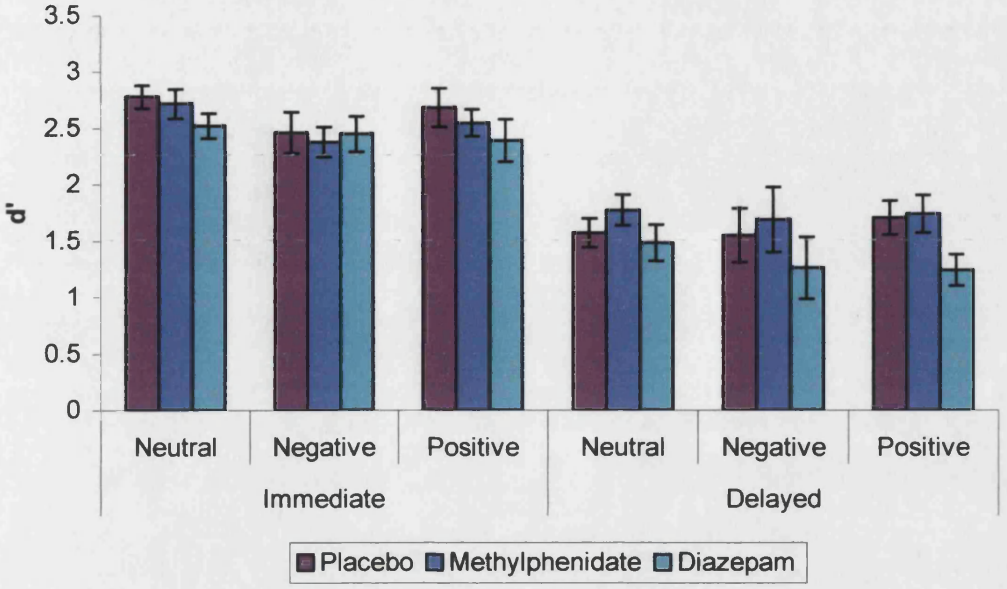


5.3.2.4. Signal detection analysis

The maximum possible value of d' in this experiment would be 3.19. The calculated values of d' are displayed in Figure 61

Values of d' were entered into a 2 x 3 x 3 (time x emotion x drug) split plot ANOVA. This showed a main effect of time $F_{1,45} = 163.95$, $p<0.001$. Old/ new discriminability was lower on day 7 than day 1. There was also a main effect of emotion $F_{2,90} = 3.19$, $p=0.050^{GG}$ whereby d' was highest for neutral pictures, then positive, and lowest for negative. There were no significant main effect of drug (p=0.154), drug x time interaction (p=0.189), or other interactions (emotion x drug $p=0.652^{GG}$, time x emotion $p=0.736^{GG}$, time x emotion x drug $p=0.855^{GG}$)

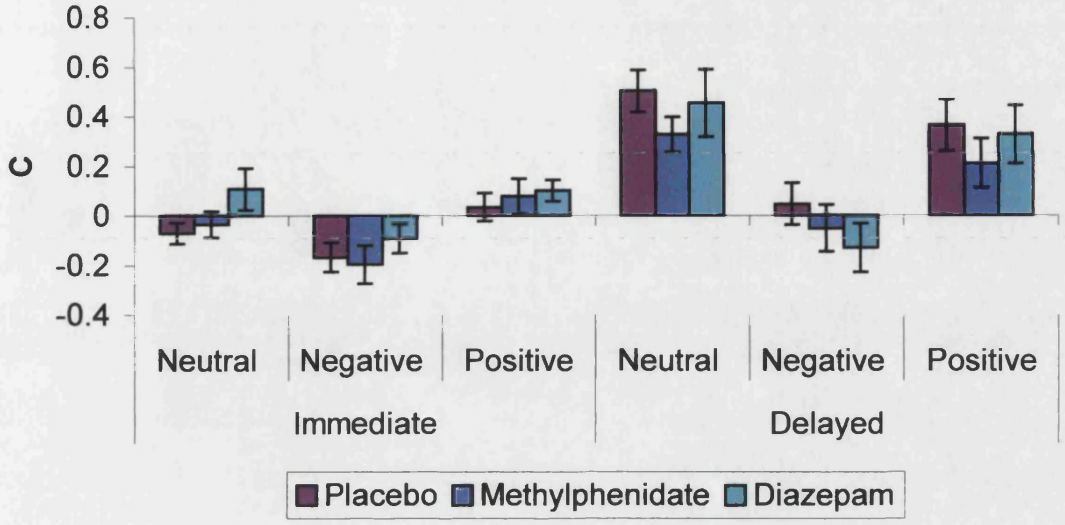
Figure 61: Mean (s.e.) d' for each drug group in each emotion category at each time point



A similar 2 x 3 x 3 split plot ANOVA was performed with the criterion statistic C. There was a main effect of emotion $F_{2,90} = 34.64$, $p<0.001$. As in Experiment 2 people used a much more conservative criterion (reflected in positive values of C) when deciding about neutral and positive pictures than they did for negative pictures (Figure 13).

A main effect of time $F_{1,45} = 42.20$, $p<0.001$ seems to reflect a more conservative bias for delayed (day 7) than immediate (day 1) recognition. There was also an emotion x time interaction $F_{2,90} = 7.22$, $p=0.002$, reflecting less change in the values of C for emotional (particularly negative) pictures than there was for neutral pictures. There was a tendency to a time x drug interaction $p=0.10$, although bias became more conservative over time in all three groups, the placebo group showed the most change in bias from day 1 to day 7. The main effect of drug was not significant $p=0.299$ and neither were any of the other interactions.

Figure 62: Mean (s.e.) C for each drug group in each emotion category at each time point.



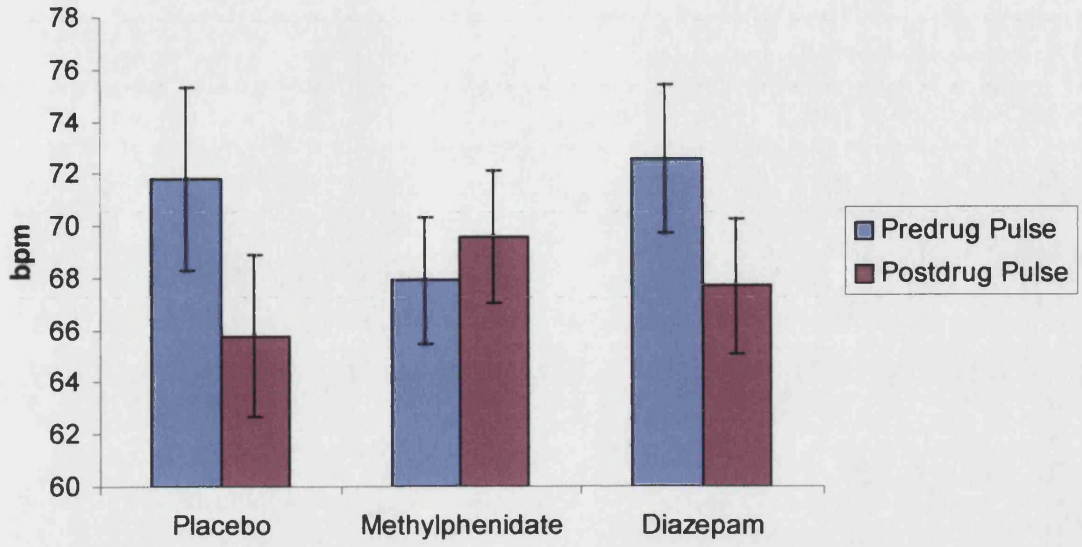
5.3.3.Control battery

5.3.3.1.Physiological measures

5.3.3.1.1. Pulse

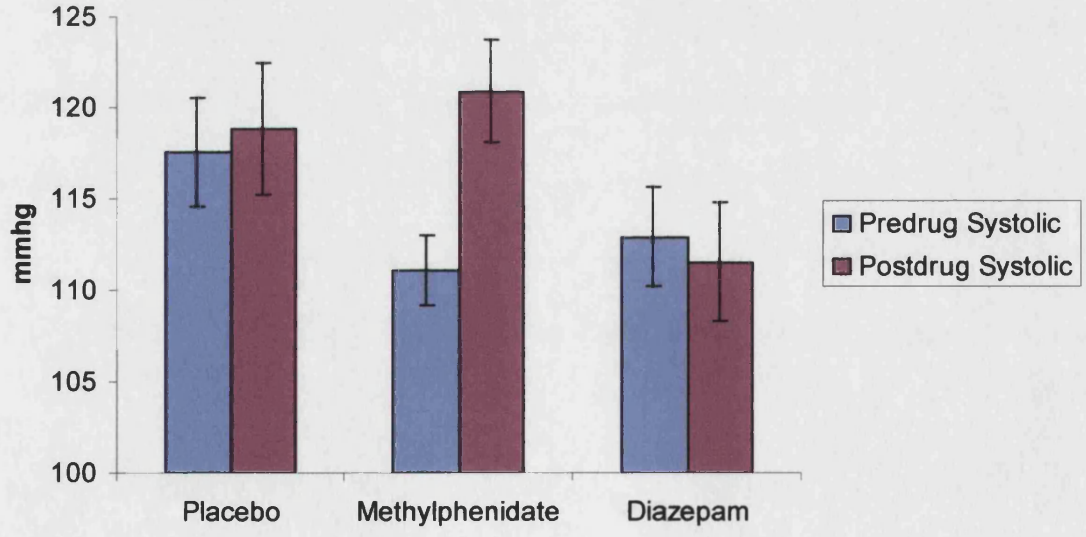
The pulse rate data showed a drug x time interaction $F_{2,45} = 6.20$, p=0.004. Methylphenidate increased pulse rate whereas the other two groups showed decreased pulse rate. There was also a main effect of time $F_{1,45} = 6.49$, p=0.014, reflecting on average pulse decreased through the course of the experiment. There was no main effect of drug.

Figure 63: Mean (s.e.) pulse rate in each drug group pre and post drug.



5.3.3.1.2 Blood Pressure

Figure 64: Mean (s.e.) systolic blood pressure in each drug group pre and post drug

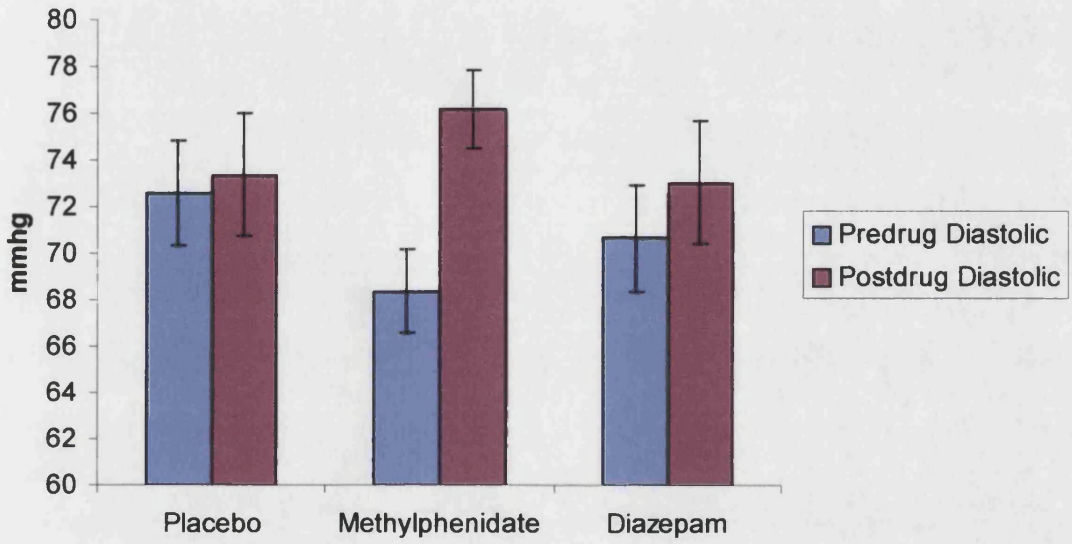


A highly significant interaction $F_{2,45}$ = 9.00, p=0.001, and main effect of time $F_{1,45}$ =8.28, p=0.006 reflected an increase in systolic blood pressure after

methylphenidate, with the other two drug groups showing little change. There was no main effect of drug.

Similarly a drug x time interaction $F_{2,45} = 6.30$, p=0.004 and a main effect of time $F_{1,45} = 18.35$, p<0.001 reflect greater increases in diastolic blood pressure in the methylphenidate group than in the other two groups.

Figure 65: Mean (s.e.) diastolic blood pressure in each drug group pre and post drug.



5.3.3.1.3. Tapping

The tapping task did not show any significant main effects or interaction (Table 21).

Table 21: Mean s.d. taps / minute in each drug group pre and post drug

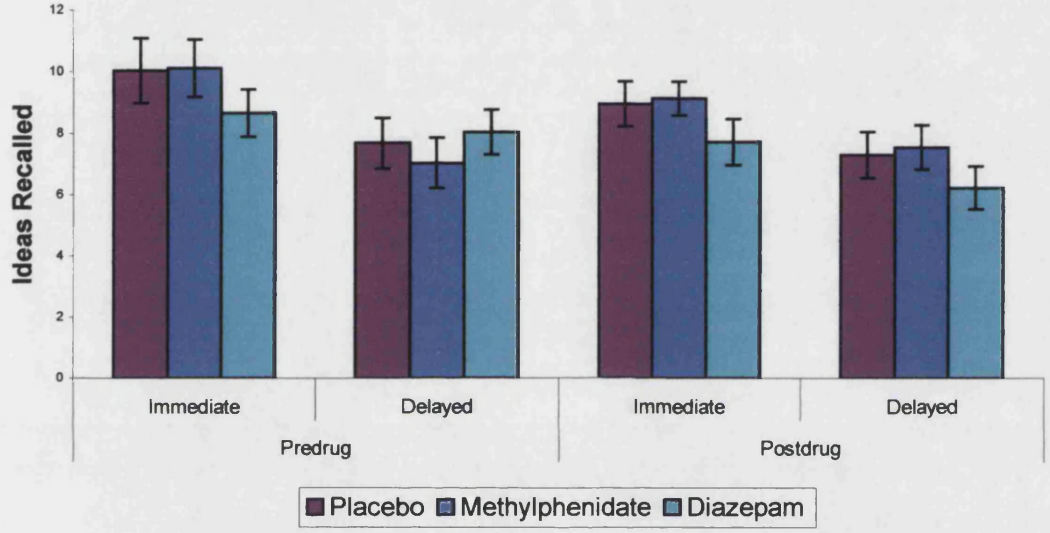
	Placebo	**Methylphenidate**	**Diazepam**
Predrug	371.06*47.33*	363.56*41.35*	364.56*45.66*
Postdrug	370.69*48.72*	357.06*45.05*	353.56*47.25*

5.3.3.2. Prose Recall

There was a drug x delay interaction $F_{2,45} = 3.69$, p=0.033, and a main effect of delay $F_{2,45} = 81.285$ P<0.001. All drug groups recalled less at delayed recall than they did at immediate recall, however this difference was *smaller* for the diazepam group. The three way interaction (drug x time x delay) was also significant $F_{2,45} = 3.39$ p=0.042. For the story learned post-drug all groups

displayed a similar difference between immediate and delayed recall, recalling slightly less ideas at delayed recall than they did at immediate recall. However for the story learned pre-drug the diazepam group recalled less than the other groups at immediate recall, and then they were also impaired at delayed recall, whereas the methylphenidate and placebo groups recalled less at delayed recall than at immediate.

Figure 66: Ideas recalled on the prose recall task in each drug group at immediate and delayed tests.



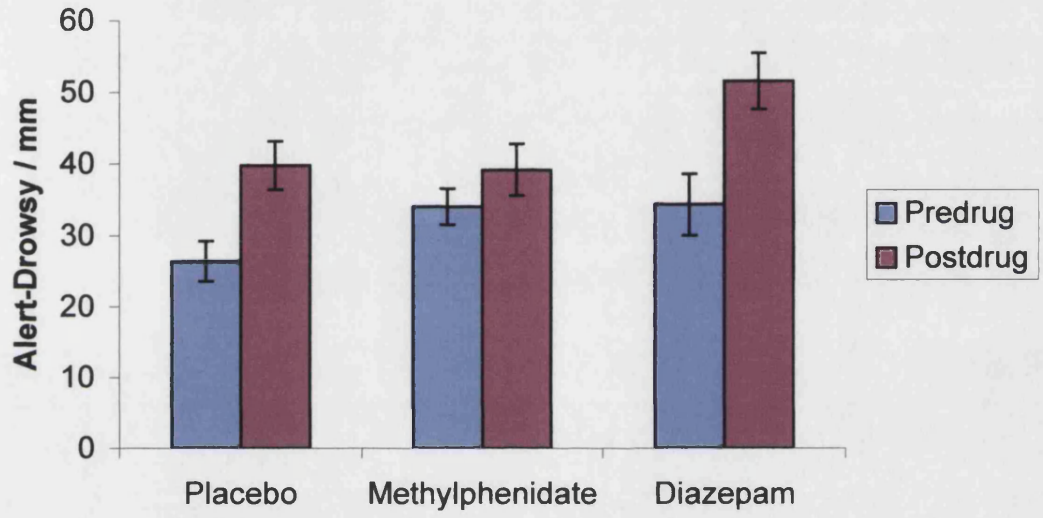
5.3.3.3 Serial sevens

Three participants were excluded from this analysis because they managed less than 7 correct subtractions in 90 seconds during the predrug testing. A sevens score was computed by subtracting number of errors from correct subtractions, for each participant. A 2x 3 (time x drug) split plot ANOVA showed a main effect of time $F_{1,42} = 6.25$, $p=0.016$. All participants got better with practice. A trend $F_{2,42} = 3.02$, $p=0.06$ towards a main effect of drug was due to poorer performance in the diazepam group (Dunnets test post hoc, cf. placebo $p=0.067$), however this was apparent both pre and post drug. There was no evidence for an interaction.

5.3.3.4. Mood Rating Scale

On the **Alert- Drowsy** subscale a trend towards an interaction $F_{2,45} = 2.531$, $p=0.091$, a trend towards a main effect of drug $F_{2,45} = 2.65$, $p=0.082$, and a main effect of time $F_{1,45} = 35.87$, $p<0.001$ were observed. All groups felt less alert with time, but this was least so in the methylphenidate group, and most so in the diazepam group.

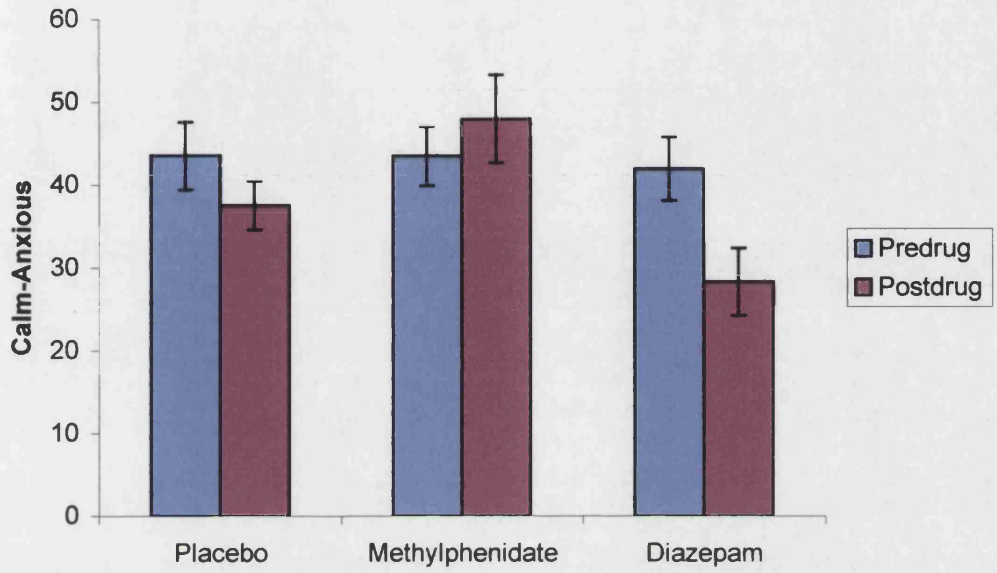
Figure 67: Mean (s.e.) rating on the alert-drowsy subscale of the mood rating scale in each drug group pre and post drug.



A main effect of time on the **Contented-Discontented** scale $F_{1,45} = 4.75$, $p=0.035$, shows all groups felt less content with time. The interaction and the drug main effect were not significant.

The **Calm- Anxiety** scale showed a drug x time interaction $F_{2,45} = 4.72$, $p=0.014$, The methylphenidate group were more anxious and the diazepam group were more calm post compared to predrug. There was also a main effect of time $F_{1,45} = 5.77$, $p=0.021$.

Figure 68: Mean (s.e.) rating on the calm-anxiety subscale of the mood rating scale in each drug group pre and post drug.

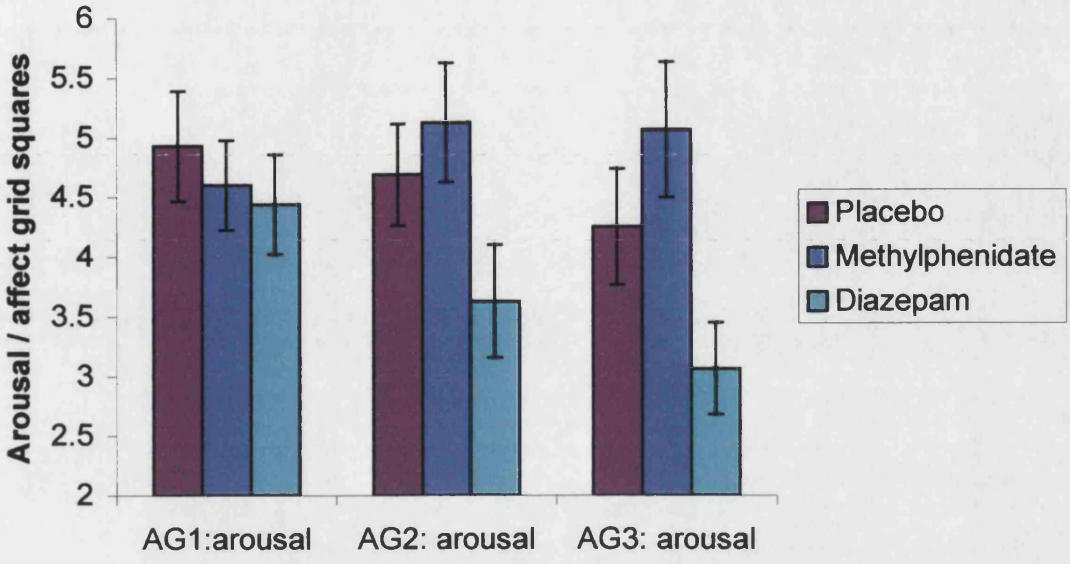


5.3.3.5 Affect Grid

5.3.3.5.1. Arousal

A main effect of drug $F_{2,45} = 3.57$, $p=0.037$ seems to reflect methylphenidate increasing and diazepam decreasing arousal relative to placebo. However there was no interaction or main effect of time.

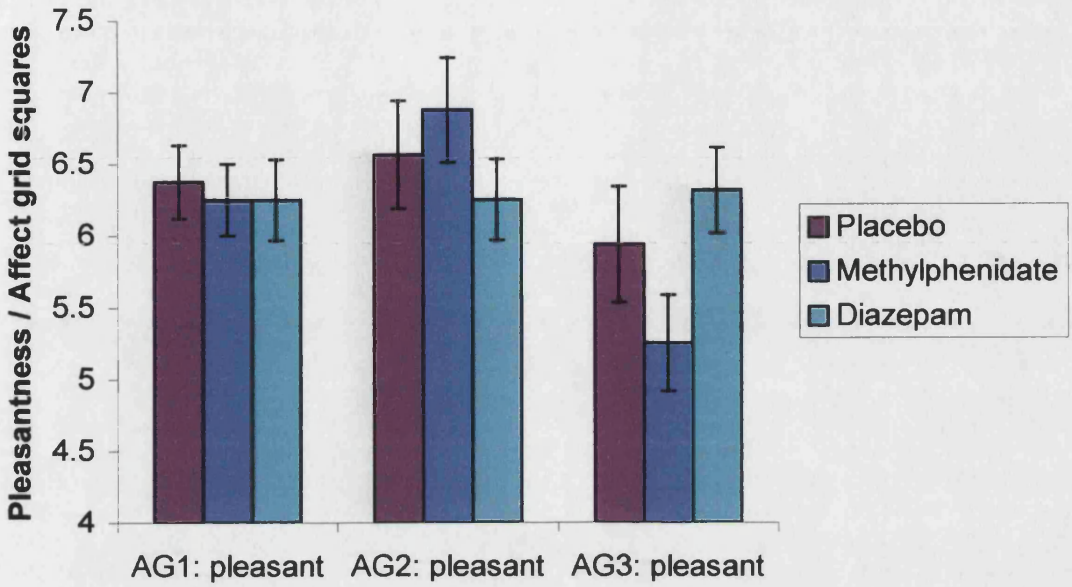
Figure 69: Mean (s.e.) rating of arousal on the affect grid in each drug group at each time point.



5.3.3.5.2. Pleasantness

A drug x time interaction $F_{4,90} = 2.51$, $p=0.048$ and a main effect of time $F_{2,90} = 5.55$, $p=0.005$ (no main effect of drug) reflected the large decrease in pleasantness between the affect grid marked at the beginning of the main postdrug test session and the affect grid marked at the end of the main test session in the methylphenidate group. This may be due to the methylphenidate group finding the aversive conditioning and dual interval picture tasks more unpleasant than the other two drug groups. However the mean difference was less than 2 affect grid squares.

Figure 70:Mean (s.e.) rating of pleasantness on the affect grid in each drug group at each time point.



5.3.4.Summary of Results

Conditioning

- After conditioning, the placebo and methylphenidate groups showed larger responses to CS+ than CS-. The diazepam group did not.
- **Habituation**
  - Amplitude of all groups responses were larger to the CS- than the CS+
    - Descriptive statistics (magnitude of individual responses) show this was due to a bigger response to the first trial which was a CS-
  - Drug treatments did not affect these unlearned responses.
- **Reinforcement**
  - Placebo group showed their greatest amplitude and highest frequency of responses to CS+US then CS+ then CS-.
  - Methylphenidate group
    - A smaller difference between amplitude of CS+US and CS+ responses than placebo.
    - Larger (but not more) CS+ responses than CS-responses

- Diazepam group: Made larger responses to CS+US than methylphenidate group (response to US was not unduly impaired), Showed no difference between the number or amplitude of responses to CS+ and CS-
- All participants could identify the CS+ when explicitly asked.

- **Extinction**
  - Neither of the measures of response size showed evidence for extinction in any of the drug groups.
  - Frequency of responses did not decrease either

Picture colour task

- Source memory
  - Source memory for negative pictures was slightly lower than the other categories at immediate test and higher at delayed test.
  - Source memory deteriorated over time
  - Source memory was impaired by diazepam
- Hits
  - More hits were made at immediate than delayed recognition
  - More hits were made for negative pictures than negative than positive or neutral.
  - Neither drug affected hits
- False alarms
  - More false alarms were made on day 7 than day 1
  - Diazepam group showed the greatest increase in number of false alarms.
  - Most false alarms were made to negative pictures
- Signal Detection d'
  - d' was lower for negative pictures and lower on day 7
- Signal detection C
  - Less conservative bias for negative pictures
  - The change towards conservativeness was greatest in the placebo group.

Control battery

- Table 22 shows a ✓ if the measure did or an X if it did not, show the predicted

- Pre to post drug increases relative to placebo in the methylphenidate group
- Pre to post drug decreases relative to placebo in the diazepam group.

Table 22: Summary of control measures

	Methylphenidate	Diazepam (10mg)
Pulse	✓	X
Systolic	✓	X
Diastolic	✓	X
Taps	X	X
Prose	X	✓
Serial sevens	X	X
MRS: alert	✓	✓
MRS: content	~	~
MRS:calm	✓	✓
AG: Arousal	X	X
AG: pleasant	~	~

5.4. DISCUSSION

5.4.1.Fear Conditioning

5.4.1.1. Diazepam impaired fear conditioning

Volunteers who had been given diazepam were impaired in their ability to acquire the conditioned skin conductance response. During the partial reinforcement phase both the number and the size of their responses to the CS+ were similar to their responses to the CS-. This shows impaired *learning* of the fear response (rather than any non-specific impairment of the sweat gland activity) in the diazepam group, as there was no difference between the placebo and diazepam groups in response to the CS+US, or the (unlearned) responses in the first habituation phase. Therefore a main finding of the present study was that diazepam impaired fear conditioning.

The fear conditioning method used was successful in that the placebo group showed a greater amplitude of response and more responses to the CS+ than they did to the CS- after the continuous reinforcement phase. This conditioned skin conductance response continued into the extinction phase.
For the diazepam group in the final (extinction) phase there was no evidence that their pattern of responses was different to the other drug groups, especially in the analysis of magnitude, which considered trials where the volunteers did not respond. This could be interpreted as showing that after a long acquisition phase which included both continuous and partial reinforcement, participants in the diazepam group did eventually learn the response to the CS+. However a more plausible interpretation is that the diazepam group had stopped responding to any of the stimuli by this stage and all the responses from this group in this phase just represent noise. Two aspects of the data from the diazepam group support this: (1) the responses in the extinction phase were very small, and (2) amplitude of responses to the CS- is slightly (non-significantly) larger than to the CS+ in the diazepam group in this phase. This is despite average response magnitude being slightly bigger to the CS+ in the same phase. i.e. the direction of the difference between CS+ and CS- changes direction, depending on whether trials with no response are counted or not. (This must be due to more small responses to the CS-, but more zero and slightly bigger responses to the CS+)

5.4.1.2. Evidence for fear conditioning after methylphenidate, despite possible impairment of the unconditioned response

In terms of response amplitude, the methylphenidate group showed clear evidence for conditioning. Their responses to the CS+ were larger than to the CS- in the partial reinforcement phase, and this difference continued into the extinction phase.
When compared to the placebo group, the methylphenidate group showed lower amplitude of responses to the CS+US combination. That this was a real effect is supported by the magnitude data, which show that on every CS+US trial the placebo group gave larger responses than the methylphenidate group. This was not reflected by smaller conditioned responses to the CS+ alone. The difference between the conditioned and unconditioned responses is smaller in

the methylphenidate group than in either of the other two groups. This could be interpreted to suggest that methylphenidate facilitated learning of the fear response.

The lower response to the unconditioned stimulus after methylphenidate is interesting as parallels can be drawn with the methylphenidate group in Experiment 1, who tended to rate the (Cahill & McGaugh 1995) story less emotional than the other groups. Possible explanations could have included participants attributing the arousal that they felt during the story to a drug effect, rather than the story, or to methylphenidate promoting feelings of well being and elation. Neither of these explanations is likely in the present experiment. The methylphenidate group reported feeling less pleasant than the other two drug groups on the affect grid that was marked after the conditioning task. If skin conductance response to the unconditioned stimuli is outside of conscious control, attribution of arousal is not a good explanation for lowered response.

In terms of response frequency the methylphenidate group did not show such clear evidence for conditioning. This was because, although on average they made slightly more responses to the CS+ than the CS-, the difference did not reach statistical significance. This was due to methylphenidate producing a lot of responses (with small amplitude) to the CS-. This fits both with a general pattern of methylphenidate induced arousal increasing propensity to respond, and with reports that methylphenidate increases the number of scorable skin conductance responses Iacono et al (1984). However, as the individual responses to the CS- were almost all of smaller magnitude than those to the CS+, the frequency data does not draw into question the strong evidence for conditioning in the methylphenidate group.

5.4.1.3. No evidence for extinction of conditioned fear

Overall there was consistent evidence for conditioning, and little evidence that conditioned responses extinguished. Amplitude of response to the CS+ was larger than the CS- during the extinction phase in all drug groups, and there was still some evidence for a difference in the responses to the CS+ and the CS- even on the final trial. As even the placebo group did not extinguish it is impossible to draw conclusions about the effects of the active drugs on extinction. The lack of evidence for extinction of the conditioned response was

surprising, particularly as participants appeared to be concentrating less on the stimuli by the end of the final phase of the experiment. Two participants (one placebo, one diazepam) even had to be withdrawn a few trials before the before the end as they could not stay awake, despite encouragement. As partial reinforcement schedules are known to cause strong conditioning this may be a good experimental design for investigating effects of drugs on extinction.

5.4.1.4.Skin conductance responses to the unconditioned stimulus

The reduction in response to the CS+US from the continuous to the partial reinforcement phases is evidence for habituation to the CS+ US combination, and as the decrease was the same for all drug groups, it seemed that habituation was unaffected by the drugs. This is supported by the first 'habituation' phase of the experiment. All three drug groups gave larger responses to the CS-, the first stimulus, and after this responses decreased in a similar way in all drug groups.

The descriptive magnitude data shows that for the first three trials of the continuous reinforcement phase, skin conductance responses to the CS+US increased. It had been thought that the CS+US might be most surprising, alarming and adverse the first time it was heard. Therefore the observation that the third CS+US trial received the response with the largest average magnitude might be an error, possibly due to the way a response was defined. Inspection of the raw data however, suggested that it is a genuine effect. It may reflect increased anxiety as participants learned that the CS+ predicted the US. This is supported by the observation that the diazepam group did not show the pattern of increasing response to the CS+US as clearly as the other two groups. However an anxiolytic effect of diazepam is not a particularly plausible explanation for this particular effect. Hamann et al (2002) suggest that the response to the CS+US is a good estimate of the response to the US alone – because responses to the US are so much bigger than responses to the CS+. Anxiety is experienced while waiting for an adverse event to occur. Therefore anxiety should not be a factor in response to the CS+US, as the adverse event has already occurred. It may however be a factor in response to the CS+ alone.

5.4.1.5. A possible effect of anxiety or the expression of fear on the learned response?

There is a possibility that the effects of the different drugs on anxiety could explain the conditioning results. Therefore it could be argued that the results could equally well be explained by the diazepam group not learning and the diazepam group not feeling anxious. Perhaps all the groups had formed the association between the CS+ and the US, but the diazepam group were less anxious and the methylphenidate group were more anxious while anticipating the US. This criticism is not unique to the present study. Conceivably the patients studied by Phelps et al (1998), LaBar et al (1995) Hamann et al (2002) and Bechara et al (1995) could also have been expressing anxiety deficits, rather than learning deficits when they were found to have impaired fear conditioning.

As noted in the introduction, this question is similar to the ongoing debate about whether the amygdala is the locus of fear conditioning or whether is it just necessary for the expression of conditioned fear.

5.4.1.6. Are we really testing implicit emotional memory?

As all participants were able to identify the CS+ when asked to choose between the two options, it is unlikely that any deficit in declarative memory for which stimulus predicted the US contributed to the results. Hamann et al (2002) argue that diminished awareness is not a good explanation for impaired conditioning as even subliminally perceived stimuli can be conditioned. However in the current experiment, when they were first asked the open question *"Did you notice any relationship between the colour and the sound"* some participants revealed that they were expecting the relationship to be more complicated than it was. For example, some tried to describe a pattern such as increasing numbers of stimuli appearing between noises, or asked if it was the interstimulus intervals rather than the colour that predicted the noise. Therefore these few people may not have been consciously expecting the loud noise when they saw the CS+. The majority (n=4) of people who gave these responses were in the methylphenidate group. Therefore an explanation for the causes of the conditioned skin conductance responses being explicit knowledge

is not supported by the large reactions to the CS+ found in the methylphenidate group.

However some members of the diazepam group also responded in this way. Perhaps their reduced explicit expectations about the CS+ predicting the US may have influenced their impaired fear conditioning. Certainly the finding of this experiment that diazepam impairs fear conditioning is in contrast to reports in the literature that diazepam leaves other forms of implicit memory intact. When non-specific sedative effects are taken into account, diazepam does not generally impair perceptual or conceptual priming, or procedural learning Curran (1999) (e.g. Bishop, Curran, & Lader, 1996; Fang, Hinrichs, & Ghoneim, 1987; Vidailhet et al, 1996). However, most of these studies have used simple perceptual or other undemanding assessments of implicit memory. Recently, Wilkinson (personal communication) found evidence for dose related impairments of 7.5, 15mg on a complex (non-emotional) procedural sequence-learning task, therefore perhaps diazepam does impair some forms of implicit memory, if tasks are sensitive enough to detect it. Squire (1992) and other theorists see conditioning as a neurocognitively distinct form of implicit memory from implicit or procedural learning. The finding that diazepam impairs one form and not others is evidence in support of this distinction. It is interesting that the distinction may also follow an implicit/ explicit distinction.

Alternatively, it could be that implicit emotional memory is not necessary for the fear conditioning task. Perhaps conclusions of the current experiment are restricted to the effects of the drugs on 'learning' rather than 'emotional learning'. This is because learning that the CS- is the 'safe' signal could be argued not to be an equivalent 'neutral memory' condition. Although there is a fear / high arousal learned association, there is no condition where participants learn a response (as opposed to a lack of response) to a neutral / low arousal signal. However, there is evidence (Bechara et al, 1995) that aversive conditioning relies on the amygdala, which is usually thought to be involved with memory for emotionally arousing material, not neutral memory. It is difficult to conceive what an equivalent low arousal stimulus and response would be.

5.4.1.7. Further research ideas for the fear conditioning method

The fear conditioning paradigm has proved informative in studies of patients with amygdala damage where the question asked has been mainly whether they do or do not show conditioned fear. However it shows potential for further exploring the phenomenon of emotional memory, particularly as it is possible to manipulate variables such as emotional arousal, and obtain a quantitative measure of how this effects this form of emotional memory e.g. Grillon and Hill (2003).

Unlike lesions, the effects of drugs are temporary. Therefore questions about the role of different neurochemical systems in different parts (e.g. association forming / expression of fear) of fear conditioning can be addressed. For example it was discussed in section 5.4.1.5 that there was a question about the effect of the role of either methylphenidate and or diazepam on anxiety in the current experiment. Ideally to address this question a further study would include a condition where conditioning takes place under the influence of placebo/ diazepam / or methylphenidate, but learning is tested after the drugs would have cleared from the body.

Another interesting feature of the current paradigm was the persistence of the conditioned response. No extinction of the conditioned response was observed. A recent report by Marsicano et al (2002) uses evidence from animals deficient in cannabinoid receptor 1 (CB1) to argue that cannabinoids have a role in the extinction of aversive memories. Therefore an interesting replication of this experiment would include a group given Δ9-tetrahydrocannabinol (THC), and predict that the conditioned response would extinguish in this group.

5.4.2 Dual interval picture task

5.4.2.1. Memory for the picture colour (source) associated with emotional pictures.

Source memory for the negative (highly arousing) emotional pictures was poorer than for the other categories of pictures (particularly neutral pictures) at immediate test and better than for the other categories of pictures at delayed test. This is similar to the findings described in the literature by Kleinsmith &

Kaplan (1963, 1964), Bradley & Baddeley (1990), Parkin et al (1982) and LaBar & Phelps (1998) and is usually interpreted as evidence for emotional arousal increasing consolidation.

As expected, source memory was poorer at delayed test than immediate test. All drug groups forgot some information during the week from all categories. This includes the highly arousing negative emotional category, although less information was lost from this category than the other categories. The classic pattern of results described by Kleinsmith and Kaplan (and LaBar and Phelps) is an *increase* in memory for the paired associates of arousing words over time. However, both Bradley & Baddeley (1990) and Parkin, Lewinsohn, & Folkard (1982) found fewer associates of emotional words were produced at delayed than immediate test, producing a pattern of results similar to the current study.

Source memory was impaired by diazepam. Regardless of the type of stimuli, the diazepam group attributed less items to the correct source than either of the other two groups. More interesting theoretically, the *pattern* of source memory across the three types of stimuli in this group was the same as in the placebo group. The methylphenidate group also showed a similar pattern of source memory to the placebo group. Therefore if the observed effect of less forgetting of the highly arousing negative emotional pictures was due to enhanced consolidation, this process was unaffected by either of the drugs used in the present experiment.

When the immediate and delayed tests were compared separately the effects of the drugs became apparent. At delayed testing, all three drug groups showed a similar pattern of memory facilitation for the negative pictures. Therefore it appears that neither drug affected emotional arousal induced memory consolidation. At the immediate test source memory followed the previously observed pattern of impairment by negative pictures in the placebo group. The pattern of source memory at immediate test was slightly different in the two active drug groups.

5.4.2.2.Recognition memory

There was little difference in hit rates for the three emotion categories on the day 1 test, but at delayed testing a week later, hit rate was highest for negative pictures, then positive, then neutral. This was unaffected by the drugs.

Therefore at first glance the hit rate data appears to confirm the hypothesis that memory for highly arousing emotional material receives enhanced consolidation and improves over time. However before reaching this conclusion two points should be taken into account: (1) a ceiling effect could be obscuring an difference between emotion categories in the day 1 data; (2) the number of false alarms also increased over time.

(1) Although little difference was observed between emotion categories on day 1 this could have been due to a ceiling effect on recognition. The mean number of pictures recognised in this test session was near the maximum, and the standard errors were small. It is possible that the negative pictures might have facilitated memory relative to the other categories on day 1, if more pictures had been used in the immediate recognition test (but see section 5.1.1). This in turn means that superior memory for negative pictures on day 7 may not necessarily be due to enhanced consolidation. The likelihood of a ceiling effect was considered before the experiment was run, and is another reason why more weight should be given to the source memory data than the recognition memory data.

(2) False alarms increased over time, and more false alarms were made to the highly arousing negative pictures. Therefore when false alarms are added to the equation there is no evidence for enhancement of consolidation.

Because of this inflated false alarm rate, recognition memory indexed by the signal detection parameter, d' was actually poorer for the highly arousing negative pictures than for the other categories. It had been predicted that emotion would improve old / new discriminability. It was considered whether this could be due to the possible ceiling effect discussed above. For the day one recognition test this could have been the case, a few participants correctly recognised all the possible pictures. However in the day 7 condition participants in all the drug groups were scoring 75% or less of the possible hits. There was no statistical evidence that the pattern of results across the three emotion conditions was different between the testing times.

5.4.2.3 Bias

Participants showed evidence for a bias towards saying they recognised negative arousing pictures. This may be the main result of interest from the dual

interval picture task. Increased levels of both hits and false alarms are reflected in a less conservative bias criterion for negative pictures than either positive or neutral pictures. Compared with immediate recognition the bias criterion for negative pictures was slightly more conservative on day 7, whereas the bias criterion for the neutral and positive pictures, was much more conservative on day 7. The general move towards a more conservative bias may reflect participants being much less confident in their memories a week later. There was a tendency for bias in the active drug groups to change less than in the placebo group.

The effect of emotion on bias seems to be robust. It has appeared clearly in both this experiment and Experiment 2. In both bias was unaffected by the different drug manipulations. As source memory was only measured from the pictures that volunteers thought they had seen before, it is possible that the strong effect of emotion on bias may supersede the findings of the source memory data. There is no way of measuring source memory independently of recognition memory bias.

This problem is not unique to this series of experiments. There is a large amount of literature about the effects of emotion on memory (reviews: Hamann, 2001; McGaugh, 2000; Christianson, 1992). However the effect of emotion on bias criteria has rarely been investigated. Bias effects in an emotional recognition memory task could be due to arousal increasing propensity to respond to the pictures, when they are re-presented during the memory test. However even in a free recall test the stimuli are 're-presented' at retrieval albeit in the participants' mind. Therefore the increased bias when remembering emotional pictures may confound other emotional memory tests. In other words, people may have encoded and consolidated just as much neutral as emotional information, because of a more conservative criterion bias they do not produce as much neutral information at retrieval. This would not be detected in most free recall tasks as too few false alarms are produced.

The effects of emotional arousal on bias may also explain the phenomena of flashbulb memory. Most people feel very confident about details in emotional 'flashbulb' memories - but these details are not necessarily any more correct than details from neutral memories they do not feel as confident in.

5.4.2.5.Methodological issues with the task

As in the previous experiments with these stimuli, memory performance for the positive pictures tended to be at a mid-level, between that for negative and neutral pictures. This may well be because it is emotional arousal, which actually causes the memory effects, not the valence of the particular emotion. As arousal tends to be highest for negative pictures, intermediate for positive, and lowest for neutral, memory performance follows the same hierarchy.
The use of a seven day delay between testings also merits comment. LaBar & Phelps (1998) expressed the idea that participants would not have the opportunity to differentially rehearse the two types of information in their dual interval taboo words task, as the interval between immediate and delayed recall was filled with other tasks. In a design where the interval is seven days it is clearly impossible to fill the time with distracting tasks. However it can be argued that even if participants are engaged in distracting tasks they may still be thinking about the previous task. In the current experiment participants were not told they are returning the next week for a memory test and so there is no more reason for them to intentionally rehearse during the week than there is during the one hour interval used in LaBar & Phelps (1998) test.

5.4.3.Control battery

5.4.3.1.Arousal

Taken together the calmness, alertness and arousal subjective effects measures showed the expected pattern of increases in arousal in the methylphenidate group and decreases in the diazepam group. The contentedness and pleasantness measures show decreases during the experiment, as has been found in the previous experiments. The extra decrease in pleasantness during the post drug test session in the methylphenidate group was not found during the previous experiments. This suggests that it was the aversive conditioning task, which increased anxiety in this particular group, as this task was not part of the previous experiments.
Pulse and blood pressure showed the predicted increases due to methylphenidate, and either decreases or no change after placebo or 10mg diazepam. Therefore neither placebo nor diazepam had an effect on pulse and

blood pressure, although participants may have relaxed as the experiment progressed.

5.4.3.2. Memory

The prose recall test did not show the predicted improvements due to methylphenidate and deficits due to diazepam. The standard effect of participants recalling less at the delayed test than they did at the immediate test (forgetting some of the story over time) was found. Apart from this all the findings seem to be due to the low performance of the diazepam group at immediate recall of the first story, that they learned before they took the drug.

The serial sevens task showed little evidence for the predicted drug effects of improvements due to methylphenidate and decrements due to diazepam. There is a possibility that this was due to different effects of the drugs influencing task performance in different ways. Several participants found the task quite anxiety provoking, and therefore the anxiolytic / anxiogenic actions of the drugs may have acted in the opposite direction to their effects on working memory.

5.4.4.Summary

In summary, diazepam was found to impair fear conditioning which is known to have similar neuroanatomical substrates to episodic emotional memory. There was also some evidence that diazepam reduced the effect of emotion on source memory at immediate test. However there was no evidence that diazepam affected consolidation of this information. Methylphenidate did not affect consolidation of source information either, although it may have increased the effect of positive emotion on source memory at immediate test. Emotional stimuli were judged with a more liberal recognition memory bias criterion. Overall the drugs had the expected effects on arousal, with methylphenidate increasing and diazepam decreasing arousal on most but not all of the control battery measures.

CHAPTER 6. GENERAL DISCUSSION

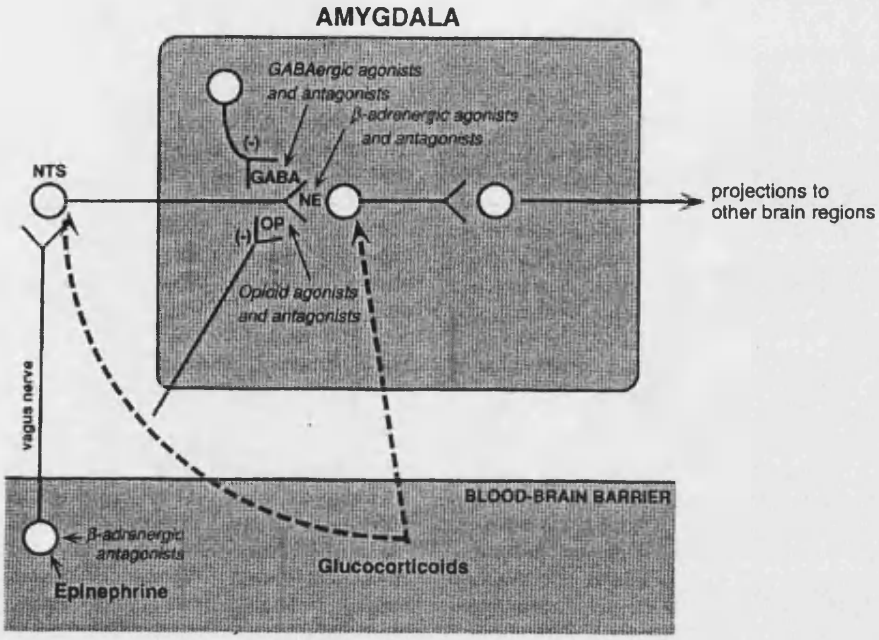
"It's been emotional ..."

Ritchie (1998):Lock, Stock and Two Smoking Barrels

This thesis began with a review of the literature about how emotional arousal influences the formation of long term explicit memories, and then reported four empirical studies. The hypothesis guiding the studies was proposed by McGaugh (e.g. McGaugh, Roozendaal, & Cahill, 2000), and is again depicted diagrammatically in Figure 71. According to this theory the influence of emotional arousal on memory occurs at the consolidation stage, and is mediated by activation of the amygdala by adrenergic and glucocortoid stress hormones. Within the amygdala this leads to noradrenaline release, which is modulated by opioid peptidergic and GABAergic systems. The amygdala noradrenaline release activates projections from the amygdala which modulate memory consolidation.

McGaugh's theory is based on extensive animal research. There has been less pertinent research with human subjects. The role of the amygdala in humans has been supported by a variety of lesion and functional neuroimaging studies. However, although the role of noradrenaline seems to have been backed up by some studies where noradrenaline action was antagonised pharmacologically with centrally acting ß-blockers, other psychopharmacological implications of the theory have not been thoroughly investigated with human volunteers. For example if reductions in catecholamine release reduce the effect of emotion on memory does increasing synaptic catecholamine levels have the opposite effect? If GABA modulates noradrenaline release in the amygdala would administration of a benzodiazepine have a similar effect to that of a noradrergic antagonist?

Figure 71: Diagram illustrating the theory of the neurochemistry of memory enhancement by emotional material: Reproduced from McGaugh (2000) p.1086



The experiments in this thesis were aimed at exploring and answering these questions. In total 192 volunteer participants took part in the four experiments. Further, more than 200 others contributed to the pilot studies which were carried out to develop the novel emotional memory tasks designed specifically for this research. A very brief summary of the emotional memory tasks administered in each experiment is displayed in Table 23.

Table 23: The emotional memory tasks reported from each experiment

Experiment 1	The Cahill and McGaugh (1995) story task	The Maratos sentences task
Experiment 2	The picture colour recognition task	The implicit memory sentences task
Experiment 3	The picture colour recall task	The LaBar and Phelps (1998) Taboo Words task
Experiment 4	The dual interval picture colour recognition task	Fear Conditioning

All the experiments also used a control battery of tests administered pre and post drug, measuring changes in arousal on various indices.

This chapter starts with a description of how the drugs altered arousal on these measures, and then considers how arousal effects may contribute to drug influence on emotional memory. This is followed by a discussion of how each drug manipulation affected emotional memory. Methodological issues that may have contributed to the findings are then reflected on. The chapter ends by drawing out implications of the findings, and putting forward suggestions for further research.

6.1 Arousal

Arousal is an ill defined concept, one which has been fractionated, both functionally and physiologically (e.g. Lacey, 1967; Robbins & Everitt, 1995). Whereas some psychologists have fractionated arousal, others have tried to reject it as a concept. For example Neiss (1988) proposed that it had outlived its utility. However, despite the difficulties in definition it is a concept that has face validity and is widely used in emotional memory research (e.g. Phelps et al, 1998; Cahill & McGaugh, 1995).

Emotional arousal can be thought of as the subjective intensity, or activation aspect of emotion. It is related to, but not necessarily the same as neural activation or physiological arousal. Thus it may be associated with cardiac measures, skin conductance, adrenaline levels, catecholamine release, and/ or electrophysiological activity. Although it is a fuzzy concept, emotional arousal has some utility in the prediction of how likely an event is to be remembered.

A main question was whether arousal modulated by the drugs would interact with arousal induced by emotional events to alter memory. Raising or lowering levels of arousal may be one mechanism by which drug manipulations modify emotional memory. Arousal might not affect memory in a straightforward linear fashion. Instead, as suggested by some of the evidence found in the current set of experiments, the relationship may be better described by an inverted U shape curve.

As various indices of arousal often do not correlate, arousal was measured on a variety of indices in each experiment: physiological (pulse and blood pressure), motor (finger tapping speed), subjective mood (affect grid and mood rating scale).

6.1.1.Methylphenidate

There was clear evidence that methylphenidate increased physiological arousal, as pulse and systolic blood pressure were significantly increased by the drug. Diastolic blood pressure (which is usually more stable than systolic blood pressure) increased in two of the three experiments. Motor arousal was increased on two of the three experiments where it was tested.

Subjective increases in arousal due to methylphenidate were found on the 'affect grid' during two of the three experiments, and on the Bond & Lader (1974) mood rating scales anxiety increased in two of the three experiments, and alertness in one of the three experiments. At least one subjective measure showed increased arousal in each experiment. Where significant increases were not found, the data tended to be in the expected direction. Therefore, overall it can be concluded that methylphenidate increases arousal levels.

6.1.2.Benzodiazepines

Benzodiazepine-induced reductions in arousal were most consistently found on the 'alertness' factor of the mood rating scale. This showed significant reductions in all four studies. The 'calmness' mood rating scale factor produced evidence for diazepam reducing anxiety in Experiments 3 & 4, and the Affect Grid showed reductions in arousal after benzodiazepines in Experiments 1 & 2, and the data were in the expected direction in Experiments 3 & 4.

The tapping task showed benzodiazepines reduced motor arousal in the first three experiments. The fourth experiment did not show a significant reduction probably because it used a lower (10mg) dose of diazepam than the (15mg) used in the other experiments. There was less consistency in benzodiazepine effects on physiological arousal: systolic blood pressure was reduced in two of the four studies, and pulse and diastolic blood pressure were unaffected by lorazepam or diazepam.

6.1.3.Propranolol

Propranolol had a similar profile to placebo on the control battery. The only measure where the propranolol group appeared less aroused was pulse rate, a standard effect of this ß-blocker.

6.1.4.Arousal effects on emotional memory measures

In summary methylphenidate increased and the benzodiazepines decreased arousal. That there was some variation between arousal measures supports the decision to measure arousal on several different indices. One question raised was whether the mechanism by which the drugs altered relative levels of emotional and neutral memory may have been through influencing emotional arousal, or the reactivity of emotional arousal to external stimuli rather than through modulation of consolidation.

The arousal measures *within* drug groups did not tend to show correlations with the emotional memory measures. These correlations were not presented because of the low power with 16 participants per group, and the problems of Type I errors. Where correlations were found they simply reflected group differences. For example the benzodiazepine treated participants were least aroused and had poorest memory.

Some evidence that both lorazepam and methylphenidate might reduce emotional reactivity came from the affect grids that were completed during Experiment 1. The ratings on the arousal dimension went up and down in the placebo group, changing on a group level in a way that suggested participants' subjective arousal levels were affected by what task they were doing. Both methylphenidate and lorazepam caused relatively stable arousal levels on this measure throughout the experiment. There was no evidence for similar effects

in Experiments 2, 3, and 4. This was because less affect grids were used and the placebo group were less labile.

Previous research (e.g. Cahill et al, 1994) has reported that the effect of β–blockers on emotional memory is not due to drug induced changes in emotional reactivity. This is deduced from a single measure that asks participants to rate how emotional they found the story stimuli on a scale of 0-10. This method was questioned in the introduction of Experiment 1, as it does not differentiate between arousal and valence aspects of emotion. Taking Mandler's (1975, 1984, 1992) perspective of these dimensions this can be thought of as the difference between cognitive evaluative knowledge of the relative desirability of the stimuli and the intensity of the experience. Therefore in Experiment1, although the same 0-10 scale was used for evaluation of the Cahill & McGaugh (1995) story task (for consistency with the literature), affect grids filled in before and after the story were also compared. The affect grid showed that both methylphenidate and lorazepam reduced the effect of the story on change in subjective arousal. There was also some suggestion that methylphenidate reduced the emotionality of the stimuli on the Cahill and McGaugh scale. Both drugs reduced the effect of emotion on memory compared with placebo on this task.

In the fear conditioning task (Experiment 4) there was some evidence that methylphenidate reduced the skin conductance response to an aversive stimulus (the unconditioned stimulus). This is another suggestion that methylphenidate may have reduced reactivity at encoding.

In Experiment 3 the possibility of drug effects on emotional response to the stimuli was investigated more thoroughly. Each individual stimulus was rated for pleasantness (valence) and arousal in the colour picture recall test and for arousal in the taboo words task. No effect of either diazepam or methylphenidate was found on any of these ratings. However both drugs caused some disruption of emotional memory in this experiment (see below.)

Taken as a whole therefore the findings from the four experiments suggest that the drugs did not affect *emotional reactivity* to the materials used. In other words changes in emotional response to stimuli cannot fully explain any subsequent drug induced differences on emotional memory. The effects of

methylphenidate and benzodiazepines on memory are due to more than a stabilisation of arousal.

6.2.Emotional memory

This section is about the observed results on the emotional memory tasks. These results will be discussed first briefly for placebo treatment, giving an overview of the pattern of memory performance that memory due to the active drugs will be compared with. This is followed by a discussion of the emotional memory effects of methylphenidate, then the benzodiazepines, and finally propranolol.

6.2.1.Placebo

6.2.1.1.Facilitation of memory for gist / central details

Memory for the gist or central information of emotional stimuli was reliably facilitated in participants given placebo. There was evidence from almost every explicit memory task that more emotional than neutral material was remembered. This was the finding for the Cahill & McGaugh (1995) story task and the Maratos sentences task in Experiment 1, the picture colour recognition test and the recognition of the primed words in the implicit memory sentences task in Experiment 2, the picture colour recall and recall of the LaBar & Phelps (1998) taboo words in Experiment 3, and the recognition in the dual interval picture colour task in Experiment 4.

Further, in Experiment 4, the placebo group also showed increased skin conductance responses to a coloured circle that had been paired with aversive noise compared to one which was not paired with the noise. Thus an emotion was 'remembered'.

In contrast no emotional enhancement was found for another implicit assessment of memory. In the perceptual priming task no evidence was found for an effect of emotion in the placebo group. It is thought that there is a facilitative effect of emotion on priming, but this effect is very small. An effect was found in the pilot study with a much larger sample size, and a facilitating effect of emotion on memory was found on the recognised words (which were a subset of the primed words.)

Overall, robust enhancement of explicit memory for emotional material was found in all four experiments.

6.2.1.2.Impairment of memory for source / associated colour

Source memory in this case is taken to mean the ink colour of the stimuli. This is a peripheral detail or an 'associate' of the central information in the picture tasks. This is in contrast with the way the term source memory is often used in psychology (to distinguish between episodic and other types of memory).
Emotion impaired memory for the source /associated colour. This was observed initially in the pilot run of the picture colour test and was replicated in Experiment 3 and the immediate test of Experiment 4, although not in the drug study of Experiment 2 (see section 6.3.1).
As predicted this effect was reversed and the source of emotional information was remembered better than that of neutral in the delayed test of Experiment 4 which took place seven days later.

6.2.1.3.The effects of delay

The task in Experiment 4 was designed to remove the possibility that a subset of the stimuli would gain extra rehearsal when they were retrieved at the immediate test. This was achieved by using a different set of pictures in a recognition test each time. Thus findings from this task provide evidence that these stimuli received extra consolidation. (Further discussion of possible explanation for this facilitation can be found in section 6.3.1 below).
This is in contrast to the other dual interval task in this series of experiments - the taboo words task of Experiment 3. More arousing 'taboo' words were recalled at *both* the immediate and delayed tests than non-arousing words. However the advantage of arousing words did *not* increase over time. This suggests that the other memory advantages of taboo words (e.g. their distinctiveness) were large enough to overshadow the relatively small effect of enhanced consolidation. As memory for the colour of emotional pictures did not have these clear advantages (immediate recognition memory for this part of the stimuli was actually made worse by emotion), the relatively small effect of enhanced consolidation emerged.

6.2.1.4.Memory retrieval bias criterion

A robust finding from the recognition memory part of the colour picture test was the effect of emotion on the bias criterion. Bias criteria were lower for emotional than neutral pictures. Thus participants were more willing to accept they had seen emotional pictures in the study session, and less willing to reject emotional pictures they were unsure about. This was initially discovered in the pilot run of the test and was subsequently found to be a robust effect, replicated in Experiment 2 and both the immediate and delayed tests of Experiment 4. This effect of emotion on bias was unchanged by any of the drug manipulations used (diazepam, propranolol or methylphenidate). This was true despite retrieval occuring while the participants were under the influence of the drug in Experiment 2 and the immediate test of Experiment 4 but not during the delayed test in Experiment 4.

This replicates other findings that there is an increased bias (e.g. Windmann & Kutas, 2001) or false alarm rate (e.g. Maratos, Allan, & Rugg, 2000) for emotional material.

6.2.1.5.Fear Conditioning

In the Fear Conditioning task in Experiment 4, placebo participants showed clear evidence for conditioning. Fear conditioning indexed by a skin conductance response has been shown to be an arousal motivated learning task that is dependent on the participant having an intact amygdala. Skin conductance in response to a stimulus that had previously been presented paired with the aversive stimulus, was compared to skin conductance in response to a stimulus that had never been presented paired with an aversive stimulus. Thus there was clear evidence that the participants had learned that the former stimulus predicted the aversive event. The conditioned response did not extinguish during the experiment.

6.2.1.6.Story Task

The story task designed by Cahill and McGaugh (1995) was used in both Experiments 1 and 2. In Experiment 1 the pattern of results after placebo was similar to the pattern that has been described for healthy undrugged participants

in the literature. Memory for the middle *emotional* section was superior to memory for either the beginning or the end *neutral* sections. However in Experiment 2 memory for the middle emotional section was not the highest, memory for the final section was. In a pilot test, performed before Experiment 1, ratings of the slides by 100 independent volunteers (appendix 1) indicated that two of the three slides in this final section were emotional. During Experiment 1 it was found that the middle emotional section was remembered best because of the effect of a single slide 'slide 8'. It was argued that this was because it is the only picture slide that was emotionally *arousing*. As discussed in chapter 2 it is qualitatively different because the picture itself contains emotional information, whereas the other slides are only emotional in conjunction with the narration. In Experiment 2 this 'slide 8' effect was not observed. Possible reasons for this (discussed in chapter 3) were that there were so many other emotionally arousing pictures presented in Experiment 2 (during the colour picture test). This may have acted to reduce the 'slide 8 effect' either by desensitising participants to emotional pictures or by the non- emotional process of making it less distinctive.

In summary healthy volunteers given placebo showed reliable evidence for facilitation of explicit memory for the central information of emotional stimuli compared to neutral stimuli. This was across a range of stimuli words, pictures, and stories. Memory for the peripheral information of source was impaired compared to neutral material when memory was tested shortly after testing, and facilitated at delayed testing. There was good evidence for fear conditioning.

6.2.2.Methylphenidate

6.2.2.1.Relative impairment of memory for high arousal stimuli

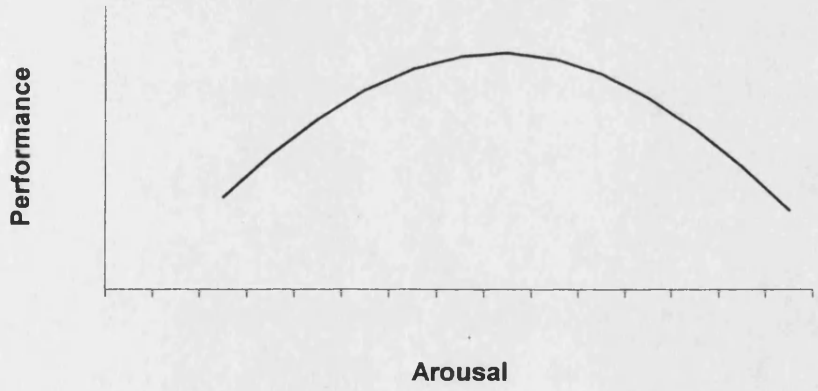
On some of the tasks in this series of experiments 40mg methylphenidate reduced the effect of emotion on memory. In Experiment 1 methylphenidate attenuated the facilitation of memory by emotion in the story task[10]. The source memory data from the picture colour test in Experiment 3 reproduced this

[10] There was some suggestion that methylphenidate also reduced emotional reactivity to this story.

finding, whereby unlike placebo participants given methylphenidate did not differ in source memory for emotional and neutral pictures.

It has been argued (section 1.2.2.) that the relationship between arousal and memory performance can be described by an inverted U shape function as illustrated in Figure 72. As arousal (and associated catecholamines) increase, performance increases until it reaches an optimal level. If arousal and catecholamine levels continue to increase above this point, performance decreases. This theory has found support in animal studies of the effects of stimulant drugs such as adrenaline and amphetamine (review McGaugh, 1973), which show that although memory increases in a dose response fashion at low doses (e.g. 0.2 – 2.0mg /kg for rodents), higher doses (e.g. 3.0-10mg/kg) impair learning of an inhibitory avoidance response.

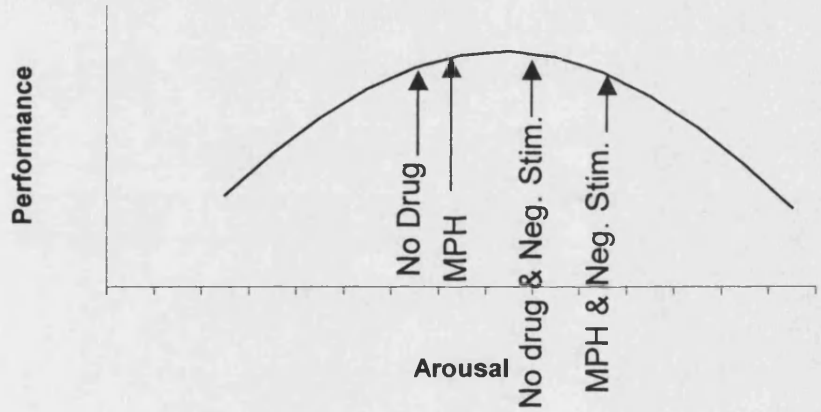
Figure 72: Inverted U shape function. As arousal increases performance may improve, to a point, beyond which performance may deteriorate.



Therefore it could be argued that the combination of highly arousing, negative emotional stimuli with the stimulant drug methylphenidate raised arousal above optimal levels. This is hypothetically depicted in Figure 73. Methylphenidate would itself move participants along the arousal scale of that curve compared with pre-drug. When exposed to arousing stimuli they are more likely to move

further along the curve to where performance deteriorates. In this way memory for these emotional stimuli would be reduced by methylphenidate.
In support of this, performance detriments in the methylphenidate group were only found for the very arousing (as opposed to merely emotional) material. For example, in the Cahill & McGaugh (1995) story task there is only a single slide where the performance of the methylphenidate group is clearly poorer than the placebo group[11]. This is the highly emotionally arousing 'slide 8' which, as already mentioned, is thought to be qualitatively different to the other 'emotional ' slides in the series.

Figure 73: Hypothetical effects of methylphenidate and negative emotional stimuli on the inverted U shaped function. (Neg stim = negative stimulus, MPH = methylphenidate)



Similarly, it could be argued that the explanation for the findings of Papps et al. (2002) was that increasing catecholamine levels with reboxetine may also have pushed participants past the optimal level of arousal and thus impaired rather than enhanced emotional memory.

6.2.2.2.Relative facilitation of memory for intermediate arousal level stimuli

The idea of the inverted U shaped function is also supported by the effect of methylphenidate on memory in the picture task of Experiments 3 and 4 where a

[11] Although looked at in another way it is this slide where the methylphenidate group showed their greatest memory.

'positive' class of emotional stimuli was used. The pictures in the positive sets tend to receive intermediate arousal ratings, between neutral and negative pictures. As was discussed previously (section 3.2.1.4) it is thought to be the 'arousing' nature of stimuli rather than their valence that modulates memory consolidation. In experiment 3 recall of these (mid arousal) positive pictures was increased by methylphenidate. In experiment 4 (immediate) source memory for the (mid arousal) positive pictures looks more like that for negative pictures after methylphenidate, (c.f. the placebo group where positive and neutral are similar). In both these instances, after methylphenidate memory for the (mid arousal level) positive pictures was similar to the placebo groups' memory for the (high arousal level) negative pictures. Therefore it could be argued that the intermediate arousal stemming from the pictures combined with the raised arousal caused by methylphenidate brought participants towards the optimal level of arousal.

A similar conclusion could be drawn from the fear conditioning data from Experiment 4. Although it is widely accepted (e.g. Grillon & Hill, 2003) that magnitude of response to an unconditioned stimulus affects the magnitude of conditioned responses, the methylphenidate group showed smaller skin conductance responses to the aversive unconditioned stimulus, and this was not accompanied by a corresponding decrease in size of responses to the conditioned (coloured circle) stimulus. So again methylphenidate appeared to have increased the effect of emotional arousal on memory.

The literature review (section1.2.2.) was critical of attempts to make sense of emotional memory data using the hypothesised inverted U shaped relationship between arousal and memory performance. This was partly due to the frequent misquotation of the Yerkes Dodson Law, and also because if several curves are hypothesised for different levels of task difficulty (see chapter 1.2.2) the hypothesis becomes unfalsifiable. However its is argued that postulating this type of relationship is useful in the present circumstances. This is because (1) the data are from similar stimuli in the same test, differing only in arousal level (i.e. emotion category), and therefore task difficulty is not such an issue; (2) the inverted U shaped function describes the findings better than a linear relationship.

6.2.2.3.No effect on consolidation?

In all these examples of tests where methylphenidate increased memory for arousing stimuli, retention was tested within 1hr of the study session. Both methylphenidate and emotional arousal were theorised to act on memory during consolidation. However on the two tests explicitly designed to test the influences of consolidation (Experiment 3: Dual interval taboo words task and Experiment 4: Dual interval picture colour task), methylphenidate and placebo produced the same pattern of memory performance *after* the delay interval. In the taboo words task (discussed below section 6.2.2.4) there was no evidence for any significant difference between either drug group and placebo in *pattern* of recall performance. Thus no evidence has been found to suggest that methylphenidate affects consolidation of emotional material.

6.2.2.4.No emotional memory effect

There were two tasks where the same pattern of memory performance was observed for methylphenidate as for placebo. These were the Maratos emotional sentences task from Experiment 1 and the LaBar & Phelps (1998) Taboo words task from Experiment 3. On these two tasks there was evidence for emotional facilitation in all the drug groups tested. There was a noticeable difference between these tests and the tasks where methylphenidate affected the balance of emotional and neutral material remembered. This difference is the use of language versus picture or aversive sound stimuli. This may be a critical distinction. As discussed after Experiment 1 (section 2.4.4) and before Experiment 2 (section 3.1.2) there are theoretical reasons for thinking that an emotional memory system may be more likely to be activated by pictures than words. Emotional memories may be 'situationally accessible' rather than 'verbally accessible' (Brewin, 2001). LeDoux (1999) describes how visual stimuli may be able to use subcortical physiological pathways to the amygdala, which may work faster and be less subject to rationalisation than the pathways taken by language stimuli. This may mean that language stimuli are more likely than pictures or simple sounds to benefit from mnemonic strategies such as elaboration or semantic categorisation.

These types of processes would have contributed to the memory facilitation of the majority of the emotional pictures in the Cahill & McGaugh (1995) story task

in Experiment 1. This explains why an interaction between the methylphenidate and placebo groups with the emotionality of material was so difficult to detect and was not observed using the new division of slides. The methylphenidate and placebo groups also showed very similar results in the recognition memory part of the dual interval picture colour memory task in Experiment 4. However ceiling effects prevent conclusions from being drawn from this.

6.2.2.5.Neutral Stimuli

The effect of methylphenidate on memory for neutral stimuli was less clear. It had been hypothesised that methylphenidate might facilitate memory for neutral stimuli. However, reports in the literature of this memory facilitation at this dose with healthy human subjects are sparse. It was accepted that facilitation like this would be hard to find, as participants in the current series of experiments were likely to be performing at their optimum level for neutral material already.
All the differences in memory for neutral material that were observed were very small (mostly nonsignificant), and therefore it might be concluded that methylphenidate does not make a significant *group* difference to episodic memory for non-arousing material in unfatigued healthy humans.

6.2.2.6.Individual differences in response to methylphenidate

One notable feature of the data was the variability in scores of participants given methylphenidate. Individual differences in response to stimulant drugs in healthy volunteers have been reported before (Fleming et al, 1995; Mehta et al, 2000; Mattay et al, 2000) and have been related to personality characteristics, cognitive abilities, and possible genetic variation. Individuals who are low in novelty seeking (Fleming et al, 1995) on baseline working memory (Mehta, 2002, Mattay et al. 2000) improve on some cognitive tasks when given methylphenidate or dextroamphetamine. Other participants who are higher on these measures are impaired by these stimulants. These characteristics have been thought to be associated with dopaminergic function and it has been proposed they might be associated with allelic variation of dopamine system genes (Mattay et al 2000). Although this has not been investigated systematically with emotional memory it could be hypothesised that a similar range of individual differences might exist. Therefore another point is that each

individual may have a different optimal dose of methylphenidate, and therefore a different curve to describe their cognitive response to stimulant drugs. To explore this possibility, one would need to carry out a dose response study with large participant numbers. As each person would ideally have their own dose response curve drawn (to allow for the possible individual differences in dopaminergic tone), enough participants would have to be included to cover every permutation of possible dose and order of testing. However this is beyond the scope of the present thesis.

In summary, on average participants under the influence of methylphenidate showed reduced emotional memory advantage for some of the most arousing stimuli. However for most of the tasks, memory in the methylphenidate group was not clearly different to the placebo group. In the tests where a difference was found there was no evidence that it was due to an effect of methylphenidate on consolidation. Therefore there was little evidence that humans react in the same way as rats to a dose of stimulant drug after a learning task. However as some of the findings can be explained in terms of the inverted U shaped curve found by some animal studies the null hypothesis is not supported either. To use a tired academic cliché - more research is needed.

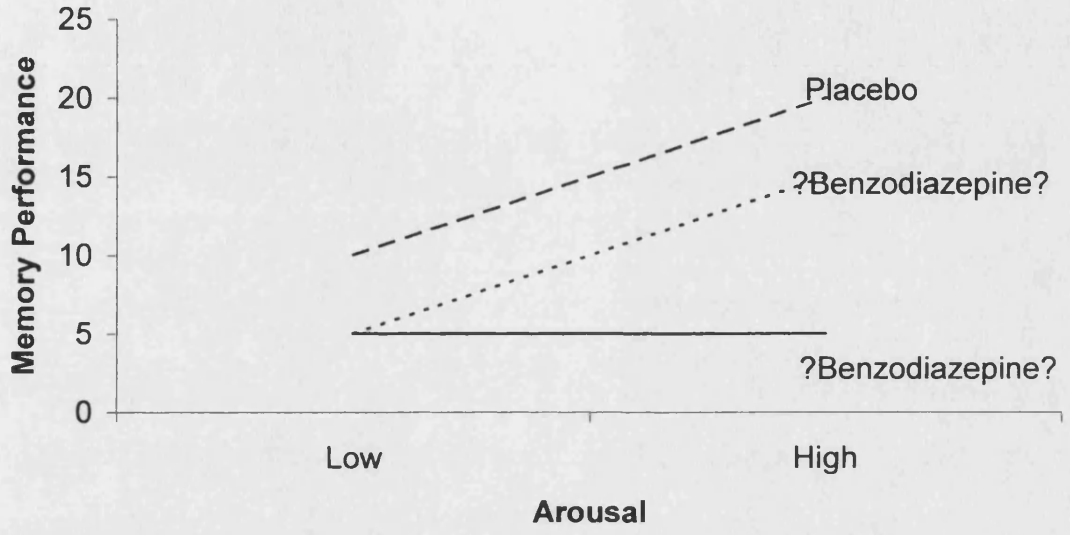
6.2.3.Benzodiazepines

6.2.3.1.Standard Mnemonic effects

Benzodiazepines reliably impaired explicit memory in all four empirical studies. 1.5mg lorazepam and 15mg diazepam (equivalent doses) (Hardman et al 2001) impaired explicit memory in *every* memory test. Further, perceptual priming (the index of implicit memory used in Experiment 2) was unimpaired despite impaired explicit memory for the same stimuli. These findings replicate previous studies of diazepam disrupting explicit memory while leaving implicit memory intact (e.g. Vidailhet et al, 1996). The smaller (10mg) dose of diazepam was used in Experiment 4. This dose slightly, impaired prose recall, and picture recognition, but significantly impaired source memory and fear conditioning. Of more interest to the current thesis was whether these drugs would disproportionately impair memory for emotional compared to neutral material. In

other words (as seen in Figure 74) would the *pattern* of memory performance across emotional and neutral stimuli be altered relative to placebo?

Figure 74: Would the pattern of memory performance across emotion categories be the same as placebo (dotted line) or different (solid line)?



6.2.3.2.Benzodiazepine blocking of emotional memory

Experiment 1 found that lorazepam disproportionately impaired memory for the middle 'emotional' section of the story task designed by Cahill & McGaugh (1995). This replicated some preliminary work by Curran and Zangara (2000). In Experiment 2 the recognition part of the implicit memory (sentences) task showed a trend towards emotional facilitation for placebo. Diazepam (and propranolol) blocked this. In the colour picture recognition task of Experiment 2 the diazepam group did show facilitated recognition memory for the highly arousing negative stimuli. However, unlike placebo controls, they showed *no* facilitation of recognition memory by the (intermediate arousal level) positive pictures[12].

[12] In the picture colour recognition test there was also no evidence for a difference between emotion categories. However this could be attributed to a floor effect, there was also no difference between emotion categories for the placebo group in this part of the task in this experiment

Memory for positive pictures was also disrupted by diazepam in the picture colour recall task in Experiment 3. Memory for the colour (source) associated with emotional pictures is peripheral information, usually impaired by emotion. However in Experiment 3, 'positive' was the only category where diazepam treated subjects performed above chance levels on (colour) source memory. Thus in a task where the standard effect of emotion was to facilitate recognition/recall and impair source memory, the diazepam group acted the opposite way but just for the positive (medium arousal level) pictures. In the dual interval picture colour task from Experiment 4, at immediate test, source memory in the diazepam group was similar across emotion categories, but in the delayed test negative emotional pictures have a memory advantage in this group – i.e. at delayed testing the pattern of performance was the same as placebo.

In Experiment 4, diazepam clearly impaired the learning of a conditioned fear (skin conductance) response. Classical conditioning is usually thought to be an index of implicit memory, and fear conditioning been found to depend on similar neuroanatomical structures to emotional memory. Thus this is more evidence that benzodiazepines impair a slightly different form of the emotional memory mechanism.

Since this series of experiments was completed a paper has been published by Buchanan, Karafin, & Adolphs (2003) which asked a similar question to this thesis. They gave participants placebo or 0.25 mg triazolam, and analysed memory for gist and detail information of pictures and their captions after a 48 hour delay. The pictures fit into neutral, negative and positive categories and some of them were taken from the IAPS like the pictures in series of experiments. Buchanan et al's 'gist' information was central information about the stimulus and thus can be thought of as analogous to the recall or old/new recognition tasks, used in the current series of experiments. Their 'detail' information can be thought of as analogous to our picture colour/ source memory (i.e. both are peripheral to the main subject of the stimulus and thus emotion was expected to impair memory for both.)

Buchanan et al (2003) found their participants who were given triazolam performed disproportionately well on multiple-choice questions about the detail information of unpleasant stimuli and disproportionately poorly on the gist

information of these stimuli. This adds to the evidence from the current thesis and from the animal work by McGaugh and colleagues reviewed in chapter 1. All this work leads to the conclusion that benzodiazepines do impair emotional-arousal modulation of memory.

6.2.3.3.The difference between positive and negative pictures

The current series of experiments found more evidence for benzodiazepine induced impairments to memory for the (intermediate arousal level) positive pictures than the more arousing negative pictures. Why was the memory for the mid arousal level positive pictures relatively impaired by diazepam, whereas memory for the highly arousing negative pictures, tended to be facilitated in this group? There are three possible reasons (1) Perhaps the memory modulating arousal was so strong for the negative pictures it resisted impairment by the benzodiazepine manipulations. (2) Perhaps memory for the negative category of pictures was helped more by the pictures' membership of a semantic category than the positive pictures. (3) Perhaps the mechanisms by which positive and negative pictures are facilitated are different and benzodiazepines only impair the formation of positive memories.

(1) As reported in previous chapters, ratings of emotional arousal induced by positive pictures tend to be lower than those of negative pictures. This was a feature of the selection of pictures available in the IAPS (Lang et al, 1999). The pictures in the IAPS that receive extreme negative ratings tend to also get high arousal ratings despite Lang et al having made explicit effort to fill the low arousal / unpleasant emotion quadrant of affective space. This issue is discussed in their manual. There are also relatively few high arousal extremely positive pictures when the data for both genders was considered. Although there are a few of these (e.g. pictures of extreme sports), the studies in the current thesis required 32, and the pictures selected also had to fit requirements of matching the versions. Thus the discrepancy in arousal induced by the emotion categories was unavoidable.

The benzodiazepine doses used in these studies were limited because too high a dose would have caused excessive amnesia. resulting in floor effects. If nothing was remembered, no conclusions could be drawn about how the different emotional categories of information were remembered. Very high

doses would also have resulted in excessive sedation and ultimately sleep. Therefore perhaps the doses used were high enough to block the facilitation by the positive pictures, which induced intermediate levels of arousal, but not high enough to block the facilitation caused by the highly arousing negative pictures. At a different level of explanation perhaps the negative pictures induced such a high level of catecholamine release a larger dose of diazepam would have been needed to inhibit synaptic action.

This can be assimilated with explanations evoking a U shaped curve as described in the previous section. If, while viewing negative pictures emotional arousal levels were around the asymptote of this curve, a large drug induced decrease in arousal (or catecholamine levels) would be needed to alter memory levels. However for positive pictures arousal may have been just near the optimal level, on a sloping side of the curve, and therefore the benzodiazepine manipulation would impair memory.

(2) The memory enhancing effects of a coherent semantic category are well known, and as proposed by Phelps et al (1998) emotional stimuli fit a semantic category of 'emotional stimuli'. How this mnemonic advantage is affected by benzodiazepines is debateable. However it is not part of the emotional memory system. In the colour picture test in the current series of experiments it is possible that the negative pictures used might gain more advantage through category association that the positive ones. This is because participants may be more familiar with emotionally positive photographs. For example we are frequently exposed to pictures of beautiful scenery, cute children, and joyful people. Therefore participants may be less likely to notice they fall into a category of positive things distinct from the category of neutral things, as both are common photographic subjects. Thus the main memory enhancing difference between the positive and negative pictures would be the level of emotional arousal. In contrast, a competing advantage for the negative pictures may be that they fit into a semantic category of 'horrible things'. Thus while benzodiazepines may have removed the advantage to do with emotional arousal perhaps they had no influence on the extra category advantage of the negative pictures.

(3) As was discussed after the pilot study before Experiment 2 (section 3.2.1.4) there is a possibility that positive and negative pictures facilitate memory by

different mechanisms. Perhaps benzodiazepines only impair memory facilitation by positive stimuli. This explanation is unlikely because there was some evidence that blockade of emotion facilitation by benzodiazepines was not valence specific. For example the Cahill and McGaugh task in Experiment 1.

6.2.3.4.No emotional memory effect of benzodiazepines?

On some of the tests in the series the benzodiazepine manipulation did not appear to disproportionately impair memory for emotional material.
For example the data from the diazepam group in the picture recall task in Experiment 3 was in the pattern usually expected of the placebo group (negative > positive > neutral). (The placebo group did not show this pattern in this particular experiment). Notably the diazepam group also produced this pattern of data in the 'hit rate' of the picture recognition tasks in Experiments 2 & 4. In these tasks false alarms were also produced and counted. The elevated false alarm rate brought the discriminibility index down for positive pictures in Experiment 2, and negative pictures in the delayed test of Experiment 4.
The other tests where the benzodiazepine group showed the same *pattern* of memory as the placebo group were the Maratos emotional sentences task in Experiment 1 and the LaBar & Phelps (1998) taboo words task in Experiment 3. Although the diazepam group showed impaired memory in all categories, the amount they recalled in each category was in proportion to the amount the placebo group recalled. As discussed (section 6.2.2) above, the same was true of the methylphenidate group. This suggests that it may be due to some feature of the task, rather than an effect of the drug. Possibly memory was facilitated by non-emotional mechanisms that covary with emotionality. These (e.g. levels of processing manipulations; Curran, 1999) tend to have similar effects in participants given benzodiazepines as those given placebo although there is an overall memory impairment in the benzodiazepine group.
Although good evidence was found for impaired explicit but intact implicit memory in the priming task in Experiment 2, the diazepam group showed no differential effect of emotion on implicit memory. However, as even the placebo group did not show enhancement of priming by emotional material it was not possible to draw conclusions about how diazepam affected emotional influences on implicit memory from this task. As the fear-conditioning task

showed that diazepam does impair conditioning of a skin conductance response this is evidence for a dissociation between these two types of implicit memory. This dissociation is widely acknowledged (see review by Squire, 1992). Although both come under the Tulving's term 'implicit memory', perceptual priming and classical conditioning are very different qualitatively. Squire (1992) discusses how the different forms of implicit memory have diverse neurological substrates. This is in contrast to declarative memory, which he proposed relies on the hippocampus whether semantic or episodic. Squire and colleagues have discussed the dissociation between conditioning and perceptual priming in terms of neuroanatomy. That these two types of implicit memory have been found here to be distinguishable pharmacologically with benzodiazepines is further evidence for a dissociation.

As the fear conditioning task only has an emotional rather than a true neutral condition (see discussion section 5.4.1) it is not known how much this fits an emotional versus neutral distinction. However it is intriguing that diazepam may impair (emotional) fear conditioning, and not (non-emotional) perceptual priming.

6.2.3.5.Effects of delay?

As discussed previously (chapter 4 and chapter 5), the standard memory effect on the dual interval picture colour task is impairment of memory for the colour (source) associated with emotional material at immediate test and facilitation at delayed test. This was the pattern observed in the placebo group. For the immediate (30mins) source memory component of experiments 2, and 4 there was little difference between emotions in the diazepam group[13]. However in Experiment 3 a slightly longer interval (study - test: aprox 1hr) was used, and positive (mid arousal) pictures had a memory advantage. For the longer (seven days) delay in Experiment 4 the highly arousing negative pictures were most accurately attributed to source – i.e. there was (normal) emotion facilitation after the consolidation period. Thus it seems that as the time between study and test increased the diazepam group was more likely to show a relative memory advantage for the source / colour of emotional material.

[13] Although it should also be noted that all source memory performance was around chance levels in Experiment 2.

Therefore if benzodiazepines do equalise memory for the associated source or details of different emotional categories of stimuli this does not happen during consolidation. Contrary to McGaugh's model the longer the time between encoding and retrieval the more likely that participants under the influence of benzodiazepines (just like placebo participants) will show an advantage for emotional material. Thus benzodiazepines may in some way disproportionately influence the amount of emotional information encoded, and not affect consolidation. This also fits with the established finding discussed in the literature review (chapter 1) that benzodiazepines improve rather than impair memory when given post-encoding (e.g. Weingartner et al, 1995).
In both the day seven test in Experiment 4 of the current thesis and the work described by Buchanan et al (2003) memory was tested after the benzodiazepine would have cleared from the body. Therefore there is a possibility that the facilitating effect of emotion in the delayed tests was due to some effect on retrieval that was blocked by the benzodiazepine in the immediate tests. A possible way to test for this is to have further groups who receive benzodiazepines at retrieval. (Weingartner, Sirocco, Curran, & Wolkowitz, 1995) argue that benzodiazepines may influence retrieval particularly for stimuli that fit into a category by a 'drug induced change in strategy of searching well established semantic memory'.
To sum up, there was enough evidence that benzodiazepines impair emotional memory to throw doubt on the null hypothesis. However the evidence may not be strong enough to firmly reject it. Additionally the theory put forward by McGaugh proposes that benzodiazepines alter the noradrenaline modulation of memory at the consolidation stage. This was not supported by the data.

6.2.4.Propranolol

Experiment1 raised the possibility that neither methylphenidate nor lorazepam has an effect on emotional memory. As it is not possible to prove a negative (evidence can be found to refute, but not accept a null hypothesis), propanolol was included in Experiment 2 as a negative control. There are several reports in the literature (Cahill et al, 1994; Nielson & Jensen, 1994; van Stegeren et al. 1998; O'Carroll et al, 1999b) that propranolol impairs human memory for emotional material whilst leaving memory for neutral material intact. Therefore it

was possible to test if the pattern of memory performance in the drug group of interest was different from in the propranolol group (as opposed to the same as the placebo group.)
However, in the emotional memory tasks used in Experiment 2 the propranolol group did not show evidence for a different pattern of performance to the placebo group. In the story task, where propranolol has previously been shown to disrupt the emotional facilitation effect, there was actually slightly clearer emotion facilitation in the propranolol than placebo group.
The tests in Experiment 2 which were designed for this thesis, showed there was facilitation of recognition memory following propranolol for the emotional (negative and positive) categories of pictures. Although there was no effect of emotion on source memory in this group this was also observed in the placebo group on this occasion.
This leads on to the question of whether the facilitation of memory observed in these tests was mainly due to the modulation of consolidation by noradrenaline in the amygdala, or some other mechanism. Theoretically if it were caused by noradrenaline action it should have been impeded by propranolol. Therefore the emotional material may have gained its advantage by being more attention grabbing, belonging to a cohesive semantic category, receiving more rehearsal, deeper encoding, or some other established psychological process. It may be significant (see section 6.3.2 below) that in the parts of the task designed to reduce these types of influence (the colour / source identification and the priming) the placebo group did not show evidence of an emotional mechanism either.

It is possible that there are more findings where human emotional memory has not been modulated by propranolol. Perhaps there is a bias in the literature that is published in peer reviewed journals. Two papers came out at a similar time, looking at the relative effects of central and peripheral ß- blockade, using the same story task. The paper that found the hypothesised effects of propranolol (van Stegeren et al, 1998) can be found in Psychopharmacology, whereas the one where the effects were not found (O'Carroll et al. 1999a) appears in Journal of Psychopharmacology

In summary Experiment 2 provided no evidence that propranolol impairs emotional memory in humans.

6.3.Methodological Reflections

"Hindsight is always twenty- twenty"
Billy Wilder 1906-2002

The studies reported in this thesis are a set of laboratory experiments. They were designed to place as much control as possible over experimental variables. All four studies were double blind and placebo controlled. 'Double dummy' procedures were used where necessary because of the different absorption times of drugs, to disguise the identity of the drug from both the researcher and participant. Volunteers were randomised into groups, with the only exception that in the later studies the numbers of males and females in each group were controlled. Thus the drug conditions should have been equivalent, differing only in the drug taken.

Independent samples designs were used. The main reason for this was that emotion was expected to have more influence on memory when learning was incidental rather than intentional. In principle a small effect of emotional facilitation might be masked by intentional learning strategies used by volunteers. If a repeated measures design was used it would be difficult to conceal that a memory test was in progress. The second time participants saw the stimuli they would probably try and remember it. The independent samples design also has the advantage that fewer stimuli are required and therefore higher quality stimuli can be selected. There was however the disadvantage that individual differences among participants could have masked experimental effects. This was particularly the case with participants given methylphenidate (see above: section 6.2.2). This may be important in the field of emotional memory research as there is evidence that individual differences such as gender (Cahill & van Stegeren, 2003; Canli et al, 2002) and personality (Canli et al. 2001) may affect the function of the emotional memory system.

The emotional conditions were also carefully controlled in order to make them as comparable as possible and this involved designing some new tasks.

6.3.1.Task selection and design

A recurring theme throughout this thesis has been the difficulty of controlling for systematic differences between emotional and neutral test material. Emotional stimuli tend to have many properties which may confer a mnemonic advantage. For example, as discussed throughout this thesis, they may be more distinctive, belong to a cohesive semantic category, be more self referent and induce participants to encode them more deeply or rehearse them more often. These are all well studied means of memory enhancement and interesting for study in their own right. The effects of both methylphenidate and the benzodiazepines on these processes are good topics for research. However they are distinct mechanisms from the area of interest of this thesis which was the noradrenaline modulated consolidation of memory.

6.3.1.1.Cahill and McGaugh task and Maratos sentences (explicit and implicit)

Much of the experimental design work of this thesis involved trying to find ways to control these effects. The tasks used in Experiment 1 had been previously used, and the authors of those tasks had different ways of addressing this issue. Cahill & McGaugh (1995) originally designed their story task to have two versions, an emotional version and a neutral version. The slides in the two versions were identical, and their emotional or neutral meaning came from the audio narration. However this introduced other differences which may have had a mnemonic effect. For example the emotional story was a coherent story, but the neutral story was more like a set of loosely related events. Because the emotional version fits a story schema of beginning which introduces characters, middle where the action happens and end which wraps up and concludes it may be easier to remember. In practice most authors only use the emotional story and compare the beginning and end 'neutral' sections with the middle 'emotional' section as was done in Experiments 1 & 2. Here the material in the two emotion categories is completely different with all the implications this entails.

The Maratos sentences were designed by Maratos et al. (2001) to overcome some of these problems by placing the same neutral word in different emotional contexts. However some participants responses raised the issue of whether the

information encoded and consolidated was an emotional-chunk rather than just the neutral word (see discussion of Experiment 1 section 2.4.4.2). Therefore other properties of the material that varied systematically with emotion may have helped to cue recall, contributing to the robust emotion effects that were observed, and hiding the subtle effects of any emotional memory mechanism. The concept of embedding neutral target words in emotional sentences was used to make a perceptual priming task in the implicit memory sentences task in Experiment 2. This should have reduced the problem of participants using an emotional chunk of information to cue recall. In perceptual priming the cue is the visual aspect of the word stem. If memory is truly implicit the semantics probably have little influence at retrieval. Thus the main difference between the conditions should be the emotional state at encoding. However the effect of emotion on memory was no longer detectable. The recognition memory part of the task is subject to the same criticism as the free recall Maratos sentences task used in Experiment 1.

6.3.1.2.Picture Colour Tasks

The picture colour task designed for this thesis (Chapter 3) was another attempt to overcome the same set of problems. The to-be-remembered material was the colour of the stimuli, which was constant across emotional and neutral stimuli. Although the predicted effect (impaired memory for the colour associated with emotional stimuli) was present in the pilot task, it was not observed in the subsequent drug study (Experiment 2). Possible reasons for this included (1) low level of colour memory, and (2) intentional encoding of colour by participants.

(1)Some participants did not remember a lot of source/ colour information. The variation between participants was also very high. Although some participants got most of the source/colour information right, others attributed most of the pictures to the wrong source. Therefore any difference between the emotion categories was lost amongst this variation.

(2) To try and increase the mean level of source memory – the low level had been noted even in the preliminary pilot work (not reported in this thesis) - participants were instructed to remember the ink colour before the study phase of Experiment 2. However incidental learning is more likely to produce emotion

effects on memory than intentional memory. The instruction may also have prevented the colour being a peripheral detail and made it more central. Alterations made to remedy this problem in Experiment 3 were the use of a rating scale to draw participants away from the idea that they were doing a memory test. Participants were also asked to report the colour information straight away to ensure it was encoded. This seemed to help. Average level of source memory rose above the chance level for the placebo and methylphenidate groups. However, colour memory was still close to chance in the diazepam group.

For Experiment 4 an idea was taken from Wilding & Rugg (1996) and at encoding each colour was matched with a judgement the participant had to make. This made the test much more like a conventional source memory task. At retrieval participants could do the source memory judgement by recalling what they were thinking of at the time they studied the picture – the memory context or episode. This effectively increased the level of colour (source) memory.

However there is the possibility that the alterations that made the colour / source more memorable may also have changed the nature of the task. Mayes et al. (1992) distinguishes between interactive and independent contexts. Interactive contexts are part of the meaning of stimuli, whereas independent contexts are independent. It is possible that in the earlier Experiments 2 & 3, the colour is *independent* of the picture, whereas in Experiment 4, because of the task demands, the source becomes *interactive*. It is further possible that the emotion of the picture influences the level of 'interaction' with the source. This may therefore be another extraneous mechanism that determines how much colour / source information is remembered.

It was originally decided to test memory for the source / colour, (a peripheral detail) of emotional pictures because the relative amounts of central and peripheral information remembered make emotional memories qualitatively different from neutral memories. However as this pattern of results can typically be observed soon after encoding, it makes sense to think about it in terms of arousal restricting attention. It is likely that this 'arousal induced myopia' is unrelated to the hypothesised amygdala based noradrenaline modulated consolidation mechanism of emotional memory. Therefore it may be

problematic to draw conclusions about drug effects on this system, based on drug effects on peripheral source / colour information. If either benzodiazepines or methylphenidate had altered the way this effect reversed over time in the dual interval task in Experiment 4 (the reversal was hypothesised to be due to differential forgetting in the two categories) this would have been a better reason to draw conclusions about consolidation (see section 6.3.1.3 below).
In Experiments 2 and 4 in addition to the colour / source memory test there was also a recognition test for which pictures had been studied. In Experiment 3 a free recall task was used. The recognition and recall parts of the task depend on completely different stimuli being remembered in each emotion condition. I.e. a completely different set of pictures were used for the neutral condition, the negative condition and the positive condition. Therefore these stimuli are bound to have other properties that covary with emotionality. This is particularly a problem in the recall task where internally generated cues must be used to retrieve the pictures. Thus this should be remembered when drawing conclusions about emotional facilitation, or lack of it, from the recall and recognition data.
Ceiling effects emerged in the recognition memory part of the picture colour tests in Experiment 2 and (particularly) the immediate (but not delayed) recognition part of the dual interval task in Experiment 4. The ceiling effects may well have disguised a facilitating effect of emotion on old/new discriminability. Therefore conclusions should not be drawn about the lack of this effect in the two tests where ceiling effects were a problem. (There was a facilitating effect of negative emotion on discriminabilty after the delay on Experiment 4) Bias effects (see section 6.3.1.4 below) are thought to be less affected by this problem because (1) false alarms were definitely nowhere near ceiling and (2) the same pattern of bias was observed in the delayed recognition task of Experiment 4 where ceiling effects were clearly not an issue.

6.3.1.3.Dual interval tasks

When LaBar & Phelps (1998) designed the Taboo Words Task, they accepted that there are many other properties of taboo words that may give them a mnemonic advantage. These properties are probably the main reason for superior recall of these words at immediate test. However amygdala based

enhanced consolidation is supposed to act to cause less taboo than non-arousing words to be forgotten, causing an interaction of emotionality with time. However in Experiment 3 *no* evidence for this effect was found. In Experiment 4 there was evidence that memory for the source (colour) associated with negative emotional pictures was worse than the other categories at immediate test and better at delayed test. Thus the predicted emotional consolidation effect was found.

A totally different subset of pictures were used to test recognition at immediate and delayed testing in Experiment 4. This may have helped to show the 'consolidation effect', as this method prevents the selective rehearsal of one set of pictures during the immediate test. The dual interval picture colour test also used a longer delay between testings than the taboo words task (one week instead of one hour). This would also have helped. A further difference between the tests that might have made the effect clearer, was testing memory for the associate (colour / source) of the emotional stimuli in the dual interval picture colour task rather than the stimuli themselves (as in the taboo words task). However as no evidence was found for the effect of memory for emotional material actually improving over time, it could be that participants *rehearsed* the emotional pictures more by thinking about them during the week, rather than enhanced consolidation.

This classic effect where memory performance for the emotional material actually increases over the delay was first reported by Kleinsmith & Kaplan (1963) who explained it in terms of high arousal stimuli being relatively unavailable at immediate test due to a 'rapidly reverberating memory trace' that led to permanent consolidation. More modern theories might perhaps refer to the action of cortisol which, although it may act in concert with noradrenaline to enhance *consolidation,* has an impairing effect on *retrieval* processes (Roozendaal, 2002).

6.3.1.4.Analysis of bias

An advantage of the recognition memory test used to assess memory in Experiments 2 and 4 was that it allowed calculation of signal detection statistics to estimate bias. This proved valuable, as it was interesting to discover that the

bias criterion was altered by the highly arousing negative stimuli. Participants adopted a lower level of caution when they were deciding if they had seen negative stimuli before than they did for pictures from either the positive or the neutral categories. This was using a statistic that is theoretically as independent as possible of participants' ability to discriminate between the old and new stimuli Snodgrass & Corwin (1988).

The effect of emotion on bias could be a sign of either or both of two slightly different processes. (1) Bias is conventionally conceived of as a degree of caution applied when judging if a memory is familiar or not. Thus when the same amount of limited information is retrieved, participants were more likely to report a memory if the event was emotional (2) participants may feel more confident in memories that contain a degree of emotion than they do in neutral memories when they have the same amount of information.

These explanations both assume participants had the same amount of information available to them. As discussed after Experiment 2, because emotional stimuli belong to a cohesive semantic category there is also the possibility that other items in the same category might be mistakenly identified for the target item. This could be especially the case if a participant had just encoded the central information of gist of an emotional picture. So if for example a participant had seen several stimuli from the category 'very bad things' including a car crash this could induce them into mistakenly believing they had seen a distractor car crash. They might be protected from doing this had the picture been neutral (for example a traffic jam), as they would have encoded more of the peripheral detail, and the category influence would not be as strong. Thus for emotional and neutral items where discriminability is equal (participants retrieve the same amount of 'true' information), they will have more 'false' information for the emotional item.

The idea that false memories might be more likely when the central material is emotional was considered (appendix 2). Previous reports (Freyd & Gleaves, 1996) have argued that emotional events may be protected from false memory by their distinctiveness, therefore several similarly arousing stimuli were used to try to prevent the emotional stimuli from being distinctive. However *no* evidence was found that arousing stimuli were more likely to be falsely remembered – they were actually less likely to be falsely remembered.

Since the completion of the experimental work for thesis a report has been published (Porter, Spencer & Birt, 2003) of a study where participants were shown IAPS pictures and then asked misleading questions about the pictures. Misleading questions were more likely to lead to false memories when the pictures were negative than when they were positive or neutral. A difference between that study and the study in appendix 2 of the current experiment is that their misleading question drew participants to believe in an untrue peripheral detail (albeit a major detail – a large animal in the scene.) It is well accepted that memory for peripheral details is often impaired by emotion.
As discussed in the conclusion of previous chapters (chapter 3, and 5) an effect of emotion on bias or on false memory has implications for much emotional memory research, including research that uses free recall techniques. Although false alarms are rare in free recall experiments, there is the possibility that when information retrieved is partial, participants would be more likely to report what they sketchily remember for emotional than for neutral information. This would be undetectable with free recall methodology.

The bias effect was very robust. Effect sizes were much bigger than the effects on discriminability and there was no suggestion that any of the pharmacological manipulations had an effect on bias. It would be interesting in a future experiment to try and manipulate bias. This could perhaps be done with verbal instructions – for example when participants are told it is very important not to falsely accuse a suspect, are they able to impose a more conservative bias criterion when identifying the perpetrator of a crime?

6.3.2.Is there an 'emotional memory' effect?

As the other possible mnemonic influences were removed, the effect of emotion on memory became much smaller. This, and the finding that emotion alters recognition memory bias, raises the central question of whether, if all the other effects could ever be eliminated altogether, would there be any measurable effect of emotion on memory?
All the studies in the current thesis made the assumption that there was an effect of emotion on memory over and above these other established memory processes. Perhaps an experiment should have been designed to test this

assumption, and to find the conditions under which the effect of the hypothesised 'emotional memory' mechanism could be maximised. However if there were no special mechanism, any such experiment would again be presented with the problem of trying to prove a negative.

6.3.3.Laboratory and naturalistic studies of emotional memory

As the hypothesised amygdala based enhanced consolidation is such a small effect compared to all the other mechanisms, perhaps trying to control these, creates a situation that would never occur in the 'real world'. There are many differences between laboratory studies and more naturalistic settings. The lab setting provides many advantages of tight control over extraneous variables and therefore allows any effects to be attributed to the experimental manipulations. However this is at the expense of realism or ecological validity.

One very important difference is that in many real world situations emotions are experienced at a level which it would be unethical to reproduce in the lab. In these real life situations, the hypothesised 'emotional memory' mechanism might have a much larger effect. In these circumstances more noradrenaline would be released, and the noradrenaline system might have mnemonic effects more clearly over and above the conventional memory mechanisms. However, entirely different mechanisms and processes might come into play. For example, it is unlikely, but not impossible that the inverted U shaped function describing the relationship between arousal and memory performance is actually the first part of a sine wave.

Another difference between the real world and the lab is that for ethical reasons participants had to be pre-warned that the tests 'contained material that some people may find upsetting'. This may have directed participants' attention to the emotionality of the material in a way that would not have been the case in a more naturalistic situation. It also may have reduced the 'shock value ' of the emotional stimuli, thereby making it less arousing. This is related to the issue that volunteers for this type of experiment are naturally self-selecting. Potential participants who would be worried by emotional stimuli, or who thought they would not like the effects of the drugs would be unlikely to put themselves forward. Further discussion about the difference between the study volunteers and naturalistic use of the drugs appears below (section 6.4)

6.4.Implications and Further Research

> *"Every man has reminiscences which he would not tell to everyone but only to his friends. He has other matters in his mind which he would not reveal even to his friends, but only to himself, and that in secret. But there are other things which a man is afraid to tell even to himself, and every decent man has a number of such things stored away in his mind."*
> *Dostoevsky: Notes from the Underground*

A discussion of the implications of a drug that could impair emotional memory recently appeared in the Times newspaper (July 10th 2003). The argument put forward was that a 'soul absolved by medication' had the frightening consequences of a world populated by *'soldiers [who were] amoral killing machines, [and] of thieves, rapists, and murderers who feel no remorse'*
One of the studies the Times article referred to was the successful pilot study by Pitman et al. (2002) showing that volunteers who were given propranolol shortly after a tramatic car accident were less likely to subsequently experience post traumatic stress disorder than people who had experienced similar accidents and were given placebo.
Before imagining a society of diabolic criminals, perhaps consider that we would not consider refusing a rape victim proper psychological treatment, or the psychiatrist the best possible range of tools to treat them. The same article in The Times reported that McGaugh posed the question - is treating a veteran who wakes up screaming, thinking of the young children they killed in Vietnam any better or worse than offering him surgery and penicillin to treat his wounds?
All the drugs investigated in the current thesis have utilities other than in the reduction of emotional memories and possible prevention of PTSD. Nielson & Jensen (1994) investigated memory in elderly patients who were treated with ß-blockers for hypertension. They found that in their control groups arousal (induced by moderate muscle tension) improved memory. In those taking ß-blockers the arousal manipulation conferred no memory advantage. If this finding extends to memory enhancement by emotional arousal, this would be problematic for such patients. Several authors (e.g. LeDoux 1999) argue that emotionally facilitated memory has evolved because we need to learn about the important things that happen to us, and this is surely still true in everyday life today. The implications may however, not be as far reaching as they first

appear because in the real world there are many other ways that emotion increases memory, e.g. by increased rehearsal, rumination or discussion of emotional events. These would remain intact in medicated people, and the possibility of deficits to emotional memory would have to be balanced against the high risk of stroke, or cardiac failure in these patients if they were unmedicated.

There has been recent speculation in the press (e.g. Bhattacharya, 2003) that a 'polypill' containing a ß-blocker amongst other drugs could be given to everyone over the age of 55 as prophylaxis against cardiac disease. Many of these people would be at less serious risk from cardiac problems than recognised hypertensive patients, and should be made aware that such a 'polypill' could lead to subtle memory impairments for emotional information –possibly the information they most want to remember.

On the surface the findings that both benzodiazepines and methylphenidate may impair the facilitation of memory for emotional material seem to have equally severe implications for those people prescribed these drugs for anxiety disorders or ADHD. However it may be less of an issue in these circumstances, as the psychopathologies may be associated with altered neurotransmitter function, leading to the need for the medication.

There is also reason to believe that psychopathology may be associated with neurotransmitter deficits in selective areas of the brain. Thus it is conceivable that ADHD patients have reduced catecholamine innervation in the prefrontal cortex but not in the amygdala.

People who are prescribed methylphenidate (Ritalin) may have fairly low endogenous catecholamine levels and the drug raises these levels, improving working memory and attention. If the relationship between emotional memory performance and catecholamine levels can be described by an inverted U shape function, unmedicated patients in need of Ritalin might be at the end of the curve where performance is low and would increase as catecholamine levels increase. If this were the case they would be in a position to have emotional memory facilitated by methylphenidate. Evidence in support of this may be research that shows methylphenidate improves instrumental learning for positive reinforcements in hyperactive boys (Christensen & Sprague 1973). The same theory leads to the conclusion that possible impairments to emotional

memory are another reason among many to avoid over-prescribing of Ritalin. If a child's catecholamine levels were not particularly low, the combination of Ritalin and emotional arousal would push them to the end of the curve where memory performance deteriorates.

On a similar line of argument, unmedicated anxious patients have been shown to have a cognitive attentional bias towards anxiety provoking stimuli (e.g. Mathews et al, 1995). Therefore one might expect more emotional information to be encoded by these people. If a prescribed anxiolytic reduced the consolidation of this information perhaps it would help normalise the amount of stressful information available for retrieval. Diazepam medicated anxious patients still have emotional attentional biases (Golombok et al, 1991) yet they feel less anxious. Perhaps reduced memory for emotional events is one mechanism that alleviates anxiety.

All the experimental work in the current thesis involved a single acute dose of either methylphenidate or a benzodiazepine. The chronic use of any drug (whether or not there was any underlying pathology) will have different effects from a single acute dose, due to neuronal adaptation leading to tolerance and sensitisation. These mechanisms added to the disorder being treated by the drug, mean current findings cannot be generalised to the effects of the drugs in treating hypertension, ADHD or anxiety disorders.

Other areas for future research include the effects of opiates on emotional memory. McGaugh put as much weight on the role of endogenous opiates as on GABA in modulating amygdala noradrenaline. Although investigating another neurochemical system was beyond the scope of this PhD, investigation of emotional processing in chronic heroin users undergoing medically managed methadone maintenance is underway. Different again are the effects of opiates prescribed for analgesia, and the effects of a single dose in healthy volunteers. Therefore the effect of opiates in all these different circumstances remains to be investigated and would be an interesting topic for further research.

There are other less well understood modulatory neurotransmitters which may also affect emotional memory. One candidate for this are the endogenous cannabinoids. THC, the active ingredient in cannabis is known to have a variety of memory impairing effects in humans (Curran et al, 2002). Work with mice who have been bred to be deficient in cannabinoid receptors found that they

were slower to show extinction on a fear conditioning task (Marsicano et al. 2002).

Another area of future research would be to examine the stages in the memory process (other than consolidation) that are influenced by emotion. There has been less systematic investigation of this compared with the effects on consolidation. (Dolan et al. 2000; Maratos et al 2001; Maratos, et al 2000; Windmann & Kutas, 2001) found evidence that patterns of brain activation were different for retrieval of emotional compared with neutral information. Roozendaal (2002) has suggested that emotion may have an impairing effect on retrieval via the influence of cortisol. The bias effects described in the present thesis can also be presumed to be active during retrieval.

As repeatedly discussed, emotion can also be expected to act at encoding, recruiting general cognitive mechanisms such as attention and elaborative encoding. In animal studies these effects are controlled for by injecting the drug of interest after the learning has taken place. There has been less work looking at the effects of post-learning injections in humans. Soetens, D'Hooge, & Hueting (1993) reported that a post learning intra muscular injection of amphetamine enhanced long term memory for a (neutral) word list. Recently Cahill & Alkire (2003) reported postlearning injections of adrenaline interacted with arousal (although this could perhaps also be interpreted as a primacy effect) to enhance memory for pictures. However van Stegeren et al (2002) were unable to find an emotional memory impairing effect of a β-blocker that would have been active post-learning.

Post learning drug effects are particularly interesting in the case of benzodiazepines. Post-learning benzodiazepine administration has been found to *facilitate* rather than impair learning Weingartner et al (1995). However McGaugh's theory proposed that the drugs act during the consolidation period. This is a discrepancy that clearly needs to be researched further. Weingartner et al (1995) suggest that it is possible that their results are due to consolidation being *facilitated* by post-learning triazolam. However they argue that this is unlikely because of the amount of time taken to absorb the oral trazolam, which was not swallowed until 10 or 30 minutes after the learning episode. They evoke a retrieval effect of benzodiazepines to explain the effect.

While this does not rule out the possibility that a pre-learning dose of a benzodiazepine could somehow be altering emotional memory consolidation processes, it makes it seem unlikely. The results of the dual interval picture colour test from the current thesis also provide evidence against this. There is some evidence from animal work that benzodiazepines impair retention rather than acquisition (Decker, Tran, & McGaugh, 1990) and that post-learning flumazenil may facilitate emotional learning (Da Cunha et al. 1999). Also postlearning injections of drugs that antagonise GABA can reduce the amnesic effect of systemic benzodiazepine injections (e.g. Dickinson Anson & McGaugh, 1997). However there is no evidence for any effects of benzodiazepines on consolidation in humans, and evidence from other pharmacological manipulations has been difficult to find. Therefore perhaps more research and a new theory is needed to account for this.

6.5.Summary

In summary any effect of either benzodiazepines or methylphenidate on episodic 'emotional memory' was subtle, small enough to possibly make it trivial compared to the range of subjective effects of both drugs and the general memory impairing effects of diazepam.

Little evidence was found to support McGaugh's model in humans. However there was enough suggestion that there might be a small effect *not* to accept the null hypothesis. There was a small amount of evidence that benzodiazepines impaired memory for emotional materials more than they impaired memory for neutral materials. However this was not consistently found.

There was some evidence that methylphenidate disrupted the balance of emotional and neutral material in memory – some suggesting that methylphenidate decreased and some suggesting it increased, the relative amount of emotional material retained. When the level of arousal induced by the various stimuli was considered, it suggested that the relationship between arousal and memory performance might fit a U shaped curve. However post-hoc explanations in terms of the inverted U are unsatisfactory, as these types of relationships can be drawn for most data and are difficult to test.

A major finding was the effect of emotion on recognition memory bias. A less conservative bias criterion was used when judging if emotional information had been seen before. Bias effects may make emotional memories appear facilitated, when they are actually not.

Another major finding was that diazepam impaired fear conditioning. However diazepam did not impair perceptual priming. This pharmacological dissociation reinforces the dissociation between different types of implicit memory drawn neuroanatomically by Squire (1992).

A central issue in drawing conclusions about the effects of drugs on emotional memory is differentiating the effect of 'emotion' from the generally co-occurring mnemonic properties of emotional stimuli. Emotional materials' distinctiveness and semantic cohesiveness, and the extra attention and rehearsal they receive all facilitate memory. Some of these processes may be affected by pharmacological manipulations. However this is not informative to the theory of 'emotional memory'. This leads to the question of whether there is actually an 'emotional memory' mechanism, separate from conventional mnemonic processes, that can be tapped by lab tasks and manipulated with psychotropic drugs.

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APPENDIX 1: Normative ratings of emotional slides.

The slides used in Cahill and McGaugh's (1995) experimental design were predefined as emotional or neutral and this definition has never been tested. Inspection of the slides leads to the suggestion that slides 9, and 10 may have been incorrectly categorised as neutral. They appear to have emotional content. Therefore in order to create a more valid categorisation of the slides ratings of emotionality for each slide were gathered from 101 participants. Statistical analysis of these ratings leads to a redefinition of these two slides as emotional. The new categorisation of the slides was confirmed as valid by analysis of memory data from Zangara and Curran (2000).

INTRODUCTION

Cahill and McGaugh (1995) designed a method to demonstrate memory enhancement for novel material in the lab. Subjects were presented with a story in the form of a set of 12 slides accompanied by an audio narration. In the emotional condition slides 1 to 4 (block 1) are considered emotionally neutral. They describe a mother and her son leaving home in the morning to go and visit the boy's father at work. Slides 5 to 9 (block 2) were considered highly emotional in nature. They describe the boy being involved in a terrible car accident and being rushed to hospital where he endures gruesome surgery. The final three slides 10 to 12 (block 3) were defined as emotionally neutral and describe the distraught mother leaving the injured boy with his father while she rushes off late to pick her youngest child up from nursery. It was found that in a surprise memory test 7 days later subjects memory tested by both free recall and multiple choice tests was better for the (block 2) 'emotional slides' 5 to 9. Memory for the seventh slide was very poor in both groups and therefore this slide was subsequently dropped from the paradigm leaving a total of 11 slides.

This demonstration has been successfully replicated many times e.g. Cahill et al 1994, vanStegeren et al 1998, O'Carroll et al 1999. However the supposed emotional content of the slides was predefined by Cahilll and MCGaugh 1995 and has never been tested. Inspection of the stimuli leads to the conclusion that some of the slides in block 3 (which was predefined as a neutral block) appear emotional in nature. These slides show the distraught mother running late to pick up her other child from nursery school. The

mother is shown holding the football belonging to her injured child, rushing to a telephone box, and then making a 'phone call with her head in her hands. (Filming abandoned toys is a favourite trick of war photographers trying to inject human interest and emotion into a picture)

Further evidence that some of the slides in block 3 may contain emotional content can be found in the study by O'Carroll et al (1999). This study proposed that retention of emotional material would be enhanced by adrenergic agonists and reduced by noradrenergic antagonists. This hypothesis was supported. For both the recall and recognition memory data there was no statistically significant difference between subjects receiving placebo, agonising, or antagonising drugs for the non-emotional block 1. Recall and recognition data for the emotional phase 2 showed differences between the three drug groups in the predicted order. However the recognition data show a statistically significant difference in memory performance between the groups in the predicted order for the supposedly non-emotional block 3. As the adrenergic manipulations are only supposed to affect memory for emotional material this suggests that some of the material in bock 3 has emotional content.

Therefore this investigation was an attempt to gain normative emotional ratings for each slide (and its accompanying narration.). It was hypothesised that these ratings would lead to an alternative classification of the slides into emotional and non-emotional groups with greater validity. It was predicted that a new classification of the slides would predict memory performance in the same way as the old classification with subjects remembering more of the emotional slides than the emotionally neutral slides.

METHOD

Participants

The slides were rated by 101 UCL medical students with a mean age of 20.17 years (range18-25) (and one participant who did not report their age), 44 males and 55 females (2 participants did not report their gender).

Procedure

Participants were given eleven rating scales with 11 discrete points ranging from 0 'not emotional' to 10 ' very emotional'. They were asked to use these scales to rate how emotional they found each slide and corresponding part of the story. The slides and audio narration were then presented to the subjects.

VALIDATION

The findings were validated using recognition memory data collected by Zangara and Curran (2000). In this study three groups of 15 participants had completed the study designed by Cahill et al (1995) as part of a battery of other tests. The three independent groups were, a placebo group, a diazepam group and a metaprolol group. Analysed using Cahill et al's division of slides into three blocks (N E N) this data shows the hypothesised main effects of block ($F_{2,84} = 7.609$, $P=0.001$)and drug ($F_{2,42} = 14.203$, $P<0.001$).

Simple effects analysis of block in each drug group showed that the placebo group had significantly improved memory for the emotional block 2 ($F_{2,28}= 4.470$, $P=0.021$). The diazepam group showed no difference in memory for the three blocks ($F_{2,28}=1.976$, $P=0.157$ NS). The propranolol group also showed a marginally significant difference between groups ($F_{2,28}= 2.731$, $P=0.083$ NS).

These data will be reanalysed using the new slide categorisation.

RESULTS

Descriptive Statistics

The mean ratings given to each slide are displayed in fig (1). The range, mean and standard deviations are presented in table (1).

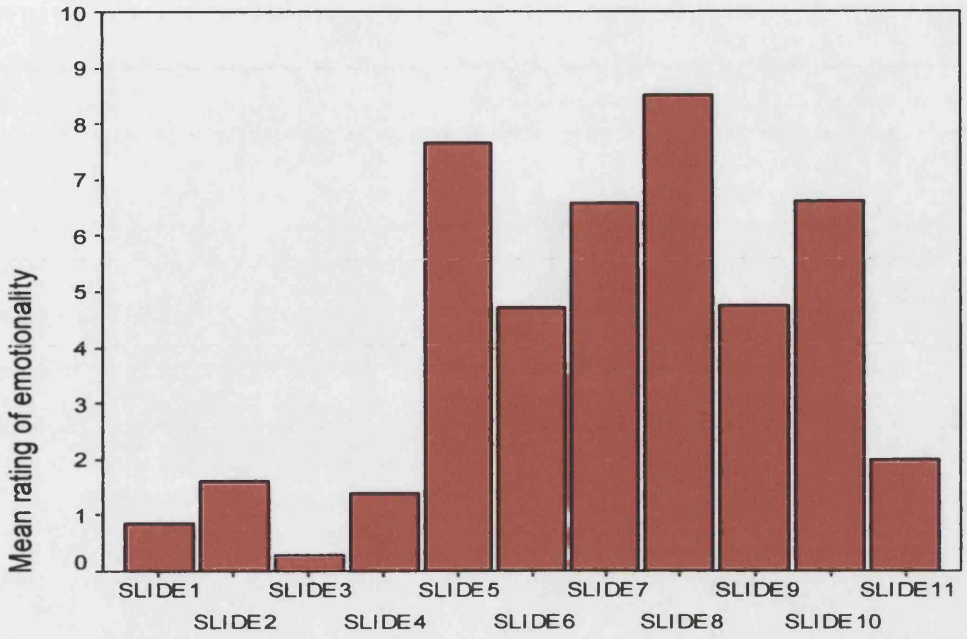


Fig 1: Mean ratings for each slide

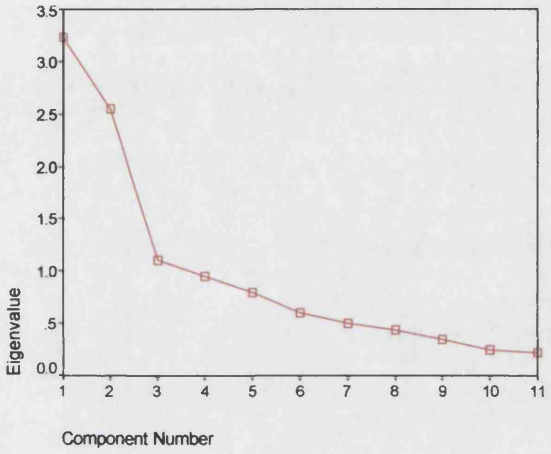
SLIDE	MEAN	SD	MIN	MAX	N	$F_{(1,97)}$	P
3	0.29	0.90	0	6	99		
						18.293	<0.001
1	0.87	1.39	0	6	100		
						10.180	0.002
4	1.40	2.21	0	10	100		
						1.757	0.188
2	1.67	1.83	0	8	100		
						2.381	0.126
11	1.99	2.34	0	10	100		
						67.102	<0.001
6	4.74	2.66	0	10	100		
						0.009	0.926
9	4.76	2.51	0	10	99		
						58.338	<0.001
7	6.59	2.36	1	10	100		
						0.005	0.941
10	6.59	2.36	1	10	100		
						20.523	<0.001
5	7.60	2.17	1	10	99		
						23.123	<0.001
8	8.53	1.65	1	10	99		

Table 1: Mean, Standard deviation, Minimum rating, Maximum rating, and Number of responses to each slide. (Displayed in order of increasing mean.) ANOVA results from repeated contrasts.

An omnibus ANOVA test showed that the slides differ significantly. ($F_{(10,97)}$ = 253.088, P<0.001) The results from the repeated comparisons of the slides are shown in Table 2. These show that statistically there is no difference between the ratings of slide 6 and slide 9 (P=0.926) and between slide 7 and slide 9 (P=0.941).

Principle Components Analysis: Principle components analysis was used to explore the possibility of separating the slides into two coherent subsets on the basis of their emotionality. In accordance with the hypothesis two factors were extracted. The validity of this is supported by the scree plot which clearly denotes the presence of two factors in the data (Fig 2).

Fig 2: Scree Plot



The solution was rotated using the varimax method. The factors produced were interpreted as 'Neutral' and 'Emotional'. Inspection of the loadings of each slide onto the rotated solution support the hypothesis that slides 9 and 10 should be considered as emotional slides. With a cut off point of 0.5 for inclusion of a variable in a factor these both fell into the factor interpreted as 'emotional slides'. Loadings of each slide on each factor are shown in table 2. Together the two factors explain 52.47% of the variance. A three factor solution only explains an extra 10% of the variance and is less interpretable than the two factor solution. Therefore the two-factor solution was selected.

Table 2: Rotated Component Matrix

*(*values below 0.25, (cut off point for inclusion in a factor 0.5).*

	Component 1 'Neutral'	Component 2 'Emotional'
SLIDE 1	.843	*
SLIDE 2	.846	*
SLIDE 3	.687	*
SLIDE 4	.847	*
SLIDE 5	*	.673
SLIDE 6	*	.503
SLIDE7	*	.810
SLIDE 8	*	.755
SLIDE 9	*	.579
SLIDE 10	*	.670
SLIDE 11	.533	*
Percent of VARIANCE	27.057	25.421

Therefore there is statistical support for the division of the slides into two groups. The neutral group contains slides 1,2,3,4, and 11 and the emotional group contains slides 5,6,7,8,9,and 10. These groupings were used in a reanalysis of Zangara and Curran's (2000) recognition memory data.

Analysis of recognition memory data

Inspection of the of the recognition memory data provided by Zangara and Curran(2000) shows an overall memory improvement for the slides classed as emotional under the new categorisation (Table 3). This difference appears to be mainly due to the placebo group having much better recognition memory for emotional than neutral material.

Table 3: Means and (Standard deviations) of the Zangara and Curran (2000) recognition data for the new grouping of emotional and neutral slides.

	Neutral	Emotional	N
Placebo	53.50 (13.86)	65.82 (7.36)	15
Metaprolol	54.42 (10.14)	59.60 (10.10)	15
Diazepam	42.77 (10.09)	45.33 (13.11)	15
Total	**50.23 (12.44)**	**57.04 (13.42)**	**45**

Analysis of this data using ANOVA shows a significant main effect of slide type (emotional or neutral) $F(1,42) = 12.647$, $P=0.001$, and of drug $F(2,42)= 13.263$, $P<0.001$. The slide type * drug interaction is almost significant $F(2,42)=2.286$, $P=0.114$. The interaction appears to be due to there being no effect of emotion on memory in the diazepam condition, a reduced emotional effect in the Metaprolol condition, and an obvious effect of emotion on memory in the placebo condition.

Simple effects analysis reveal that slide type (emotional / neutral) only just has a significant effect on memory in the Metaprolol condition $t(14)=-2.149$, $P=0.050$. There is no significant effect of slide type in the diazepam group $t(14)=-9.03$, $P=0.382$. A significant difference was found in the placebo group $t(14)=-0.012$, $P=0.012$ in their memory for emotional vs neutral slides.

DISCUSSION

As predicted the volunteers rated slides 9 and 10 as emotional. These slides received identical mean ratings to slides in the emotional phase. Therefore there can be no grounds for claiming that slide 7 is emotional with a mean rating of 6.59 and slide 10 is non-emotional when it also received a rating of 6.59. The same applies for slides 6 and 9 with mean ratings of 4.74 and 4.76 respectively.

There is also no justification for classifying slide 6 as emotional but slide 10 as non-emotional as slide 10 receives a significantly higher rating than slide 6.

Therefore Cahill and Mc Gaugh's classification of slides 5-8 as emotional and slides 1-4 and 9-11 as non-emotional is rejected. Instead it is proposed that a two-way division of the slides should be performed. Under this slides 1,2,3, 4 and 11 will be classified as emotionally neutral, and slides 5,6,7,8,9, and 10 are to be classified as emotional.

This division provides greater support for O'Carroll et al's (1999) hypothesis. Their data shows enhanced recognition memory for the third block, which according to this analysis consists of 2/3 emotion material and only 1/3 neutral material.

The analysis of Zangara and Curran's (2000) data shows that the redivision can work in practise. Zangara and Curran's hypothesis was that participants given placebo would show enhanced memory for emotional material and that participants given metoprolol or diazepam would not show this enhancement. This hypothesis was supported by analysis under Cahill and McGaugh's three-way division of slides. This analysis shows that the hypothesis is still supported by analysis under the new categorisation of slides.

There are some surprisingly low minimum ratings on some of the more emotional slides. For example slide 8 shows the young boy's severed feet, and one person gave this a rating of 1 (0 represented not at all emotional). Perhaps this is an artifact of using medical students volunteers. Smith and Kleinman, 1989 describe how medical students have to learn to change their emotional reactions as they undertake their training. In some individuals this can involve a phase of emotional detachment from the human body. However despite these unexpected extremes the standard deviations of the scores did not seem unreasonable.

APPENDIX 2: False memory for taboo words

INTRODUCTION

Experiment 2 found that although emotionally arousing pictures improved discriminability in a recognition memory task, they had a much greater / more robust effect on bias. Emotional pictures cased a liberal bias i.e. participants were more likely to respond that they had seen them before, irrespective of drug group. The possibility that emotional arousal could be inducing false memories was discussed.

A standard technique for investigating false memory is the word list learning paradigm described by (Roediger & McDermott 1995). Participants are presented with a list of words that are all strong associates of an unpresented 'critical lure'. For example participants presented with a study list of *bed, rest, awake, tired, dream, wake, snooze, blanket, doze, slumber, snore, nap, yawn, drowsy* are very likely to 'recognise' the unpresented word *sleep* in a later memory test.

(Freyd & Gleaves 1996) argued that argue that this is only true for the innocuous stimuli used by (Roediger & McDermott 1995) and that "sexually relevant and emotionally charged words" would be unlikely to be falsely recalled. However more recently (Pesta, Murphy, & Sanders 2001) found that it is the distinctiveness of these types of words that protects them from being falsely recalled. However, as the volunteers in (Pesta, Murphy, & Sanders 2001) experiment were mainly listening to lists of innocuous words, they were not in a state of arousal at encoding (and hence consolidation) which is when arousal is often argued to affect memory (McGaugh 2000). (Payne et al. 2002) found that participants learning (neutral) word lists while under stress (arousal?) caused by a simulated public speaking scenario were more likely to produce critical lures than control participants not under stress.

(LaBar & Phelps 1998) et al have shown the feasibility of using taboo words as arousing stimuli in a memory task.

Therefore it was predicted that in an experiment modelled on that of (Roediger & McDermott 1995) with some arousing (taboo) word lists and

some unarousing word lists. Participants would be more likely to rate the taboo critical lures as previously seen, with more confidence than the unarousing critical lures. It was also expected that the standard effect of more of the taboo words that were actually presented at study would be correctly recognised (with more confidence) than the presented non-arousing words.

METHOD

Subjects

30 healthy volunteers completed the study.

Materials

Critical lures and Word Lists

Six critical lures (3 taboo, 3 non-arousing) were used. 'Penis' was used as a critical lure following the comments by (Freyd & Gleaves 1996) and work by (Pesta, Murphy, & Sanders 2001), the other taboo critical lures (faeces and murder) were selected from the taboo words provided by (LaBar & Phelps 1998). These lures were selected on the basis that they were at most weakly associated with each other. The non-arousing critical lures (sleep, foot, chair) were selected as they had the lowest arousal ratings on the ANEW (Bradley & Lang 1999) of the critical lures provided by (Roediger & McDermott 1995).

Fourteen associates of each critical lure (the neutral lists were taken from Roediger, the taboo lists were constructed for the experiment) were recorded onto a cassette tape at a rate of one word every 2 seconds. The lists were presented in a fixed pseudo random order. The last 7 words from (Roediger & McDermott 1995)'s 'window' and 'slow' lists were used as primacy and recency controls.

Recognition Memory Test

The recognition memory test was constructed in the same way as described by (Roediger & McDermott 1995). For each of the 6 word lists, one critical lure, two previously presented words, two weakly associated unpresented words, and two unrelated recognition test words appeared. The taboo unrelated words were chosen as the least related words from (LaBar &

Phelps 1998), the unrelated non-arousing words were taken from the Roediger lists not used in the present experiment. Each recognition test list appeared in the order described by (Roediger & McDermott 1995), starting with the strongest associate that had been presented on the cassette tape, and ending with the critical lure with the other words distributed randomly between. In addition 2 of the primacy and 2 of the recency control words appeared in the recognition test list.

Table 1: Words appearing in the recognition test

Critical Lure	**Weak Associates**	**Unrelated words**	**Presented words**
Chair	Couch, Floor	Cotton, instrument	Table, Cushion
Foot	Dancing, inch	Door, apple	Kick, shoe
Sleep	Peace, baby	Boy, valley	Bed,dream
Penis	Pelvis, Syphilis	Cocaine, nigger	Dick, Urinate
Faeces	Fart, Waste	Amputate, tits	Toilet, diarrhoea
Murder	Molest, Hurt	Bastard, nipple	Kill, knife

Procedure

Participants were presented with an instruction sheet / consent form. This informed them that they would hear a long list of words presented on a tape recorder. They were asked to listen carefully to the words as soon after hearing them there would be a memory test for the words. The instruction sheet also contained the following phrase taken from (Pesta, Murphy, & Sanders 2001) .

"WARNING: A few of the words presented in this experiment are sexually-charged, vulgar or offensive. If you would rather not be exposed to these types of words, please do not participate"

After the participant had read the instructions, had an opportunity to ask questions and signed the consent form, they listened to the cassette tape of

words through headphones. Following this participants completed the single and double digit cancellation tasks described by (Curran et al. 2002) as a non-verbal distracter task.

They were then given the recognition test. Where they were asked to rate how confident they were that each word appeared on the previously presented list. The rating scale was '4 = Definitely old, 3 = probably old, 2=probably new, 1= definitely new'. Once participants had completed the recognition task it was explained that some of the words had not been presented on the list, and that the test was designed to make them have false memories, and the majority of people do produce false memories in similar circumstances.

Statistics

A 2 x 4 RMANOVA will be used to compare (taboo vs non-arousing) x (critical lures vs presented words vs weakly related words vs unrelated words).

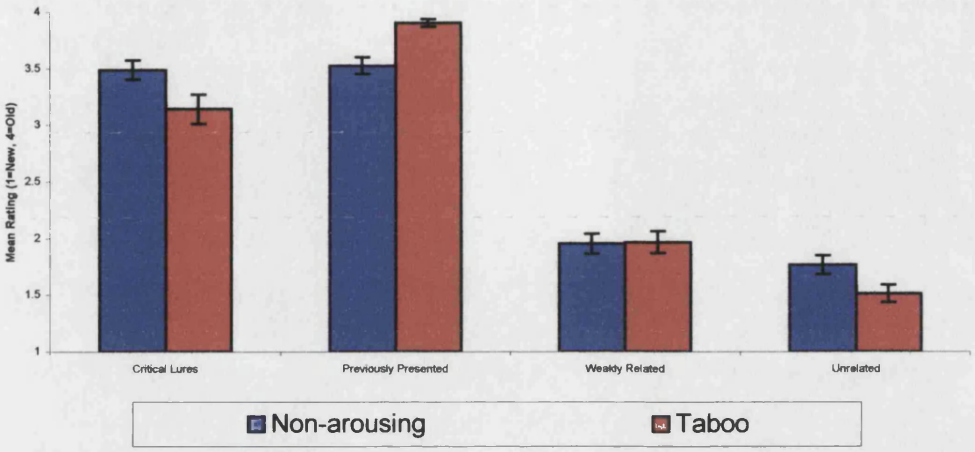
Simple effects analyses will then be carried out using paired samples t-tests, comparing the effect of emotion within each presentation category.

RESULTS

Mean (s.e.) rating for each category of words are presented in figure 1. Scores of two and below indicate that participants did not believe words were presented on the tape. Scores of 3 and above indicate participants believed the words were on the list. Therefore it appears that on average participants recognised the list words and thought they recognised the critical lures. They did not recognise the unrelated or weakly related distracter words.

For the non-arousing words participants were just as confident they had seen the critical lures as the presented words. For the taboo words they were more confident they had seen the presented words and less confident they had seen the critical lures.

Figure 1: Mean (s.e.) rating for each category of words



The RMANOVA showed an emotion x presentation category interaction $F_{3,87}$ = 9.98 $p<0.001^{GG}$. For words they had actually seen, confidence was higher in the recognition judgement of taboo words than non-arousing words, and vice versa for critical lures. For unrelated, unpresented taboo words there was higher confidence they had not been previously seen.

There was also a main effect of presentation category $F_{3,87}$ = 322.28, $p<0.001$, Critical lures and previously presented words were more likely to be recognised than weakly related and unrelated unpresented words. There was no main effect of emotion $p=0.396$.

The results of the simple effects analyses are shown in Table 2.

For the critical lures the difference between recognition of taboo and non-arousing arousing word did not surpass the Bonferrroni corrected critical probability. However it would be hard to conclude there was no difference between the emotion categories with out risking a type 2 error. There is a definite trend towards higher confidence of false recognition for non-arousing critical lures.

There was significant evidence that participants had more confidence that taboo previously presented words were old, than they had for non-arousing previously presented words.

There is also significant evidence that for unrelated words there was more confidence that taboo words were new.

For the weakly related words there was no difference between the emotion categories.

Table 2 Simple effects paired samples t-tests (Critical p=0.0125)

	T(29)	p
Critical Lures	-2.23	0.034
Previously Presented	4.47	<0.001
Weakly Related	.113	.911
Unrelated	-3.30	0.003

Figure 2: Mean (se) rating for each of the critical lures

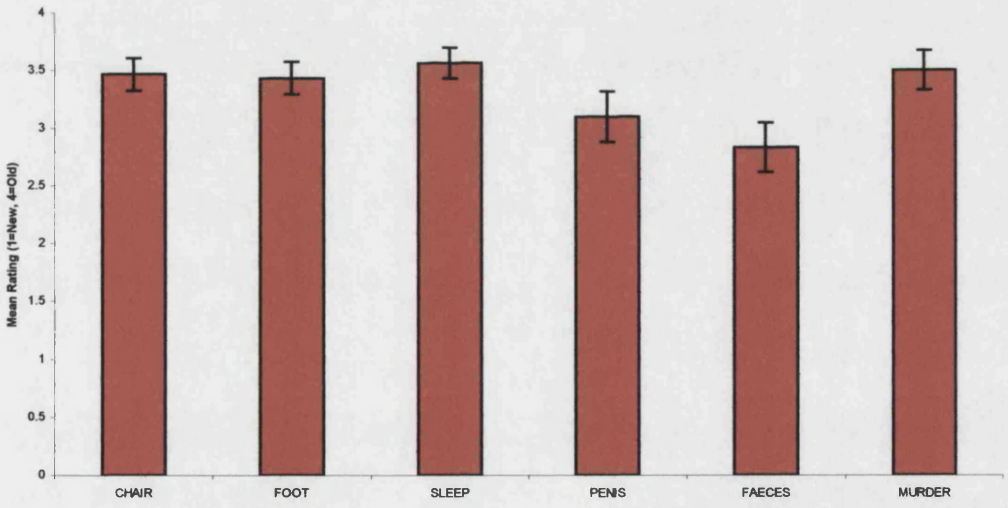


Figure 2 shows the mean rating for each of the critical lures.

DISCUSSION

This study found that taboo words were more likely to be remembered, with more confidence than neutral words. However taboo words were less likely to be falsely 'remembered'. Therefore it is tempting to draw the conclusion

that memory is actually facilitated by taboo words. Thus the increased bias for emotional stimuli observed in Experiment 2 is not due to just an increased propensity to respond to arousing stimuli.

However the study has the limitation that other features of the words such as distinctiveness, familiarity and word frequency in language were not matched across the two types of words. It is noticeable that the least distinctive arousing word, 'murder' was the taboo word with the highest level of false memory. (Although it can also be argued that despite being categorised 'taboo' by (LaBar & Phelps 1998) the word 'murder' is not actually taboo). Therefore it could be argued that participants were more likely to realise the taboo lures were not on the study list because they are so distinctive. Although in the present experiment an effort was made to control for distinctiveness, this was done within categories rather than across categories. Taboo words in the present experiment were not particularly distinct from the study list – as there were several other taboo words in the study list. However they were not matched with the low arousal words on (1) frequency in the language, or (2) likelihood that they might appear in psychology experiment schema.

Therefore a conclusion that arousing material does not increase propensity to false memory may be premature. It would be worthwhile to do another study with these problems controlled for as if emotional arousal does increase susceptibility to false memories it has important implications. Firstly it is important to the interpretation of the work in the current thesis. Experiments 2 and 4 showed that emotional material alters the bias criterion. Signal detection calculations were used to separate out the effects on bias from the effects on old / new discriminability. The other tests that did used recall rather than recognition may also have been effected by false memories that were undetected. However, false memory may not be the only mechanism leading to an inflated bias criterion. (Windmann & Kutas 2001) provide ERP data suggesting that emotionally violent words are distinguished from neutral words much too early for a false memory effect. This study has implications for the taboo words study of the current thesis. It seems that taboo words are not more likely to be falsely remembered than

less arousing words. Therefore, where participants show a higher level of recall for the taboo words it is likely they are actually remembering more of these words. This is relevant as a possible criticism of the taboo words study was that a large number of exemplars of the category of 'profanities' were used. Therefore participants could feasibly produce the pattern of results observed just by producing several exemplars of that category.

The work may also have wider implications. The high levels of confidence people tend to have in their emotional memories, may be justified. There may also be implications for discussions about 'fantastic memories' in documented cases of child abuse.

APPENDIX 3: Test order in Experiment1

Information sheet and consent form

Medical screening

Predrug

Pulse and Blood Pressure

Tapping

Mood rating scale

POMS

Picture grid memory task

Tablet one administered

Affect grid 1

Practice sentences

Practice Autobiographical Memory

Tablet two administered

Postdrug

Pulse and blood pressure

Tapping

Mood rating scale

POMS

Affect grid 2

Autobiographical memory task

Sentences: study & immediate test

Affect grid 3

Facial expression recognition

Affect grid 4

Sentences: delayed recall

Picture grid memory test

Affect grid 5

Cahill and McGaugh story

Affect grid 6

Day 7

Drug guess questionnaire

Mood rating scale

POMS

Affect grid 7

Story task multiple choice

Affect grid

Autobiographical memory recall

Sentences day 7 recall

APPENDIX 4: Test order in Experiment 2

Medical screening

Predrug

Information sheet and consent form

Prose story

Mood rating scale

Affect grid

Pulse and blood pressure

Tapping

Prose story 'immediate' recall

Tablet one

Practice faces and voices tasks

Tablet two

Postdrug

Prose story

Affect grid

Pulse and blood pressure

Tapping

Prose story 'immediate' recall

Picture colour test: study

Affect grid 3

Emotional voices task

Affect grid 4

Picture colour test: test

Affect grid 5

Sentences presented

Facial expression recognition

Stem completion and recognition

Affect grid 6

Facial expression recognition (Postdrug cont.)

Affect grid 7

Cahill and McGaugh story

Mood rating scale

Affect grid 8

Physiological data

Prose recall: delayed (both stories)

Day 7

Story task: multiple choice

Drug guess questionnaire

Open questions about pictures

APPENDIX 5: Test order in Experiment 3

Information sheet

Consent form

Screening

Predrug

MRS

Pulse and blood pressure

Tapping

Prose story & immediate recall

Serial sevens

Capsule 1

Explain SAM

Explain Affect grid

Capsule 2

View and rate pictures

View and rate taboo words

Taboo words immediate recall

MRS

Pulse and blood pressure

Affect grid

Tapping

Prose story & immediate recall

Serial sevens

Aggressive stories task

Emoitonal voices

Delayed recall of prose 1 & 2

Picture free recall

Taboo words delayed recall

MRS

Affect grid

APPENDIX 6: Test order in Experiment 4

Information sheet

Consent form

Screening

Predrug

Prose story and immediate recall

Pulse and blood pressure

Tapping

MRS

Serial sevens

Capsule1

Capsule 2

Postdrug

Prose story and immediate recall

Pulse and blood pressure

Tapping

MRS

Serial sevens

View and rate pictures

Skin conductance conditioning

'Immediate' picture recognition

Delayed recall of both prose stories

Day 7

Delayed picture recognition

Spot the word

Digit span

Drug guess

APPENDIX 7: Sentence stimuli, Experiment 1

Version 1

He was training to be a **lawyer** at one of the oldest firms in the city
The **tissue** was covered in blood and pus
She put the **rice** on to boil and set the time for 20minutes
She froze when she saw the maniac's **shadow** in her garden
The **bus** went from Salford to Manchester
He wrung her **neck** slowly until he heard it snap
The **dancer** was raped as she returned home from the show
A **diplomat** in Greece gave the speech
She put a pan on the stove and turned on the **gas**
He howled as they sawed through the gangrenous **bone**
They stripped any **gold** off the murdered Jews
The **teacher** told the children to get their books out
They sliced open his distended **stomach** and sucked out the bile
He carried the child down the **stairs** and into the nursery
The **train** traveled at one hundred miles per hour
He clubbed the seal's head open for the sake of **fashion**
The bullies urinated over his **uniform**
The **wind** blew their hair out of place
On their way through the forest they passed a scout **camp**
Cockroaches crawled over the uncovered **butter**

Version 2

They stabbed the **lawyer's** eyes with needles
She pulled out a **tissue** and wiped her brow
They scrambled in the dirt for grains of **rice**
She looked at the sundial and read the time by its **shadow**
The **bus** crashed into the wall killing the children
She put a scarf around her **neck**
The **dancer** warmed up before starting her routine
They poured petrol over the **diplomat** and burnt him alive
She put her head in the oven and turned on the **gas**
The medics looked at the x-ray of the **bone**
The security men put the **gold** into the safe
The **teacher** repeatedly molested the young boys
He patted his **stomach** and remarked that he was now full
He threw the woman down the **stairs** and watched her hit every step
The **train** arrived full of rotting corpses covered in excreta
The book was aimed at people who were interested in **fashion**
They wore a **uniform** most days to school
The **wind** blew the shelter down killing the family
The concentration **camp** stank of burning bodies
The supermarket sells **butter** and other groceries

APPENDIX 8: Stimulus sentences from the implicit memory sentences task: Experiment 2

Version1A

Ten thousand people died when the bomb exploded at the **concert**
The **bride** stepped onto the curb
The hurricane **wind** left no one in the village alive.
You can buy **butter** in the corner shop
Their father was permanently paralysed when he fell from the **ladder**
One species of bird to be found here is the **starling**
Blood leaked from her skull as he smashed it repeatedly against the **stone**
He patted his tummy and remarked that it had been a good **breakfast**
maggots had crawled through his eye sockets and were eating his **brain**
The **train** moved quickly towards Birmingham
The **cousins** were tied up, blindfolded and shot
They think the tower on the **hill** was built before the war
Her heart sank as she looked at the **scan** and saw the tumour
The tourist will visit the **temple** in the morning
The nine year old boy was molested repeatedly by his **teacher**
The zookeeper gave the **bear** his food
Screaming, they clung to the deck of the sinking **boat**
She rinsed the boiled **rice** and added it to the mixture
The bullies urinated over his **uniform**
The yard **stick** was kept in the workroom

Version 1B

Ten thousand people were at the **concert**
The **bride** was raped before the wedding
The **wind** was cold that day
Cockroaches crawled over the **butter**
He climbed the **ladder** and cleaned the gutter
The **starling** became tangled in the netting and eventually died
The ground was paved with **stone**
he vomited his **breakfast** across the table
The children learned about the **brain**
the toddler ran into the path of the approaching **train**
His **cousin** has gone to Swindon
He died of a heart attack on the way up the **hill**
They took the **scan** into the laboratory
The tourist found the **temple** desecrated, filled with rotting corpses covered in excreta
The nine year old girl read the book with her **teacher**
He murdered the majestic **bear** for the sake of a fur coat
They went to see the **boat** in the harbour
The emaciated children scrambled in the dirt for grains of **rice**
The book told the history of their **uniform**
The **stick** struck the tiny girls head with a sickening crack

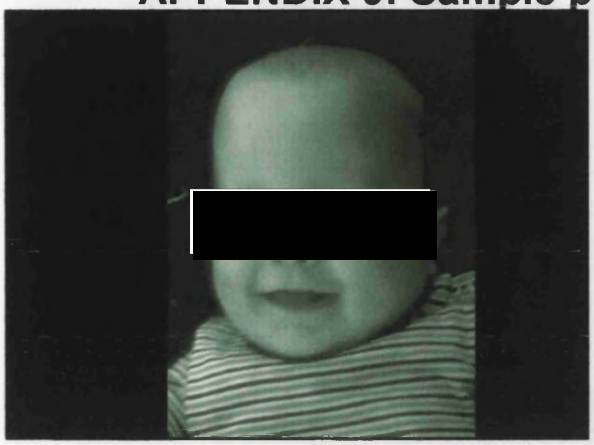
Version2A

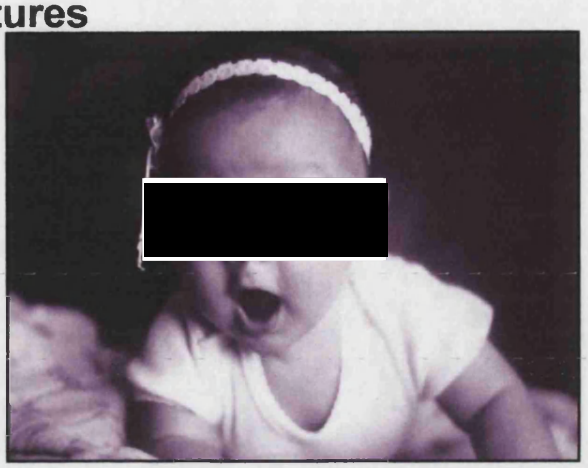
Blood ran from her skull as he smashed it repeatedly against the **concrete**
They think the **bridge** over the river was built before the war.
The harsh **winter** left no one in the village alive
One species of **butterfly** to be found here is the cabbage white
The **lady** was raped on her wedding day
She climbed the **stairs** and cleaned the carpet
He vomited a fowl substance from his **stomach** across the table
You can buy **bread** in the corner shop
The tiny girl's head struck the **branch** with a sickening crack
The **traffic** moved quickly towards Birmingham
The **managers** were tied up, blindfolded and shot
The **guest** will visit the mosque in the morning
Ten thousand people died when the bomb exploded in the **crowd**
She scooped the **flesh** from the papaya and added it to the mixture
The nine year old boy was molested repeatedly by his **uncle**
They went to see the **ship** in the harbour
A mass of cockroaches crawled through his **dinner**
The book was aimed at people who were interested in **fashion**
She shuddered when she found the cancerous growth on her **bone**
The meter ruler was kept in the **studio**

Version 2B

The ground was paved with **concrete**
Their father was permanently paralysed when he fell from the **bridge**
The **winter** was cold that year
The **butterfly** became tangled in the netting and eventually died
The **lady** stepped onto the curb
He died of a heart attack on the way up the **stairs**
He patted his **stomach** and remarked that it had been a good meal
The emaciated children scrambled in the dirt for the **bread**
The children swung from the **branch.**
the toddler ran into the path of the oncoming **traffic**
His **manager** has gone to Swindon
The **guest** found the mosque desecrated, filled with rotting corpses covered in excreta
Ten thousand people were in the **crowd**
Maggots had crawled beneath his skin and were eating his **flesh**
The nine year old girl read the book with her **uncle**
Screaming, they clung to the deck of the sinking **ship**
The zookeeper gave the panda his **dinner**
He murdered the adorable seal for the sake of **fashion**
They sent the **bone** x-rays to the laboratory
They broke into his **studio** and urinated over his work

APPENDIX 9: Sample pictures





APPENDIX 10: Stimuli used in the 'taboo words' task

Taboo words provided by Phelps and Labar. Low arousal words taken from the ANEW Bradley et al (1999). Columns are arousal, valence, and frequency ratings from the ANEW (where available), number of hits returned by AltaVista, and number of syllables.

High Arousal	Valence	Arousal	Freq	AltaVista	Syllables	Low Arousal	Valence	Arousal	Freq	AltaVista	Syllables
masturbate	4.35	5.27		4,885	3	nonchalant	4.74	3.12	1	1,188	4
Herpes				5,541	2	dreary	3.05	2.98	6	6,684	2
cocaine				13,880	2	subdued	4.67	2.9	8	15,018	2
Whore	1.61	5.54	2	82,807	1	bored	2.95	2.83	14	67,484	1
asshole				89,300	2	gentle	7.31	3.21	27	80,579	2
Horny				134,158	2	lazy	4.38	2.65	9	132,395	2
Rape	1.08	7.38	5	193,640	1	sleep	7.2	2.8	65	236,359	1
Molest				896	2	dustpan	3.98	3.43	.	657	2
amputate				563	3	kerchief	5.11	3.43	1	374	2
homosexual				81,293	4	indifferent	4.61	3.18	11	16,047	3
orgasm	8.45	7.9	7	183,789	2	relaxed	7	2.39	14	136,505	2
penis	6.25	6		109,641	2	foot	5.02	3.27	70	440,176	1
Fuck				2,168,063	1	peace	7.72	2.95	198	723,599	1
Tits				1,876,806	1	quiet	5.58	2.82	76	550,887	1
Shit				96,922	1	clouds	6.18	3.3	38	68,042	1
nipple	5.48	4.73		1,597,308	2	item	5.26	3.24	54	1,393,299	2
Fart				100,234	1	bowl	5.33	3.47	23	92,554	1
Incest				114,533	2	messy	3.15	3.34	3	110,041	2
murder	1.83	7.58	19	123,035	2	cottage	6.45	3.39	19	132,443	2
bastard	3.36	6.07	12	92,833	2	museum	5.54	3.6	32	484537	2
TOTAL	32	50	45	7,070,127	38	TOTAL	105	62	669	4,688,868	34
MEAN	4	6	9	353,506	2	MEAN	5	3	35	234,443	2

Appendix 11: Control Battery Measures / Mean *sd*

		E1			E2			E3			E4		
		Pre	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**
MRS: Alert – Drowsy	**Placebo**	41.54	46.74	37.92	37.15	44.83	50.50	44.40	44.89	45.08	26.34	39.78	
		12.36	*12.23*	*16.08*	*15.42*	*16.25*	*18.13*	*1.11*	*1.11*	*1.43*	*11.35*	*13.63*	
	Methylphenidate	46.36	49.88	42.83				44.27	44.10	44.01	33.92	39.09	
		7.59	*16.33*	*10.48*				*1.37*	*1.69*	*1.32*	*10.37*	*14.83*	
	Diazepam	42.36	58.29	37.37	42.89	65.43	62.40	44.61	46.73	46.70	34.26	51.51	
		11.82	*10.72*	*13.17*	*11.44*	*6.29*	*14.82*	*1.25*	*1.47*	*1.49*	*17.22*	*15.69*	
	Propranolol				39.79	45.84	46.53						
					15.14	*13.34*	*18.61*						
MRS: Content – Discontent	**Placebo**	43.90	38.58	37.98	36.96	36.83	48.64	57.75	57.83	57.87	27.73	31.13	
		12.29	*11.16*	*14.95*	*17.29*	*17.58*	*18.19*	*1.12*	*1.08*	*1.03*	*14.02*	*10.09*	
	Methylphenidate	43.90	41.56	43.73				57.57	57.45	57.79	31.29	33.56	
		11.89	*7.56*	*11.41*				*1.27*	*1.39*	*0.97*	*12.88*	*15.62*	
	Diazepam	39.34	37.25	39.93	40.40	42.00	43.06	58.07	57.89	58.17	29.86	32.53	
		11.65	*13.53*	*12.74*	*9.41*	*10.80*	*6.07*	*1.24*	*1.23*	*1.18*	*12.22*	*10.56*	
	Propranolol				37.40	38.84	40.30						
					12.61	*10.92*	*13.38*						
MRS: Anxious –Calm	**Placebo**	46.94	37.53	38.97	42.84	38.31	36.28	49.26	49.05	49.18	43.50	37.50	
		14.62	*15.26*	*15.51*	*18.18*	*14.98*	*17.80*	*1.34*	*1.18*	*1.61*	*16.34*	*11.66*	
	Methylphenidate	46.63	45.56	52.94				49.47	49.99	50.08	43.44	47.91	
		12.38	*20.51*	*14.41*				*1.46*	*2.29*	*1.30*	*14.69*	*21.87*	
	Diazepam	40.28	31.78	42.78	38.38	30.84	29.75	49.70	47.56	47.94	41.84	28.28	
		15.29	*14.43*	*16.75*	*14.02*	*12.36*	*12.59*	*1.16*	*1.56*	*1.42*	*15.34*	*16.29*	
	Propranolol				35.41	37.97	37.41						
					13.69	*11.65*	*14.20*						

Appendix 11: Control Battery Measures / Mean *sd*

		E1			E2			E3			E4		
		Pre	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**
MRS: Alert – Drowsy	**Placebo**	41.54	46.74	37.92	37.15	44.83	50.50	44.40	44.89	45.08	26.34	39.78	
		12.36	*12.23*	*16.08*	*15.42*	*16.25*	*18.13*	*1.11*	*1.11*	*1.43*	*11.35*	*13.63*	
	Methylphenidate	46.36	49.88	42.83				44.27	44.10	44.01	33.92	39.09	
		7.59	*16.33*	*10.48*				*1.37*	*1.69*	*1.32*	*10.37*	*14.83*	
	Diazepam	42.36	58.29	37.37	42.89	65.43	62.40	44.61	46.73	46.70	34.26	51.51	
		11.82	*10.72*	*13.17*	*11.44*	*6.29*	*14.82*	*1.25*	*1.47*	*1.49*	*17.22*	*15.69*	
	Propranolol				39.79	45.84	46.53						
					15.14	*13.34*	*18.61*						
MRS: Content – Discontent	**Placebo**	43.90	38.58	37.98	36.96	36.83	48.64	57.75	57.83	57.87	27.73	31.13	
		12.29	*11.16*	*14.95*	*17.29*	*17.58*	*18.19*	*1.12*	*1.08*	*1.03*	*14.02*	*10.09*	
	Methylphenidate	43.90	41.56	43.73				57.57	57.45	57.79	31.29	33.56	
		11.89	*7.56*	*11.41*				*1.27*	*1.39*	*0.97*	*12.88*	*15.62*	
	Diazepam	39.34	37.25	39.93	40.40	42.00	43.06	58.07	57.89	58.17	29.86	32.53	
		11.65	*13.53*	*12.74*	*9.41*	*10.80*	*6.07*	*1.24*	*1.23*	*1.18*	*12.22*	*10.56*	
	Propranolol				37.40	38.84	40.30						
					12.61	*10.92*	*13.38*						
MRS: Anxious –Calm	**Placebo**	46.94	37.53	38.97	42.84	38.31	36.28	49.26	49.05	49.18	43.50	37.50	
		14.62	*15.26*	*15.51*	*18.18*	*14.98*	*17.80*	*1.34*	*1.18*	*1.61*	*16.34*	*11.66*	
	Methylphenidate	46.63	45.56	52.94				49.47	49.99	50.08	43.44	47.91	
		12.38	*20.51*	*14.41*				*1.46*	*2.29*	*1.30*	*14.69*	*21.87*	
	Diazepam	40.28	31.78	42.78	38.38	30.84	29.75	49.70	47.56	47.94	41.84	28.28	
		15.29	*14.43*	*16.75*	*14.02*	*12.36*	*12.59*	*1.16*	*1.56*	*1.42*	*15.34*	*16.29*	
	Propranolol				35.41	37.97	37.41						
					13.69	*11.65*	*14.20*						

Appendix 11: Control Battery Measures / Mean *sd*

		E1			E2			E3			E4		
		Pre	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**	**Pre**	**Post**	**EOS**
Serial 7s	**Placebo**							22.50	22.63		19.20	21.67	
								9.01	*12.40*		*10.35*	*12.12*	
	Methylphenidate							17.19	22.75		21.65	24.00	
								9.92	*8.96*		*11.61*	*13.60*	
	Diazepam							22.25	18.50		13.19	14.44	
								9.69	*10.19*		*7.22*	*9.14*	
	Propranolol												
Taps	**Placebo**	368.88	361.38		379.50	365.38		351.63	348.13		371.06	370.69	
		37.80	*44.08*		*53.31*	*59.48*		*33.70*	*33.00*		*47.33*	*48.72*	
	Methylphenidate	366.38	373.38					377.06	385.06		361.59	356.06	
		34.99	*33.51*					*35.53*	*46.55*		*40.86*	*43.81*	
	Diazepam	365.44	335.69		366.25	340.38		373.06	337.56		364.56	353.56	
		35.43	*41.58*		*35.68*	*42.54*		*32.24*	*65.04*		*45.66*	*47.25*	
	Propranolol				347.31	340.81							
						28.52							

APPENDIX 12: Ethics committee approval letters

Experiment 1.....Study no:00/0076

Experiment 2.....Study no: 01/0078

Experiment 3.....Study no: 02/0200

Experiment 4.....Study no: 02/0237

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The Joint UCL/UCLH Committees on the Ethics of Human Research

Committee A Chairman: Dr F D Thompson

Please address all correspondence to:
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1st floor, Vezey Strong Wing
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e-mail: iwona.nowicka@uclh.org

Dr V Curran
Reader in Psychopharmacology
UCL
Sub-Department of Clinical Health Psychology
Gower Street

July 24, 2000

Dear Dr Curran

Study No: **00/0076***(Please quote in any correspondence)*
Title: **Effects of acute doses of methylphenidate and diphenhyframine on processing facial expressions**

Further to your letter dated 1st July, there I agree to the following change in the original protocol:

- You can substitute lorazepam (2mg) for diphenhydramine (50mg).

There are no objections to the amended version of the Information Sheet.

The study can be continued.

Yours sincerely

Dr F D Thompson
Chairman

University College London Hospitals is an NHS Trust incorporating The Eastman Dental Hospital, The Hospital for Tropical Diseases, The Middlesex Hospital, The National Hospital for Neurology & Neurosurgery, The United Elizabeth Garrett Anderson Hospital and Hospital for Women, Soho, and University College Hospital.

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The Joint UCL/UCLH Committees on the Ethics of Human Research

Committee Alpha Chairman: Professor André McLean

Please address all correspondence to:
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1st Floor, Vezey Strong Wing
112 Hampstead Road, London NW1 2LT
Tel. 020 7-380 9579 Fax 020 7-380 9937
e-mail: iwona.nowicka@uclh.org

Professor V Curran
Sub-Department of Clinical Health Psychology
UCL
Gower Street

July 16, 2001

Dear Professor Curran

Study No: **01/0078** *(Please quote in all correspondence)*
Title: **Effects of an acute dose of diazepam and propanolol on processing of and memory for facial expressions spoken words and visually presented information.**

Thank you for your letter dated 18th June addressing the points raised by the Committee. There are no further objections and the study can go ahead. However, it was requested that the following sentence should be inserted in the information sheet: "You should not take part in this study if you ever suffered from asthma." Please send us the final version of the information sheet for completeness of records.

Please note that it is important that you notify the Committee of any adverse events or changes (name of investigator etc) relating to this project. You should also notify the Committee on completion of the project, or indeed if the project is abandoned. **Please remember to quote the above number in any correspondence.**

Yours sincerely

Professor André McLean, BM BCh PhD FRC Path
Chairman

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University College London Hospitals NHS

NHS Trust

Committee Alpha Chair:
Professor André McLean

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Tel: 020 7380 9579
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19 February 2003

Our Ref: RM/SB/03A203

Professor H Curran
Sub- Department of Clinical Health Psychology
Gower Street
UCL

Dear Professor Curran

REC Ref No: 02/0200
REC Name: Committee A

Thank you for your letter of the 26 November 2002. Please accept our apologies for the severe delay in responding to you.

There are no ethical concerns and I am happy to approve this study amendment by Chairs Action. I am also pleased to advise you that this study amendment will be notified to the ethics committee at the next meeting on 6 March 2003.

Best wishes,

Yours sincerely

Raymond MacAllister
Chair

University College London Hospitals NHS

NHS Trust

Committee Alpha Chairman:
Professor André McLean

The Joint UCL/UCLH Ethics Committee
Research & Development
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19 February 2003

Our Ref: RM/SB/03Alpha0043

Professor H Valerie Curran
Sub Department of Clinical Health Psychology
Gower Street
UCL

Dear Professor Curran

REC Ref No: 02/0237 *(please quote in all correspondence)*
REC Name: Committee Alpha *(please quote in all correspondence*

Study Title: Effects of placebo, methylphenidate, and diazepam on conditioning of a skin conductance response (SCR), and consolidation of episodic memory for emotional material

Thank you for your letter of the 26 November 2002. Please accept our apologies for the severe delay responding to you.

There are no ethical concerns and I am happy to approve this study amendment by Chairs Action. I am also pleased to advise you that this study amendment will be notified to the ethics committee at the next meeting on the 6 March 2003.

Best wishes,

Yours sincerely

Professor A McLean
Chair