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Temporal memory in human amnesic subjects and rats with specific brain lesions

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Temporal Memory in Human Amnesic Subjects and Rats with Specific Brain Lesions

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Declaration.

The work contained in this thesis was carried out by the author between 1989 and 1992 while a postgraduate student in the Department of Psychology at the University of Durham. None of the work contained in this thesis has been submitted in candidature for any other degree.

Abstract.

Temporal processing was assessed in a group of alcoholic Korsakoff subjects, post viral encephalitic subjects, alcoholic control and normal control subjects. Subjects were tested on their ability to reproduce and estimate intervals of time ranging from 3 to 96 seconds. Also, a computerised analogue of the fixed interval procedure used with animals was designed and used to test subjects' estimations of intervals of 15 and 30 seconds. Memory for temporal order was also assessed using an object recency task which also incorporated a recognition memory test.

It was found that Korsakoff subjects were impaired at all intervals both in the temporal estimation tests and the fixed interval procedure compared to the alcoholic control subjects, whereas the post-encephalitic subjects performed similarly to the normal control group. Both amnesic groups, however, were severely impaired on the test of temporal order memory. The results suggested that these two aspects of temporal processing were unrelated and that neither was related to severity of amnesia. There was no evidence to support the view that amnesic subjects' temporal order deficits are a result of frontal lobe dysfunction, but the temporal duration judgments correlated significantly with tests of cognitive estimation suggesting a contribution of frontal lobe function to estimation of temporal duration.

Temporal order memory was assessed in rats with either radiofrequency lesions of the fornix or aspiration lesions of medial prefrontal cortex using a delayed non-matching to sample procedure. Neither lesion group was impaired on this test of recency memory although both were impaired on a spatial non-matching task. These results are discussed in relation to previous animal studies and their implications for human amnesia.

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CHAPTER 1
General Theory of Temporal Processing

The study of temporal processing has taken on a perceptual framework but has been plagued by problems of definition. There appears to be not so much disagreement but little agreement as to the nature of the stimulus that represents the temporal characteristic, for example, whether it can be assigned to the external environment or placed purely within the organism.

Much of the animal literature concerned with the perception of time aims at establishing the properties of an internal clock and the psychophysical laws governing such a mechanism. Human studies have had little success in replicating the results of operant procedures used with animals but have concentrated on the perception and estimation of intervals varied quantitatively and qualitatively. This has brought many experimenters to the conclusion that it is not the duration interval itself that is the unit of perception but the events that serve to structure time.

For this reason attention has focused on the recency and frequency of events as a means of studying temporal processing. However there are animal studies that, although not aimed at the study of time as such, do show that the sequential ordering of events in the environment are important determinants of behaviour. For example, experiments involving classical conditioning paradigms are strongly determined by the ordering of events as are many memory tasks. The experience of time is one of flow. The present immediately becomes the past and the experience of time is inextricably linked to memory processes (Michon, 1975).

The aims of this research is to establish those regions of the brain involved in temporal processing. Evidence from animal studies, to be reviewed later, strongly implicates the hippocampus in such processing and particular emphasis will be placed on the role of this structure. The research looks at memory for time in terms of duration estimation and the memory for temporal order as it is unclear whether these two aspects of temporal processing are dependent on the same mechanisms. In addition, the research attempts to establish a correspondence between studies carried out on animals and those carried out with human subjects, that is rats having circumscribed brain lesions and human amnesic subjects. The literature will be reviewed concerning the nature of temporal processing in animals and humans followed by a review of studies involving brain lesioned animals and human amnesics.

1.1. Operant Procedures

1.1.1. Animal Studies - Methodology

A number of operant procedures have been devised to study time that depend either upon temporal regulation of the subject's own behaviour or upon temporal discriminations. Temporal regulation of behaviour may be required as a condition of reinforcement or occur as a by-product of the schedule.

i) Fixed Interval (FI):- In a Fixed Interval schedule a reinforcement is made available at fixed intervals of time so that the first response that is emitted once the interval has elapsed is rewarded. The signal for the start of the intervals may be the last reinforcement or the trials may be discrete. That is, an inter-trial interval may be given following reinforcement and a new interval signalled by a stimulus instigated by the experimenter or by the subject itself. The subject may be given a limited period in which to respond (limited hold). If no response is made during this time a new trial is commenced.

Patterns of responding in animals typically show what is called scalloping. For a period of time following reinforcement there is a pause in responding. After this pause the animal begins responding at an increasingly accelerated rate as the time of the next reinforcement approaches. Alternatively a pattern of responding called break-and-run may be adopted in which responding is continued after the pause at a sustained rate until the next reinforcement. The post- reinforcement pause is evidence of the temporal regulation of the subjects own responses. However, temporal regulation is not a necessary requirement of this schedule. The subject may adopt a strategy of continuous regular responding that will result in reward but will not show any evidence of temporal regulation, a situation more commonly occurring in human operant studies.

An adaptation of the discrete trials Fixed Interval procedure is the peak procedure. This involves two types of trials randomly mixed. On *'food'* trials the first response after a fixed time is rewarded. On *'empty'* trials no food is given and the trial lasts for an extended period of time and ends independently of responding. It is generally found that the rate of responding peaks at the time that the subject would receive food on the rewarded trials. There are, therefore, two main measures of performance - peak time, the time of the maximum response rate measured from the start of the trial, and peak rate, the value of the maximum.

ii)Differential Reinforcement of Low Rates of Responding (DRL):- In the DRL schedule a response is reinforced only if it follows the preceding response by a specified temporal interval. In this schedule, then, temporal regulation is a necessary requirement for reinforcement. Responses emitted before the critical delay reset the timer and are, of course, not rewarded. As a consequence response rates are reduced rather than increased as in FI. A limited hold can also be used in DRL so that responses must be made within a limited period of time before or after which they will not be reinforced. The most relevant data in DRL performance are inter-response times.

*iii) Temporal Discrimination Procedures:-*Temporal discrimination procedures involve temporal aspects of the environment rather than temporal aspects of behaviour as conditions of reinforcement.

In the temporal generalization procedure a signal is presented on each trial for some duration. If the signal presented is of a specific duration, for example 4 secs, the subject will be reinforced if a response is made. If, however, the signal is of a longer or shorter duration responses will not be rewarded. There is generally a limited period in which a response may be made, followed by a relatively long inter-trial interval.

The response measure is the probability of a response as a function of signal duration. The function usually rises to a maximum near the reinforced signal duration and then falls in a fairly symmetrical fashion with a slight positive skew when the data are plotted on a linear time scale.

For the bisection procedure a signal is presented for some duration, between 2 and 8 secs, for example. The subject is then given a choice of two responses, one response is rewarded if the signal was short (2 secs) and the other response is rewarded for a long signal (8 secs). A response made to a signal of intermediate duration is not rewarded. The response measure is the probability of a *"long"* response as a function of signal duration. It typically rises in an ogival fashion that is fairly symmetrical on a logarithmic time axis.

The basic characteristics of these temporal discrimination procedures have been used in many other ways to produce useful timing studies. They vary in the number of reinforced signal durations, the number of response alternatives and the response measures to name but three.

1.1.2. Properties of the Internal Clock.

The reliability with which an animal responds to temporal attributes in the environment, as displayed in the many studies involving classical and instrumental conditioning, has led researchers to investigate the properties of the internal mechanism responsible for the discrimination of time. The clock is presumed to be an internal central mechanism. Evidence for this comes from studies that show cross-modal transfer from one sensory modality to another in temporal discrimination tasks. Meck and Church (1982) used both a long/short duration discrimination and a temporal generalization procedure to show cross modal transfer from sound to light and vice versa. They did show, however, that discrimination performance was better for sound than for light, a phenomenon also demonstrated in pigeons (Stubbs, Dreyfus & Fetterman, 1984) and humans (Goldstone & Lhamon, 1974). Transfer from light to sound was also greater than from sound to light. This does suggest that the clock is a central mechanism but that timing is also affected by the nature of the stimulus.

Such cross modal transfer could be accomplished by a single timing mechanism, but rats can time more than one duration simultaneously (Meck & Church, 1984) suggesting more than one timing mechanism that can process in parallel. In this experiment a FI procedure was used with a light signalling the overall 50 sec interval, which was divided into 10 sec segments by a noise signal presented for 1 sec at the 11th, 21st, 31st and 41st sec. As the two signals indicated the occurrence of the same reinforcement it is difficult to say whether they were timing the two signals totally independently or as part of the same overall pattern.

In the final experiment rats were trained on a FI schedule using either a visual signal or an auditory signal. When presented with a compound signal in both visual and auditory modes the response rate curve was shifted to the left by some 10 secs. The authors concluded that in this instance the rat was responding to only one of the interval signals.

Animals can, however, perform complex tasks requiring the integration of more than one interval duration. Pigeons, given a sequence of four visual stimuli in the order red-green-red-green, can add together the two red durations and the two green ones and respond on the basis of whether the total red duration was longer than that of the total green (Stubbs et al, 1984). Rats also can integrate two successive signals. Using the peak procedure Roberts (1981) showed that a blackout in the signal increased peak time by the length of the blackout. It would appear that the clock can be stopped and restarted as required and that successive durations can be integrated.

To account for these findings Church (1984) proposed a psychological process model of timing. It is composed of four major parts: clock, working memory, reference memory, and comparator. The clock is composed of a pacemaker, switch, and accumulator. The pacemaker is defined as an internal mechanism that generates pulses. These pulses are switched into an accumulator. The pulses related to the signal on the current trial are compared to a remembered number of pulses in reference memory that led to reinforcement. The comparator can combine the value from accumulator with a value in reference memory according to a response rule to make a decision. If a response is made and reinforced, the value is stored in reference memory.

As a test of this model Meck (1983) carried out an experiment that dissociated clock speed and memory processes by pharmacological manipulation in rats. A short/long temporal discrimination task was used and the effect of drugs on clock or memory processes was inferred from the pattern of change in the point of subjective equality of the psychophysical functions under training and testing conditions. The logic behind this is that drugs that affect the clock should have an initial behavioural effect but that this should disappear with repeated trials as the animal learns to rescale time. Also there should be a rebound effect when the drug is removed. But if the drug affects the memory processes its effects should be permanent with no rebound effect when the drug is removed.

It was found that methamphetamine increases clock speed and haloperidol decreases it. This points to the role of dopamine as a major determinant of the timing mechanism of the rat as methamphetamine increases the effective level of dopamine whereas haloperidol decreases it. A similar pattern can be produced by manipulation of diet. Prefeeding with standard diet or high carbohydrate such as sucrose decreases clock speed whereas prefeeding with a protein such as casein increases speed (Roberts, 1981). Footshock stress was found to have a similar effect in that continous footshock increases clock speed whereas abrupt termination of the shock decreases it.

Vasopressin, oxytocin and physostigmine were found to decrease whereas atropine increased the remembered durations of intervals. Physostigmine inhibits the acetylcholine degrading enzyme, increasing the effective level of acetylcholine, and atropine blocks acetylcholine receptors. This suggests acetylcholine receptors are involved in the memory component of the model. As drug administration during training and not testing was relevant the transformation of the value from working memory to reference memory is affected and not the transformation of a value in reference memory to the comparator. In other words it is storage rather than retrieval that is being manipulated.

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There are two ways in which elapsed time may be compared with remembered time. A count-down timer would commence with the critical value in the accumulator and count down until it reached 0 in a similar way to an egg timer, and a count-up timer would function in a similar way to a stop-watch beginning at 0 and counting up to the critical value stored in reference memory. Roberts (1981) showed that rats use a count-up timer in a variant of the peak interval procedure in which rats begin timing the interval in the presence of one stimulus and then shift to timing the interval in the presence of another stimulus. With a light stimulus food was primed at 20 seconds and with a tone stimulus food was primed at 40 seconds. On shift trials the stimulus was changed from light to tone at 5,10 or 15 seconds and no food was given as in the peak interval procedure. A count-down timer would read 15, 10 or 5 seconds left depending on the time of the shift. If the animal does not reset its timer at the shift, peak time would occur 15, 10 or 5 seconds after commencement of the tone stimulus; if it does reset the timer at shift, peak time would occur 40 seconds after the shift. The rats, in fact, showed a peak response rate 40 seconds after the start of the trial which would be predicted from a timer that counts up continuously from the start of the trial and compares the accumulated values with the value appropriate to the current stimulus.

In summary, animals have a central internal timing mechanism that can time intervals of different lengths sequentially and simultaneously using a linear time scale. The clock functions as a stop-watch using a count-up mechanism which can be stopped and re-started, integrating successive intervals. Stimuli in different modalities can differentially affect the timing mechanism and this mechanism can be dissociated from memory processes by pharmacological, dietary and environmental manipulations.

1.1.3. Other factors involved in timing.

Although animals do appear to have some internal mechanism that enables them to regulate their behaviour temporally, there are many internal and external factors that may affect such a clock.

In animal studies temporal regulations are largely a function of the contingencies of reinforcement. It has been found that rate of responding in FI schedules is directly related to the amount of reinforcer when different quantities of reinforcer are used in the same session (Staddon, 1970). If the same quantity of reinforcer is used constantly across sessions there is no change in the distribution of responses (Harzem, Lowe & Davey, 1975). There is also variation of the post reinforcement pause as a direct function of the previous reinforcement (Staddon, 1970).

Similar findings have been reported with DRL schedules. There is an inverse relation between quantity of reinforcement and the quality of temporal regulation as measured by a reduction in inter-response time and lowering of efficiency ratio in pigeons (Lejeune & Mantanus, 1977). Varying the quantity of reinforcer, therefore, has an effect not only upon the animals' responding but may also have an effect on the actual timing mechanism. There has been no evidence for a differential effect of quality of reinforcer.

The quantity of the reinforcer is not the only source of proactive interference. As with many other tasks there is a general non-specific effect of proactive interference when using massed trials as opposed to discrete trials. Church (1980) isolated the response made by the rat on the previous trial as a source of interference in a temporal discrimination task. If a response was not permitted on the previous trial the duration of the signal on that trial had no effect on performance.

Temporal regulation and discrimination are therefore dependent upon factors additional to the internal clock mechanism.

1.1.4. Human Operant Behaviour.

The responding of human subjects on operant procedures using temporal schedules of reinforcement typically do not show the same patterns as those seen in animal studies. As mentioned in the previous section, animal responses to FI contingencies generally show temporal regulation in the form of a pause-respond pattern, such as scalloping (Branch & Gollub, 1974; Dews, 1978; Lowe & Harzem, 1977), or break and run (Cumming & Schoenfeld, 1958; Schneider, 1969; Staddon, 1972)

Human studies show either a consistently high response rate throughout each interval (Leander, Lippman & Meyer, 1968; Lippman & Meyer, 1967) or a very low response rate consisting of one or two responses each interval (Baron, Kauffman & Stauber, 1969; Leander et al., 1968; Lippman & Meyer, 1967). These response patterns are not an artifact of different experimental set-ups as both types of responding have been seen within one study (Leander et al., 1968; Lippman & Meyer, 1967). High rates of responding show no sensitivity to FI parameters (e.g. Leander et al., 1968) whereas low rates vary as a function of the schedule (e.g. Baron et al., 1969).

A number of explanations have been put forward to explain the lack of sensitivity of human subjects to operant schedules. These are mainly based on the procedural differences between animal and human experiments. In animal studies shaping is used to

establish responding whereas human subjects are given instructions. Giving explicit instructions as to the nature of FI schedules produces an orderly progression of response rates as a function of reinforcement intervals (Baron et al., 1969). Uninstructed subjects, however, generally show continuous high rates of responding although this is not true of all subjects (Baron et al., 1969; Leander et al., 1968; Lippman & Meyer, 1967) Awareness of the reinforcement contingency is related to performance and some uninstructed subjects do acquire this awareness (Leander et al., 1968).

Matthews, Shimoff, Catania and Sagvolden (1977) used a yoked Variable Ratio-Variable Interval Schedule to compare performance after shaping of key presses with performance after demonstration. If responding was established by demonstration, schedule sensitivity did not appear. When responding was established by shaping, ratio schedules maintained higher response rates than interval schedules. This was also dependent, however, upon the subject making a consummatory response. When the appropriate key press was made, a red light indicated that a reinforcer was available. A button then had to be pressed to advance the counter. Animals generally have to interrupt their operant behaviour to make a consummatory response such as eating. In human studies, on the other hand, the reinforcement deliveries are in the form of points on a counter that usually involve less marked stimulus changes and no consummatory response.

Response cost has also been used as a way of manipulating response patterns on Fixed Intervals. For every unreinforced response a point is taken off the counter. Under these circumstances subjects who have not received explanatory instructions as to the nature of the schedule as well as those who have, show low and differentiated rates of responding (Baron et al., 1969). In the same experiment the importance of previous reinforcement histories was examined. Giving explanatory instructions did not improve performance in subjects who had already established poorly differentiated behaviour in the no instructions condition.

Although these manipulations produce some sensitivity to the temporal schedules they do not produce the pronounced pause-respond pattern seen in the animal literature. There are the occasional small scallops produced but this is not a consistent pattern in any one individual or experiment. One procedure, however, that does produce the post reinforcement pause is one that involves performance of a secondary signal detection task to obtain reinforcement. When reinforcement conditions are satisfied on the FI schedule a dial is illuminated, movement on this dial must be identified before reinforcement is given (Azrin, 1958; Holland, 1958; Laties & Weiss, 1963).

Lowe, Harzem and Bagshaw (1978) adapted this dual task by providing two response panels. One was used for responding to a DRL schedule *(Panel A)* whilst the other illuminated a clock for 0.5secs when pressed *(Panel B)*. The two experimental conditions centred around the nature of the clock made available by pressing Panel B. In the binary clock condition the *"clock"* produced was a light, i.e. if reward was available on Panel A at the time of pressing panel B this light contained a green circle; if no reward was available on panel A then the green circle was absent. In the digital clock condition the clock produced showed the time in minutes and seconds since the last reinforcement on panel A.

The schedule included a limited hold (LH), that is a response is rewarded only if it occurs before a specified interval. Therefore, panel B could be used to assess the appropriate time to respond on panel A in order to maximize reinforcement. Given efficient DRL performance, responding on panel B was effectively on an FI schedule with LH, with the FI interval being the same length as the DRL schedule on panel A.

The response obtained on panel A was the same for both experimental groups, a single response per reinforcement. Both groups were relying on panel B to maximize reinforcement. It is in their response patterns on panel B in which the differences lie. In the binary clock condition the response pattern showed a post-reinforcement pause, followed by a constant terminal response until reinforcement, i.e. break-and-run pattern. In the digital clock condition the response was scalloped. Even schedule-dependent variables which had only previously been reported in animal work such as the negative relationship between relative post reinforcement pause and schedule value were shown.

All subjects reported that they felt that reinforcement was dependent on the passage of time. Those in the binary clock condition also reported internalised counting whereas those in the digital clock condition did not. The binary clock group paused after reinforcement until they felt that the time was up and then commenced responding until a reinforcement was indicated on panel B. The digital clock group, however, were told exactly the length of time to reinforcement so their responding accelerated as they knew this time was approaching.

Given the appropriate circumstances human subjects do, therefore, produce response patterns similar to those in animals. Using the appropriate tasks, comparisons between human and animal response patterns become possible.

In conclusion, humans do not show the same response patterns as animals in operant procedures such as FI. They show a consistently high response rate that is not sensitive to schedule parameters or very low rates which vary as a function of the schedule. Variables such as instructions, responses, response cost, previous reinforcement history have been manipulated to produce some sensitivity to the temporal schedules but not the pause-respond pattern seen in the animal literature. Tasks requiring secondary signal detection have achieved this to some extent. For example, procedures using secondary responses that give access to a digital clock displaying time since reinforcement in a DRL schedule produces the scalloped pattern of responding seen in FI studies in animals.

1.2. Temporal Order
1.2.1. Human Studies

The studies of human operant responding would appear to be *pure* measures of duration discrimination i.e. that it is time itself which is the stimulus of perception. A number of experimenters, however, would dispute that this is the case, asserting that it is not the *duration* itself but the *sequential order* of events within the duration that determine time estimates (Fraisse, 1984; Michon, 1975; Ornstein, 1969; Vroon, 1972). On the other hand, Crowder and Green (1987) feel that serial order and time have been confounded in many experiments and that there should be a clear distinction between the two.

Intuitively one feels that the subjective experience of time is very much dependent upon events in the external and internal environment. Feelings of boredom, impatience or anticipation often seem to produce a lengthening in experienced time. Experimental evidence points to a number of such variables that influence estimation of durations.

An obvious comparison to make on considering the nature of the perceived stimulus is the difference between estimations of *filled* intervals and those of *empty* intervals. Results of such experiments are contradictory. While it has been reported that inter-interval tasks have no effect upon duration estimation (Crowder & Green, 1987), others have found that when the duration is filled with complex stimuli it appears longer (Ornstein, 1969) and that an empty interval appears longer than a filled one.

One explanation of these equivocal results is in terms of differences in task demands. An important factor that is varied between and within experiments is whether the estimation is made retrospectively or prospectively. In the prospective paradigm subjects are explicitly told beforehand that they will be required to make an estimation of the duration of an interval. Under retrospective conditions subjects receive an unexpected

test of duration estimation after the interval. Another important variable is the degree of processing capacity required by the inter-interval tasks.

It is generally found in prospective studies that performing some effortful and difficult task shortens the perceived duration (Hicks, Miller, Gaes & Bierman, 1977; Hicks, Miller & Kinsbourne, 1976; McClain, 1983). An attentional capacity model would explain this in terms of the more capacity that is allocated to non-temporal tasks the less capacity is available to attend to time.

The effects of increased attentional demand upon retrospective judgements are less clear. Some studies have found that the more difficult the task the longer the perceived duration (Ornstein, 1969; Underwood, 1975). Other studies have produced the opposite result (Vroon, 1970) and yet others have found no effect of task difficulty on retrospective judgements (Hicks et al., 1976, McClain, 1983). Brown (1985) found that retrospective judgements were generally less accurate than prospective judgements but that they were both affected in a similar manner by increases in task demands. Shorter and more inaccurate judgements were given with increases in interval task complexity.

There has been some debate as to whether temporal information is processed automatically. Hasher and Zacks (1984) developed a number of criteria that they felt should be satisfied in order to attribute automaticity to information processing. First, automatic processing is independent of the individuals intentions. It will not, therefore, be manipulated by instruction e.g. incidental or intentional. Second, it is invariant across a wide range of ages, educational background, social class etc. and is insensitive to training. Third, it places no demands on information processing capacity. Most studies on both sides of the debate have used temporal order paradigms, but the studies quoted above concerning the retrospective and prospective estimations of intervals would suggest that the perception of duration does not fulfill the criteria for automaticity. Both prospective and retrospective estimations have been shown to compete for processing capacity with other non-temporal information. Prospective or intentional instructions as opposed to retrospective or incidental instruction have a differential effect on performance.

Tzeng and Cotton (1980) propose, in their study-phase retrieval model, that the processing of the sequential ordering of events occurs automatically. Items in a list are encoded against the contextual background of previous items in the list. The later items prompt retrieval and rehearsal of earlier associated items resulting in the automatic encoding of information concerning the temporal order. Evidence for this comes from an experiment in which subjects learned a list of categorizable words presented randomly. Relative

recency judgments were much better for related words than for unrelated words (Tzeng & Cotton, 1980; Winograd & Soloway, 1985). That reminding or study phase retrieval can act as a cue for temporal order judgments would appear to be the case but there is no evidence to suggest that this is indeed automatic.

Michon and Jackson (1984) dispute that temporal coding is automatic and provide evidence to the contrary. Temporal order retention suffered under incidental (subjects were instructed to expect a recognition test) but was much improved under intentional instructions. In another experiment subjects were instructed to recall half of the words in a list and to forget the other half. Words that were to be recalled produced better performance on an incidental temporal order test than the *'forget'* cued words. This result was more marked for concrete words than for abstract words (Jackson, Michon & Vermeeren, 1984). They conclude by saying that just being in the rehearsal set is not a sufficient condition for temporal coding to take place but that it is also dependent on encoding strategies which are typical of deliberate processing.

This is confirmed in a further experiment in which subjects were asked to verbalize their encoding of a list of words for recall (Michon & Jackson, 1984). Simple rehearsal did not yield correct judgements of temporal position whereas constructing one connected story that was repeated at retrieval produced good temporal order retention. A series of unconnected stories produced good within-story temporal ordering but poor between-story temporal retention.

Tzeng and Cotton's (1980) contextual association hypothesis of temporal order judgements is elaborated and extended to duration judgements in Block's (1982) contextual change model. According to this model changes in environmental context and process context (the cognitive processes that a subject engages in) will affect estimations of remembered duration. Using a retrospective comparative duration judgement, Block (1982) varied contextual change between two durations as well as within a duration. When the environmental context remained unchanged between the two time intervals a positive time-order error occurred. This is a common finding in such comparative judgements in that the first of two equal durations is judged to be longer than the second. The contextual change model explains this by assuming that cognitive context changes rapidly at the beginning of a novel experience. When the environmental context was changed between the two intervals the time order error was eliminated. In a manipulation of process context subjects processed words at either one of two levels (structural or semantic) or at both levels within a duration. Changes in process context lengthened remembered duration but effects of process and environmental context

change were not additive. These experiments provide evidence for the hypothesis that the greater the encoded and retrievable contextual changes, the longer is the remembered duration of the time period.

A further set of experiments (Block, 1986) manipulated process context prior to a comparative duration judgement. In support of his previous findings the preceding task caused a relative lengthening of the duration that required a different kind of cognitive processing. A further finding, however, contradicted the assumptions of the model in that an imagery task that maximized the number of varied contextual associations was judged as shorter, rather than longer, than an imagery task that minimized the number of varied contextual associations. A modified version of the model proposes that it is an overall change in context from a preceding duration that is the critical factor.

Both sets of experiments did show, however, that duration judgements are dissociable from other memory processes. In the first set of experiments subjects carried out tests of list discrimination and memory for serial position on the words studied during the time intervals. It was found that list discrimination improved with change of context whereas serial discrimination within a list was unaffected. It is not surprising, however, that a change of context between lists of words does not affect within list serial discrimination but the contextual association hypothesis of Tzeng and Cotton (1980) would expect that process context change within a list would improve serial position judgements. In the second set of experiments subjects were given recall and recognition tests in addition to the list discrimination and serial order tests (Block, 1986). Although the preceding task had an effect on remembered duration, depending on the type of cognitive processing carried out during that duration, it had no effect on recognition, recall, list discrimination or serial order judgement. This suggests that duration judgements are not dependent entirely on memory processes as measured by recognition and recall even using a retrospective duration judgement paradigm which is in effect testing a subjects memory of a temporal duration rather than the ability to estimate an ongoing duration as in a prospective duration judgement procedure. It would also suggest that time estimation may be independent of temporal order memory.

Duration judgements, therefore, are dependent upon the way in which they are measured, that is retrospectively or prospectively, the tasks that are carried out during those intervals, and internal and external contextual factors prevailing in and around durations to be estimated. Both temporal order and temporal duration judgements cannot be considered as automatic processes but are dependent upon deliberate processing strategies.

1.2.2. Animal studies of sequential discrimination.

That animals are sensitive to the order of events in the environment can be seen from a number of different laboratory tasks. Serial anticipation tasks use sequences constructed from the size of food reward. Rats are trained to run down an alley to receive a reward, the size of which (number of pellets) is varied from trial to trial. The rat learns to run quickly in anticipation of large rewards and slowly in anticipation of small rewards (Hulse & Dorsky 1977).

In contrast to serial anticipation tasks which test an animal's ability to anticipate a sequence that is consistent from trial to trial and that provide feedback at each point in the sequence, sequence discrimination tasks require the animal to discriminate one sequence of events from several other sequences of the same events and feedback is provided only at the end of the trial. An example of such an experiment is where pigeons are trained to discriminate a sequence of two colours from other sequences of the same two colours (Weisman, Wasserman, Dodd & Larew 1980). It was found that the pigeons used both elements in the sequence in making their discrimination but the final element was particularly important in making the correct discrimination.

There are a number of ways in which such a sequence discrimination could be made. Using a retrospective scanning scheme the animal would hold each stimulus in working memory and at the end of presentation of the test stimulus scan backwards comparing the remembered list of stimuli with a list of the positive sequence held in reference memory in order to make a decision. The order of appearance of the stimuli could be represented in memory by trace strength or directly by reference to an internal clock and temporal tagging.

Alternatively a prospective conditional discrimination means that the discrimination of each element in the sequence is conditional upon the immediately preceding element. In this case the animal processes a sequence until it reaches a stimulus that does not match the corresponding stimulus in the positive sequence and then stops processing further stimuli. Evidence for such a scheme comes from the finding that pigeons are capable of deciding and reporting that a particular sequence is negative even before the sequence ends (Weisman, Gibson & Rochford, 1984; Terrace, 1986). This means that it is not necessary for the animal to hold a coherent, ordered representaion of the sequence to carry out such a discrimination.

Roitblat, Scopatz and Bever (1987) and Roitblat, Bever, Jelweg and Harley (1991)

provide evidence that pigeons do, in fact, use hierarchical representations in three item sequence discriminations. They used a technique to estimate the degree to which each element and combination of elements in the sequence were controlling discriminative performance. Early in acquisition the pigeons' performance was controlled by individual elements whereas later in training the birds' performance was controlled by higher order units, that is by the first and third elements. This is inconsistent with the prospective conditional discrimination scheme, as it suggests that birds wait until the end of the sequence to make decisions regarding the identity of the sequence and that performance is controlled by more abstract representations that include information about events and their order.

There is also evidence that pigeons can *chunk* items in a list to facilitate memory in a similar way to humans. Five-item lists consisting of three colours followed by two geometric shapes or four colours and one geometric shape are learned faster and responded to with shorter latencies than homogenous lists of all colours or all geometric shapes (Terrace, 1991). The integrity of the chunk was maintained if the animal was required to learn a second list in which the chunk occupied the same ordinal position (Terrace & Chen, 1991a) and also when it occupied a different ordinal position (Terrace & Chen, 1991b).

When recalling a list of items human subjects generally exhibit a U shaped serial-position curve, that is, memory for the first and last items in the list are better than memory for intermediate items. Attempts have been made to replicate this finding in animals. Some studies have demonstrated a U-shaped function in monkeys (Buchanan, Gill & Braggio, 1981; Sands & Wright, 1980; Wright, Santiago & Sands, 1984) and rats (Dimattia & Kesner, 1984; Kesner, Measom, Forsman & Holbrook, 1984; Kesner & Novak. 1982), whereas others have obtained only a recency effect (Dimattia & Kesner, 1984; Gaffan & Weiskrantz, 1980; Roberts & Smythe, 1979).

This correspondence between human and animal performance is found only under certain circumstances. For both pigeons and monkeys it has been shown that the delay interval between presentation of the last item in the list and test is important in producing the U- shaped curve. Pigeons exhibit a recency effect at 0s delay, recency and primacy at 1 and 2 s and primacy only at 10s (Santiago & Wright, 1984). Monkeys show recency only at 0s, primacy and recency at 1,2 and 10s, and primacy only at 30s (Wright, Santaigo & Sands, 1984). This they explain in terms of the interaction of pro- and retroactive interference over time. The large amount of retroactive interference interferes with remembering the first list items. Dissipation of retroactive interference

with time allows the primacy effect to emerge whereas proactive interference is usually small and grows with time interfering with memory for the last items and eventually eliminating the recency effect.

DiMattia and Kesner (1984) suggest that, in rats, studies resulting in a primacy and recency effect use a matching procedure and those showing only a recency effect use a non-matching procedure. For example, serial position effects in rats are often tested using a radial arm maze, the rat being forced to enter a number of arms in a random order and then given a choice between a previously presented arm and a novel arm. In a matching procedure the rat must choose the previously presented arm and in a non-matching procedure the rat must choose the novel arm. Choosing the novel arm is an easier task for rats as it utilizes the rats natural predispositions. The matching task, therefore, being a harder task depends upon effortful processing, thus producing more processing of the initial items in the list resulting in a primacy effect. A U-shaped serial position curve is also exhibited in a procedure in which the rat, after entering seven arms of the maze, is required to choose the earlier arm from a choice between the first and second arms, the fourth and fifth arms or the seventh and eighth arms (Kesner & Novak, 1987). This again is interpreted in terms of automatic and effortful processing as the task requires effortful processing by placing a sufficient load on the cognitive system. It does not explain, however, why effortful processing differentially effects the first and last items of the list and not the intermediate ones.

Dale (1987) carried out an analogous task with human subjects in which the subject sat in the centre of a circle of lights. In the item recognition condition the subject saw a list of seven lights and was then required to make a choice between either the first, fourth or seventh light and the eighth non-list light, the correct choice being the non-list light. This procedure was similar to that used by DiMattia and Kesner (1984). The order recognition condition used a similar procedure to that used by Kesner and Novak (1987). A correspondence was found with the rat data in that the item recognition condition produced a recency effect whereas the order recognition produced both a primacy and recency effect. When a delay of 30s was introduced the curves remained U-shaped unlike the findings of Santiago and Wright (1984) and Wright et al. (1984) with pigeons and monkeys, although it is possible that a similar effect might have occurred at a longer delay. Dale (1987) however suggested that neither the interference theory nor the effortful processing theory could account for their data, but it does show a striking correspondence between performance of temporal order judgements by humans and animals.

1.3. Conclusions.

It would appear from the foregoing literature review that human temporal processing is much more complex than that of animals. This, and the variability of findings in the human literature, may be purely a reflection of the number and variability of procedures used to assess temporal discrimination in humans. The operant procedures used in animal experiments use a prospective paradigm employing 'empty' intervals. Retrospective paradigms assess memory for temporal duration whereas prospective paradigms assess judgement of time in passing and may involve different processes. Operant procedures used with humans have been largely unsuccessful but this may be overcome by adapting the procedure as proposed by Lowe et al. (1978). This would provide a more appropriate way of assessing temporal estimation as inaccurate judgements are more likely to occur when a person must *translate* a duration experience into a conventional verbal unit such as seconds.

The internal clock model proposed by Church (1984) fits findings from the animal and human literature that subjective and actual duration is linearly related but fails to take account of the numerous cognitive factors that play an important part in human temporal processing. Studies manipulating the type of task carried out during the interval show that factors such as attention, amount of information processing capacity, the strategies used, and the context in which the judgement is made all affect judged duration. This does not rule out *internal clock* models but suggests that they are too simplistic. Neither does it suggest that time is processed in a different way by animals. It was shown that factors other than the duration itself do affect timing in animals but few such variables have been studied systematically.

An alternative to the *internal clock* model of timing is the view that temporal judgements are made by reference to the type or number of events that occur within the interval. A number of variations of this viewpoint have been put forward which explain duration experience in terms of the storage size in memory of the encoded stimulus information (Ornstein, 1969); attentional allocation during the interval (Hicks, Miller & Kinsbourne, 1976); and memory change models such as Block's (1982) contextual change hypothesis. One difficulty with such models is that their explanations tend to be purely descriptive and circular in that they do not propose any independent way of measuring, for instance, change in cognitive context or storage size. It is difficult to ascertain which specific cognitive processes are involved when a person remembers the amount of contextual change, the amount of storage space required or the attention allocated to some information. It is clear, though, that the estimation of durations do depend upon events occurring in the duration and the number and order of events may

be one cue to duration but there is no evidence to suggest that it is the only cue. Block (1986) did, in fact, use a manipulation that affected duration judgement but not serial order judgement. A dissociation has also been shown in both animal and human experiments between duration estimation and memory processes suggesting that duration judgement is not solely dependent upon memory for events within the duration.

It remains unclear, then, as to whether temporal order and temporal duration are dependent upon the same or similar processes so it would be expedient to consider them as independent but related. Neither is it clear whether duration judgement is dependent upon memory processes. Internal clock models would suggest that it is not, whereas cognitive models suggest that duration experience is inextricably tied to memory processes. This question will be considered in the following sections.

CHAPTER 2
Lesion Studies

2.1. The Hippocampus.

There is little disagreement that the hippocampus is involved in memory processes. The exact nature of this involvement, however, has caused great debate over the last two decades which is far from being resolved. Two of the more influential theories propose a spatial mapping or working memory hypothesis but some researchers have proposed that the hippocampus may also be involved in temporal processing either exclusively or in addition to other theories. Indeed, the evidence is highly suggestive that this may be the case. The evidence from animal studies for the role of the hippocampus in memory for time and sequential order will be discussed in the following sections.

2.1.1. Operant Procedures.

It is generally accepted that hippocampal lesions produce deficits in DRL responding in rats, pigeons and monkeys. The following citations will refer to studies using rats unless otherwise stated.

There is some dispute, as to whether the DRL deficit is in the timing component of the task or whether hippocampal animals cannot inhibit previously well established responses. Several authors have reported low or normal rates of responding on Continuous Reinforcement Schedules (CRF) and significantly higher rates of responding when transferred to intermittent operant schedules (Clark & Isaacson, 1965; Schmaltz & Isaacson, 1965;). When CRF pretraining is omitted and DRL is established from the outset the deficit in DRL appears to be attenuated (Schmaltz & Isaacson, 1965). This failure to inhibit previously established reponses is further supported by evidence of decrements in reversal learning generally exhibited by hippocampal lesioned animals (Riddell, Malinchoc & Reimers, 1973).

In contrast, other studies report equally high levels of responding on CRF as on DRL schedules (Haddad & Rabe, 1969; Reilly & Good, 1989 (pigeons)). Suggestions accounting for this have been made in terms of increased arousal associated with expected reinforcement and a lack of inhibition of motor responses (Gray, 1984; Jackson & Gergen, 1970 (monkeys)).

Hippocampal animals do, however, show inhibition of responses in temporal discriminations under certain circumstances. In a FI60 schedule, rats with large hippocampal

lesions showed higher response rates in the later segments but not earlier segments (Haddad & Rabe, 1969). Similarly Ellen and Powell (1962) found that sham operated control rats learned to withold responding sooner than lesioned rats but by the sixth day of training there was no difference between the groups. The lesions in this study were small, though, and limited to the anterior hippocampus. Overresponding was attenuated in a study by Braggio and Ellen (1976) by providing a cue light when reinforcement was due in a DRL20 schedule. When the cue light was removed the hippocampally lesioned animals continued to emit fewer responses.

Overresponding, therefore, is not necessarily the cause of deficits in performance measured in terms of the number of rewards earned and hence the animals' temporal discrimination. Boitano, Dokla, Mulinski, Misikonis and Kaluzynski (1980) used an incrememtal step DRL paradigm to show that the length of the interval is an important factor in the deficit displayed by hippocampectomised rats. The lesioned rats performed like controls up to a DRL of 5 seconds but only 3 out of 11 rats performed normally at DRL11 and only one succeeded at DRL14 and up.

In a Peak Interval Procedure, Roberts (1981) showed that peak time and peak rate are independent measures of timing performance (see section 1.1.2.). Fimbria-fornix lesions produce comparable response rate functions to normal rats in Peak Intervals of 10s, 20s and 50s (Meck, 1988; Meck, Church & Olton, 1984; Olton, Meck & Church, 1987). The lesioned animals are inhibiting responses and displaying sensitivity to temporal duration. The most striking feature of their performance is a consistent left shift in peak time by an amount relative to the fixed interval by about 20%. The apparent permanence of this left shift in peak rate suggests that the internal clock is unaffected by fornix lesions as the rats do not learn to rescale time to coincide with reward but that the time of reward stored in reference memory was reduced (Meck, 1983; 1988). A similar pattern of results was found with a temporal bisection procedure (Meck, Church & Olton, 1984). Rats were trained prior to undergoing fimbria fornix lesions and then tested post-operatively. The lesion did not affect sensitivity to duration as the difference limen was the same as that in training but the point of subjective equality was shifted to the left, again suggesting a decrease in the time of reinforcement held in reference memory. If duration judgements are processed by storing the amount of time that has passed in working memory one would expect sensitivity to duration to be affected in these experiments. It would appear, therefore, that the 'clock' works independently of working memory.

The results of peak interval experiments question the validity of the working memory hypothesis with their implications of deficits in reference memory for temporal events, although working memory has also been shown to be affected by fimbria fornix lesions in response schedules. When a gap is inserted in the interval of a FI peak procedure normal rats can add the duration before the gap to that following the gap to show a peak time consistent with the time of reward. Rats with fornix lesions, however, time the interval from the end of the gap (Meck, Church & Olton, 1984).

Interpretation of lesion studies must of course take into account the site, extent and method of lesioning. There is some disagreement as to the area of the hippocampus involved in the deficits seen in response schedules. Haddad and Rabe (1969) found anterior hippocampal lesions had no effect on FI responding whereas Johnson, Olton, Gage and Jenko (1977) found DRL was disrupted by anterior hippocampal but not posterior hippocampal ablations. Total transections of the fimbria-fornix reliably produce impairments in response schedules (Johnson et al., 1977) and it would appear that neurotoxic lesions such as those made with ibotenic acid produce lesions that are functionally similar to, but less effective than, aspiration or radio frequency lesions (Sinden, Rawlins, Gray & Jarrard, 1986). The best account of the variation in findings is that performance is dependent not so much on site but extent of damage to the hippocampus and its projections (Sinden et al., 1986). Brookes, Rawlins, Gray and Feldon (1983) found that there was no differentiation between medial and lateral septal lesions in DRL tasks suggesting that the task cannot differentiate between sites of septo-hippocampal damage.

Rats show a consistent, well established, deficit in temporal schedules that is not a consequence of a failure to inhibit responding. It is suggested that this is not an impairment of timing, per se, as proposed by the internal clock model but is an impairment in reference memory. This causes problems for the working memory hypothesis and is not easily encompassed by the spatial mapping model. It is proposed that the extent of damage to the hippocampus and not the site of the lesion that is responsible for the deficit.

2.1.2. Classical Conditioning.

The spatial mapping theory of hippocampal funtion argues that the hippocampus acts as part of a neural system that forms a cognitive map of the environment (O'Keefe & Nadel, 1978). Evidence for this comes from electrophysiological recordings that showed the activity of single cells in the hippocampus correlate with the animals location in the environment when rats are required to solve problems in a radial arm maze

(Olton, Branch & Best 1978), or elevated T maze (O'Keefe, 1976), and also in freely moving rats (O'Keefe & Dostrovsky, 1971). In addition, rats with hippocampal or fornix lesions are impaired in their ability to solve problems which require spatial mapping (O'Keefe & Black, 1978; O'Keefe, Nadel, Kieghtly & Kill, 1975; Olton, Walker & Gage, 1978). One area of research that cannot be accounted for by such a view has focussed on classical conditioning of the rabbit's nictitating membrane response (NMR). It is unlikely that spatial cues play any role in the rabbit NMR preparation as the animal remains virtually motionless throughout the conditioning session and the conditioned stimuli (CS) and unconditioned stimuli (US) are delivered in the same spatial locations at all times. Results from experiments using the rabbit NMR have been interpreted by many researchers as evidence for the involvement of the hippocampus in temporal processing (Berger & Thompson, 1978; Moore, 1979; Soloman, 1979, 1980) which functions in addition to spatial processing.

Classical conditioning depends upon the organism perceiving the temporal relationship of events or the sequential order of events in the environment. A conditional response (CR) is evoked if the conditional stimulus (CS) is in close temporal proximity to the unconditional stimulus (US). There is a growing amount of evidence which suggests that the hippocampus is involved in the processing of such temporal relationships although the precise nature of this involvement is not clear.

Electrophysiological studies have shown that neural activity in the hippocampus is correlated with conditioning of the rabbit's NMR. Berger, Alger and Thompson (1976) reported an increase in activity of the pyramidal and granule cell layers of the dorsal hippocampus which was highly correlated with the rabbit NMR. The increase in activity began from the second CS-US pairing and occurred within the first eight pairings and preceded the CR by 35-40 msecs, but only under conditions where behavioural learning occurred. Also the hippocampal electroencephalogram (EEG) has been shown to predict the rate of acquisition of NMR prior to conditioning (Berry & Thompson, 1978). Animals displaying high levels of activity in the high-frequency range (8-22Hz) conditioned more slowly than animals that displayed a higher level of activity in the low frequency range (2-8 Hz). More recently, Weisz, Clark and Thompson (1984) interpolated single pulse electrical stimulation of the perforant path, recording the monosynaptic population spike response from dentate granule cells, during acquisition of the NMR. There was a marked increase in excitability of this monosynaptic field potential that closely paralleled the development of the learned behavioural response over the days of training. Thompson (1990) points out the similarities between the enhanced pyramidal neuron response in classical conditioning and the enhanced pyramidal neuron

response (long term potentiation) following tetanus of input pathways which is considered as a putative mechanism of memory storage. Although such studies would suggest that the hippocampus is involved in the learning of simple classically conditioned asociations, the results of lesion studies appear somewhat contradictory. Using a delay conditioning paradigm in which the CS and US overlap, hippocampectomy does not disrupt acquisition of the rabbit's NMR (Schmaltz & Theios, 1972). It is possible that the hippocampus is essential only under certain circumstances as hippocampectomy has been found to disrupt more complex conditioning tasks. For example, disruption of Latent Inhibition (LI) and Kamins Blocking effect have been reliably demonstrated (Soloman, 1977; 1979;1980; Soloman & Moore, 1975).

In LI a series of non-reinforced pre-exposures to a stimulus retards conditioning to that stimulus when it is subsequently paired with an US in normal rabbits. Hippocampal rabbits show no such effect. It may be that the lesioned animal cannot associate the two events, i.e. the pre-exposure of the CS and the pairing of CS and US, across time. Blocking is typically carried out in a two stage design. In Stage 1 a tone CS is paired with an eyeshock US until the CR is well established. Stage 2 consists of acquisition of a compound CS, i.e. the tone from stage 1 and a light. When the CR is well established animals receive non-reinforced presentations of the tone and the light presented singly. Normal animals produce a CR to only the tone whereas no blocking effect is seen in hippocampectomised animals. They respond to both the tone and the light. Again as in the LI condition exposure prior to the final CS-US pairing appears to be forgotten. Only the most recent events appear to have any salience for the hippocampal animals, they cannot form a contingent relationship between an event in the more distant past and present events (cf Rawlins, 1985).

Post-trial hippocampal stimulation (PTS) immediately following the termination of the US retards acquisition of the CR (Salafia, Chaia & Ramirez, 1977; Salafia, Romano, Tynan & Host, 1979). More than twice as many trials are needed for conditioning but once the CR begins to emerge conditioning proceeds at a normal rate. Hippocampal PTS given after conditioning had been established had no effect on production of the CR. Hippocampal stimulation appears, therefore, to interfere with the establishment of the memory for the CS-US relationship but once this memory has been established hippocampal stimulation has no effect on the memory trace.

Electrical stimulation of the hippocampus overlapping pre-exposure in a LI procedure can both attenuate and augment LI depending upon the intensity of the stimulation (Salafia & Allan, 1980). Lower levels of stimulation augment LI whilst intense hippo-

campal stimulation attenuates it. In the same experiment they found that stimulation overlapping CS-US presentation in the absence of pre-exposure had little effect on conditioning. For this reason they suggest that in earlier experiments using PTS the decrement may have been due to the effects of PTS on attentional processes rather than on conditioning. The stimulation in PTS may be producing a retrograde amnesia similar to that exhibited by ECT patients so that the CS-US pairing is forgotten whereas giving stimulation during the CS-US pairing does not affect the establishment of the CS-US pairing but possibly events immediately prior to that.

To test the hypothesis that the hippocampus is involved in the association of temporally remote events a number of studies have been carried out using a trace conditioning paradigm. Unlike delay conditioning in which the CS and US overlap, in trace conditioning the US follows the CS after a fixed period of time (ISI) in which no stimuli occur. Unfortunately, there is little agreement as to whether hippocampectomy disrupts acquisition of this task. James, Hardiman and Yeo (1987) and Port, Romano, Steinmetz, Mikhail and Patterson (1986) found no impairment in acquisition of the rabbit NMR using the trace conditioning procedure. However, Soloman, Vander Schaaf, Thompson and Weisz (1986) and Moyer, Deyo and Disterhoft (1990) did find an impairment at ISI's of 500ms with dorsal hippocampal and complete hippocampal lesions. When transferred to a delay conditioning paradigm the animals learned the task normally (Soloman et al., 1986). Performance appears to be dependent upon the temporal gap that must be bridged, in that Moyer et al. (1990) found no deficit in acquisition at ISI's of 300ms although there was evidence of a resistance to extinction.

One consistent finding, however, is that hippocampectomy affects onset latency of the CR. In normal well-trained animals the peak amplitude of the CR occurs at about the US onset. For the CR to be optimally reinforcing it must overlap with the US. Therefore, an important part of what subjects learn in classical conditioning is when to make the response (Ebel & Prokasy, 1963). In the foregoing experiments, whereas control animals exhibited CRs that show peak amplitude just prior to the US onset, animals with hippocampal lesions showed short latency CRs which peaked prior to US onset. It appears that the hippocampus plays some part in modulating the timing of the conditioned response. Port et al. (1986) found the short latency CRs with an air puff US in hippocampectomised animals but using a periorbital shock US these animals exhibited longer latency CRs whereas cortical animals timed responses consistently for both US conditions. They suggest that the different US types activate different neural structures and that a tone-air-puff association could involve a system predisposed to responses of short latency and a tone-shock association could involve a system predisposed to re-

sponses of longer latency. A loss of modulation in hippocampal lesioned animals could reflect the predisposition of the basic neural mechanism underlying the association.

Electrophysiological studies, then, provide strong evidence for the involvement of the hippocampus in classical conditioning. Results of lesion studies are less clear. Delay conditioning is not disrupted by hippocampectomy but more complex procedures such as LI and Blocking are disrupted. It has been suggested that these studies show that the hippocampus is involved in the association of temporally remote events. Trace conditioning procedures, however, do not resolve this issue as some studies have not found an impairment when hippocampectomised animals are required to associate non-contiguous events but they do point to a role for the hippocampus in the modulation of timing of the CR.

2.1.3. Sequential Order

The spatial mapping view of hippocampal function draws a distinction between spatial processing and temporal processing. The hippocampus presumably acts as the neural substrate for spatial processing but not temporal processing. As an animal explores its environment it makes associative links between places and itself. It may be erroneous, however, to consider such links in isolation. An organism's environment is multi-dimensional and as it moves through space it also moves through time. The concept of time may, therefore, be intrinsically involved in the perception of space and distance. The psychological processes involved in spatial memory tasks may have a significant temporal dimension (Moore, 1979).

The working memory hypothesis, on the other hand, does explicitly account for the temporal dimension of events. Olton et al. (1979) described working memory as 'a process responsible for coding the information about the temporal context in which an event happens, distinguishing one instance of a class of events from all other instances of that class. As a result, it is very prone to temporal interference effects.' This can be compared to reference memory which does not require associations with temporal context. What this means in terms of the animal tasks under discussion is that hippocampal ablation disrupts information required for only a single trial whilst leaving memory for information required for many trials intact.

A typical example of a task requiring working memory, but which excludes a spatial component, is the delayed matching or non-matching to sample task (DMS/DNMS). At the beginning of each trial a sample is presented. After some delay the sample is presented along with another item. The animal is rewarded for choosing the sample in a

matching procedure or the alternative item in a non-matching procedure (DNMS). The sample item on each trial is stored in working memory as this information is useful for that trial only. Other aspects of the task such as *always choose the most or least familiar"*, depending upon the paradigm used, where to get the food from etc. is stored in reference memory as it is information used on every trial. The task is one of recognition memory that requires the animal to make choices dependent upon the relative familiarity of an object.

Results of DNMS studies in monkeys are variable. Hippocampal lesions have produced impairments in acquisition of the task (Mahut, Zola-Morgan & Moss, 1982; Zola-Morgan & Squire, 1986) but not relearning when the animals have been trained pre-operatively (Mishkin, 1978; Murray & Mishkin, 1983,84). One possible explanation is that the hippocampus is involved in the acquisition and storage of information (the DNMS rule) but other structures maintain more permanent memories (Barnes, 1988). When working memory is further taxed by the introduction of a retention interval or the monkey is required to remember a list of items hippocampal lesions produce a moderate to severe impairment (Mahut, Zola-Morgan & Moss, 1982; Zola-Morgan & Squire, 1986) although Murray and Mishkin (1983) found no impairment with increasing delay in a tactual version of the task. Fornix lesions, on the other hand, show no deficit in acquisition (Gaffan, 1974; Mahut, Zola-Morgan & Moss, 1982) but are impaired at relearning the task post-operatively (Bachevalier, Saunders & Mishkin, 1985). Performance on retention intervals and lists have been found to be mildly (Bachevalier, Saunders & Mishkin, 1985), moderately (Gaffan, 1974) or not impaired (Mahut, Zola-Morgan & Moss, 1982). Using an analogue of the DNMS task given to monkeys Aggleton, Hunt and Rawlins (1986) found no impairment in acquisition or with increasing retention interval in rats with large hippocampal aspiration lesions and Rothblat and Kromer (1991) found no impairment in relearning.

All these studies used a large set of stimuli so that the animal sees each object only once a session, once a week, or once only i.e. trial unique. Procedures that employ a small set of stimuli presented repeatedly within a session tax, to a greater extent, the animal's ability to place the occurrence of a particular item in its temporal context. If, for instance, just two, three, or four stimuli occur several times in a session the animal must assign a temporal tag to each occurence of the stimulus in order to make a correct choice at test. Such a manipulation assesses more directly an animal's ability to make temporal order judgements and are therefore more pertinent to the present discussion.

Several studies have been carried out which have used such a design but the results have been inconclusive. Although all use a DMS or DNMS paradigm the procedures vary considerably. Raffaelle and Olton (1988) used two stimuli, a plain white box and a plain black box, in a DMS task with fornix lesioned rats. Complete fornix lesions produced a severe impairment at relearning the task post-operatively and animals with partial fornix lesions were initially impaired but improved over sessions to the standard of that of controls. Olton and Feustle (1981) used a four arm maze in which visual and tactual cues were salient, each arm being rotated between each response so that they did not maintain their spatial relationship to each other. The rat was required to make at least one response to each arm in a non-matching procedure. After fornix lesions the animals showed no relearning of the task. So in both non-matching and matching procedures rats with fimbria-fornix lesions are impaired at relearning the task. A different set of results has been reported in monkeys. Owen and Butler (1981) found fornix lesioned monkeys to be unimpaired with two stimuli in a non-matching procedure but impaired when a large set of stimuli were used. In a later study (Owen & Butler, 1984) they reported an impairment with a large but familiar set of stimuli and no impairment with trial unique stimuli, a result which contradicts to some extent their previous findings.

Jagielo, Nonneman, Isaac and Jackson-Smith (1990) also found impairments with electrolytic lesions of the hippocampus in rats. Using two stimuli the rats were required to relearn a simultaneous matching task and also to acquire a non-matching version. The lesioned animals were impaired in both conditions. However, Aggleton et al. (1986) found no impairment in rats with large hippocampal aspiration lesions using four stimuli in a DNMS Y-maze task and Sutherland, McDonald, Hill and Rudy (1989) also found no impairment at relearning a DNMS task with kainic acid hippocampal lesions using three stimuli. An impairment was only found in a cross-modal version of the task. Aggleton et al. (1986) also attempted using just two stimuli but neither lesioned animals nor controls could learn the task.

Inconsistencies in the results of these experiments cannot be accounted for by procedural differences such as matching or non-matching designs and neither is there a consistent difference between type of lesion i.e. fornix or hippocampal. Rawlins, Lyford and Seferiades (1991) examined the procedural differences that may account for the different outcomes in the Raffaelle and Olton (1988) and Aggleton et al. (1986) studies. Using a DMS design they assessed post-operative learning in a maze similar to that used by Raffaelle and Olton (1988). At acquisition they used the same pair of 'Aggleton' goal boxes throughout. These goal boxes contained distinctive visual and tactual

cues, in the form of three dimensional objects and different patterns and surface textures of the box itself. Both fornix and hippocampal lesioned animals were impaired at learning the task but their performance improved to well above chance levels as testing proceeded, a result mid-way between that of the original two studies. There was no significant difference between the effects of fornix and those of hippocampal lesions.

Using trial-unique 'Aggleton' boxes there were no longer significant lesion effects, supporting the result of Aggleton et al. (1986). On using stimuli designed to replicate the Raffaelle and Olton (1988) study lesioned animals showed a clear impairment. Rawlins et al. (1991) concluded that there were two important variables to account for some of the discrepancies in such tasks, one being the nature of the stimuli and the other the extent to which stimuli are reused within a test session. All the studies resulting in impairments (Jagielo et al., 1990; Olton & Feustle, 1981; Raffaelle & Olton, 1988) used boxes that differed only in surface texture and paint finish. Of those reporting no impairment, Aggleton et al. (1986) used three dimensional stimuli but Sutherland et al. (1989) used black and white boxes similar to the Raffaelle and Olton (1988) stimuli. The rats in this study were trained on the task with additional olfactory cues although the lesioned animals performed like controls on a *visual cue only* version of the task.

The most notable difference between the Sutherland et al. (1989) and Raffaelle and Olton (1988) studies was the type of lesion. Sutherland et al. (1989) used kainic acid lesions which spare fibres of passage. Although Aggleton et al. (1986) used large aspiration lesions there may have been an interaction of type of lesion and the type of stimuli used, but this is unlikely as the hippocampal aspiration lesions totally transected the fimbria- fornix. Rawlins et al. (1991) suggested that the two variables they identified served to increase between and within-trial interference; goal boxes varying in surface texture and tone having an overlap of stimulus features causing within- and between-trial interference and the re-presentation of target stimuli in a session producing between-trial interference. This is consistent with the notion that the hippocampus is necessary for placing episodes in their correct temporal context. Mahut, Zola-Morgan and Moss (1982) suggested that monkeys with hippocampal lesions show an abnormal sensitivity to pro- and retroactive interference as they show significantly more errors than controls on middle and last items of a list (DNMS) but no impairment on the first items. In addition both monkeys and rats with hippocampal lesions learn a single object discrimination as readily as controls but are severely impaired when required to make multiple associations concurrently (Mahut, Zola-Morgan & Moss, 1982; Moss, Mahut & Zola-Morgan, 1981; Rothblat & Graham, 1989; Wible & Olton, 1988). In the Moss

et al. (1981) and Mahut et al. (1982) studies performance was consistent with increased pro- and retro-active interference. Animals with fornix lesions, however, were unimpaired at concurrent discriminations. Rats with hippocampal lesions show increased sensitivity to interfering effects in pattern discriminations after exposure to a prior problem or an interpolated problem involving stimuli that are very similar to the original discriminanda (Winocur, 1979). Similarly, when interference is introduced into the intertrial interval of a single lever delayed alternation go/no-go procedure by allowing them to respond on the other lever, hippocampal rats show a differential impairment (Winocur, 1985). Further evidence for interference comes from much of the early work of hippocampal effects on reversal learning in which hippocampally ablated animals have no trouble in acquiring simultaneous discriminations but are much slower than controls in reversing these discriminations (Douglas & Pribram, 1966; Silveira & Kimble, 1968). However, Jagielo et al. (1990) disputed that increased interference was responsible for the deficit in their matching task as performance did not worsen as the session went on. If anything, there was a slight improvement in the lesioned animals' performance.

Jagielo et al. (1990) proposed that performance on the DNMS and DMS tasks is dependent upon the conditional nature of the task. When just two stimuli are used, whether a response is rewarded is dependent upon the tone of the sample arm that the rat has just experienced as compared to the Aggleton et al. (1986) procedure in which the rat must learn always to approach the novel object. First order Pavlovian conditioning is not affected by hippocampal lesions but more complex conditioning operations are (See section 2.1.2 on classical conditioning of the rabbit NMR). Ross, Orr, Holland and Berger (1984) found that rats with hippocamapal aspiration lesions could acquire a simple CS-US pairing but not a compound CS-US pairing. In a series of very similar studies Davidson and Jarrard (1989) and Jarrard and Davidson (1990) found that relearning and acquisition of a compound CS was unaffected by lesions of the hippocampus made with ibotenic acid. Other studies have shown impaired conditioning to compound CS's in hippocampal lesioned rats (Leaton & Borszcz, 1990; Rudy & Sutherland, 1989) whereas Markowska, Olton, Murray and Gaffan (1989) found no impairment in a spatial conditional discrimination in fornix lesioned rats.

Some researchers have proposed that an impairment in conditional operations can explain many of the spatial deficits obtained with hippocampal lesions (Leaton & Borszcz, 1990) in that a chain of conditioned expectancies guide a rat through a complex maze. Hirsh (1980), suggested that episodic memories could function as conditional operators in the form of historical markers. That is behaviour can be conditional upon

referring particular events to a temporal marker, as, for instance, in reversal learning. The initially established learning would be true in the past, while subsequent learning would be considered true in the present.

There is some evidence that hippocampal animals behave differentially toward temporal and environmental context. Rudy and Sutherland (1989) suggested that lesioned animals condition more to background stimuli. This they explain in terms of their configural association theory which states that the hippocampus is necessary for acquiring the representation of a compound stimulus that is distinct from its elements. If this system is not intact the animal cannot discriminate contextual stimuli when the target stimulus is present from contextual stimuli when the target is not present. Winocur, Rawlins and Gray (1987) provide evidence in support of this as they also found an exaggerated conditioning to contextual stimuli in hippocampal rats. Most experiments hold environmental context constant between learning and retention which may aid the performance of animals with hippocampal lesions. Winocur and Olds (1978) trained rats with hippocampal lesions and controls on a visual discrimination and then tested recall in either the same or different environmental context. Both groups learned the original discrimination at the same rate and whereas the controls showed excellent resavings at retest regardless of context, the hippocampal animals showed good recall in the *'same context'* condition but were markedly impaired on the *'different context'* condition. Hippocampal rats also take more trials to criterion if they learn a visual discrimination in the same context as a previously learned tactile discrimination than if they learn in a different context (Winocur & Gilbert, 1984). This context effect can be compared to similar findings in human amnesic subjects, which will be discussed in the following section, i.e. that amnesics encode events but fail to discriminate among past events on the basis of spatial and temporal context.

Kesner (1980) proposed a role for the hippocampus in the encoding of contextual information in his attribute theory. He assumes that long-term memory consists of a bundle or set of traces, each representing some attribute of the learning experience and that different neural units subserve different attributes. To the hippocampus he assigns the encoding into long-term memory of long-term temporal and absolute spatial attributes of specific episodes.

The question of the nature of the impairment in DNMS and DMS is far from resolved but the evidence points strongly to hippocampal involvement in the processing of contextual information. Another set of tasks which place similar demands on working memory and on which fornix lesions have a differential effect is Win Stay/Lose Shift

and Win Shift/Lose Stay. Rawlins, Maxwell and Sinden (1988) trained rats on a two lever operant response on either one of the two schedules. In the Win/Stay condition the rats were required to press the lever that had been presented in the information stage if it had been rewarded and to press the other lever if it had not. Alternatively the Win Shift condition required the rat to press the lever that had been presented in the information stage if that lever had not been rewarded and to press the alternative lever if the presented lever had been rewarded.

Rats with fornix lesions were impaired in their performance on the Win Shift task but were only impaired on the Win Stay task when the inter-response interval reached 10 secs. Rawlins accounts for this according to his temporal discontiguity hypothesis. That is, the hippocampal system acts as a large capacity temporary memory store which is used to store information about associated events which are separated in time. Win Stay and Win Shift tasks differ in their degree of temporal discontiguity. The association made at the time of a Win Stay presentation is the association that is used on the choice trial whereas on a Win Shift trial the association made at the time of presentation is not the association to be used at choice. The animal must make an association between one event at presentation and a different event at choice in the Win Shift condition.

It is difficult to say whether the rat is using a different memory process in the two tasks, whether it is the rule that the animal cannot learn or whether it is simply a case of task difficulty. Gaffan (1983) suggests that the Win Shift condition requires further mediational processing whereas the Win Stay condition relies on simple associative memory. The suggestion that this mediational processing depends upon the hippocampal system connecting via the mammillary bodies and thalamus to the frontal lobes was made by Warrington & Weiskrantz (1981) in an analysis of the human amnesic syndrome.

As far as the working memory hypothesis is concerned both tasks should be impaired with hippocampal system damage. However, viewed in terms of temporal processing if the Win Shift task requires further cognitive mediation this will place greater demand on the attentional capacity of the animal leaving less attention to be directed towards temporal events in the same way that increases in filler task difficulty affects temporal discrimination in humans (See section 1.2.1.).

Several studies have assessed sequence discrimination in rats. A study by Olton, Shapiro and Hulse (1984) assessed the ability of rats to learn a set of sequential responses. That is, the rats learned to enter the arms of a radial arm maze in a certain order dependent upon the number of reward pellets found at the end of each arm, i.e. in the

order 18, 6 and 1 pellet. On some trials the rats were forced to enter an arm out of sequence.

After 5 weeks of testing the animals learned to optimize their responses, for instance, after being forced to arm-6 the rats went to arm-18 and then arm-1 and after being forced to arm-1 they went to arm-18 and then arm-6. After undergoing fornix lesions the animals relearned to optimize responding after 6 weeks on *no forced run* trials but when given a forced run to an arm out of sequence they would repeat the whole sequence unnecessarily, e.g. when forced to arm-6 they then went to arm-18, repeated the visit to arm-6 and then entered arm-1. They could remember the sequential rule and could carry out the responses in the correct order remembering at what point they were in the sequence but could not use this information to carry out a more complex problem.

Kesner & Novak (1982) also showed a disruption of sequential memory after dorsal hippocampal lesions. Using a radial arm maze they produced a serial position curve in rats by testing their ability to remember in what order the arms of the maze had been entered. Normal rats, like humans, showed good immediate retention for the first and last items in the list i.e. primacy and recency effects. Hippocampal lesions disrupted the primacy but not the recency component of the serial position curve. After a ten minute delay all components of the serial position curve were impaired.

Similar sequence discrimination deficits have been found in monkeys. Kimble and Pribram (1963) reported no retardation of learning a simple visual discrimination by monkeys with bilateral hippocampal lesions but impairments in a *self-ordered* and an *externally-ordered* sequence discrimination of only two items.

In conclusion, the spatial mapping view of hippocampal function does not explicitly account for a temporal function of the hippocampus whereas processing of temporal context is implicit in the working memory hypothesis. Studies examining non-spatial working memory tasks such as DNMS have been inconclusive but inconsistencies may be due to procedural differences that affect levels of interference between stimuli or to the conditional nature of the task both of which may involve a temporal component. Sequential discrimination experiments point more consistently to a role for the hippocampus in memory for temporal order.

2.2. The Prefrontal Cortex.

Another brain region that has been implicated in temporal processing is the prefrontal cortex. In humans frontal cortex damage produces an impairment in sequential behaviours and recency memory. This is of importance when considering the temporal ordering behaviour of amnesics, some of whom have complementary frontal lobe pathology. The data relating to amnesics will be discussed in a later section. The present discussion concerns the effects of lesions in the dorsolateral prefrontal cortex of monkeys and the corresponding medial prefrontal cortex of rats.

Prefrontal cortex lesions typically produce deficits in delayed reaction tasks such as delayed response (DR) and delayed alternation (DA). This is true both of rats (Brito, Thomas, Davis & Gingold, 1982; Bubser & Schmidt, 1990; Kolb, Nonneman & Singh, 1974; Van Haaren, De Bruin, Heinsbroek & Van De Poll, 1985) and monkeys (Bachevalier & Mishkin, 1986; Bauer & Fuster, 1976; Passingham, 1975). Prefrontal cortex lesions often show an initial impairment that improves with practice, whereas hippocampal lesions, when they do produce an impairment are more severe and more permanent. There does, however, appear to be great variability between individuals in the effects of hippocampectomy on DA in monkeys (Waxler & Rosvold, 1970).

Studies using rats have sometimes produced inconsistent results but this is due, in part, to differences in size and site of lesion. There is little standardization of histological descriptions and a lack of well defined boundaries of prefrontal cortex. A number of studies have compared large and small medial prefrontal cortex lesions in rats, using a T maze spatial alternation task and shown that performance is dependent upon size of lesion and involvement of the prelimbic area of the prefrontal cortex (Silva, Boyle, Finger, Numan Bouzrara & Almi, 1986; Thomas & Brito, 1980; Thomas & Spafford, 1984) although permanent DA deficits have been exhibited with lesions restricted to medial agranular cortex (frontal area 2 of Zilles (1985)) and dorsal anterior cingulate area (de Brabander, de Bruin & Van Eden, 1990; Van Haaren, de Bruin, Heinsbroek & Van de Poll, 1985).

The exact nature of the deficit underlying delayed reaction tasks is unclear. The cognitive impairment responsible for performance in such tasks has been attributed to an attentional deficit due to increased distractibility by internal and external stimuli (Bubser & Schmidt, 1990); a spatial mapping deficit (Mishkin & Manning, 1978); a working memory impairment (Brito & Brito, 1990); or an abnormality of temporal processing (Fuster, 1980; Kesner, 1986; Kolb, 1984).

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There is a great deal of evidence to suggest that the impairment exhibited by prefrontal cortex lesioned animals does indeed involve a spatial component. Mishkin and Manning (1978) found that although principal sulcus lesions in monkeys produce a marked spatial alternation impairment, object alternation was only slightly and transiently impaired. Similarly, Butter (1969) found that monkeys with dorsolateral lesions were impaired on a spatial reversal task but not an object reversal task. Tests of object recognition in monkeys such as the DMS procedure produce no impairment with lesions of dorsolateral prefrontal cortex (Bachevalier & Mishkin, 1986; Passingham, 1975) or a slight transient impairment (Mishkin & Manning, 1978) whereas reversible lesions of cooling of the prefrontal cortex produce an impairment with increasing delays (Bauer & Fuster, 1976; Fuster, Bauer, & Jervey, 1985). This impairment could be due to damage in other areas of the prefrontal cortex as ventral frontal lesions commonly result in high levels of perseverative interference and as a result produce severe impairments in DMS tasks (Bachevalier & Mishkin, 1986; Mishkin & Manning, 1978).

More striking are the results of spatial tasks carried out with rats having medial prefrontal cortex lesions. They are consistently and severely impaired on the 8 arm radial arm maze task and more mildly but significantly impaired on the Morris water maze (Kolb, Pittman & Sutherland, 1982; Kolb, Sutherland & Whishaw, 1983). But the medial frontal cortex is more than just a spatial analyzer as rats with lesions in this area can learn a position habit but show severe deficits in subsequent reversals (Wolf, Waksman, Finger & Almi, 1987).

It is a common finding that impairments in DA with prefrontal lesions are more pronounced with increases in delay (Bauer & Fuster, 1976; Van Haaren et al., 1985) which has led to the proposition that prefrontal cortex is involved in working memory (Brito & Brito, 1990). Poucet and Herrman (1990) suggested that it is not an impairment in working memory *per se* but an attentional impairment that is responsible for the deficits. In this study rats with medial prefrontal cortex lesions were tested on a task requiring spatial reference memory and a task requiring spatial working memory. The rats were initially impaired on the reference memory task but improved over sessions to the performance of controls whereas they were impaired throughout testing on the working memory version of the task. However, the prefrontal lesioned animals improved within sessions on both tasks, being mainly impaired on trial one of each session. Poucet and Herrman (1990) concluded that the animals were impaired at acquiring information about spatial location prior to trial one. Support for attentional hypotheses comes from the consistent finding that prefrontal lesioned animals display increased activity during task performance and in open field observation (Brito & Brito, 1990). Bubser and

Schmidt (1990) put forward a similar view based on the differential effects of prefrontal lesions on delay and non-delay alternation tasks. They suggest that the prefrontal animals suffer more from interference occurring during the delay which, they state, is consistent with an attentional defect or alternatively a lack of behavioural inhibition.

Kolb (1984) proposed that the results of delayed reaction tasks suggest that animals, like humans with frontal lobe lesions, are impaired at recalling the serial order of past events. This does not, however, explain the negative findings of non-spatial delay tasks but as discussed in relation to hippocampal function, spatial processing may be closely interrelated with temporal processing. Pribram, Plotkin, Anderson & Leong (1977) suggested that DR tasks involve primarily the ability to respond in a spatial context whereas in DA the spatial factor serves primarily the sequential or temporal aspect. They manipulated both the temporal and spatial aspects of the DA task and found that temporal structuring i.e. introducing a longer delay between each R-L couplet, eliminated the impairment whereas performance was enhanced by providing distinguishable spatial cues but the effect was weak.

Electrophysiological evidence points to an involvement of the prefrontal cortex in both the spatial and temporal aspects of delayed reaction tasks. Some cells in the monkey dorsolateral prefrontal cortex are differentially excited by a cue depending upon its spatial position and some alter their pattern of activity in relation to the length of the delay period (Fuster, 1984; Kojima & Goldman-Rakic, 1982). Fuster (1984) proposed that the prefrontal cortex serves to integrate behaviour temporally having a retrospective function of temporary memory for recent events and a prospective function of preparation for coming events.

Deficits in performance on delayed reaction tasks are very indirect evidence for the involvement of the prefrontal cortex in temporal processing. However, studies attempting to establish an impairment in timing abilities have yielded inconsistent results. Performance of monkeys with prefrontal cortex lesions on DRL schedules has been reported to be unimpaired (Manning, 1973; Stamm, 1963a), initially impaired but recovered with continued training (Glickstein, Quigley & Stebbins, 1964), and even facilitated (Stamm, 1963b). Using a FI procedure monkeys have been shown to be severely disrupted (Pribram, 1961) and unimpaired (Manning, 1973). Rosenkilde, Rosvold and Mishkin (1981) found that monkeys with lesions in the principal sulcus were unimpaired on a time discrimination task in which length of time since the last trial signalled the spatial position of the correct foodwell. This study was carried out to show that the temporal structuring used by Pribram et al. (1977) in a DA task merely

changed the task to one of temporal discrimination i.e. after a long delay go right, and after a short delay go left, and that monkeys with frontal lesions can perform temporal discrimination procedures quite normally.

Rats with medial prefrontal cortex lesions have been shown to have a modest deficit in DRL (Nonneman, Voigt & Kolb, 1974; Numan, Seifert & Lubar, 1975; Rosenkilde & Divac, 1975) or no deficit at all (Finger, Altemus, Green, Wolf, Miller & Almi, 1987; Kolb, Nonneman & Singh, 1974; Neill, Ross & Grossman, 1974). In a peak interval procedure rats with medial prefrontal cortex lesions show a right shift in peak time of 20% of actual duration (Meck, Church, Wenk & Olton, 1987; 1989; Olton, Wenk, Church & Meck, 1988). This effect is permanent suggesting that the impairment is due to a distortion of the time entered in reference memory. This indicates a complementary role for the contributions of the prefrontal cortex and the hippocampal system in timing tasks. Hippocampal lesions produce a left shift in peak time as opposed to the right shift by frontal lesions.

Olton et al. (1988) also proposed that the prefrontal cortex is not involved in working memory as rats with lesions in this area can successfully respond on probe trials in which a gap is inserted in the duration. The animal must hold the length of the duration prior to the gap in working memory and then continue timing the duration after the gap. In contrast, rats with fornix lesions exhibit an amnesia for the gap. In addition, prefrontal cortex lesioned rats are unable to time two durations simultaneously. If a second shorter duration is introduced after commencement of an initial longer duration, the peak time for the second duration is accurate and then, when that duration has ended, they time the first duration as if it had been absent during the second. This again, points to an attentional deficit rather than a general impairment in temporal processing. Rats with damage to the hippocampal system are not impaired in the simultaneous timing task.

Tests of sequential memory have shown that rats with prefrontal cortex lesions cannot remember the order of presentation of spatial locations in the radial arm maze even when only two locations are to be recalled or when they can self-order a sequence of four or eight arms (Kesner & Holbrook, 1987). When the spatial locations are held constant from trial to trial a clear dissociation is found between item and order memory. When the spatial locations are varied from trial to trial the rat has no impairment for item memory of the first location but has for subsequent locations as well as an impairment for order memory.

Kesner (1990) also tested memory for frequency using the radial arm maze procedure. The rat was forced to enter five arms of a maze, one of which was a repeat of a previously entered arm. The animal was then given a choice between the repeated arm and a non-repeated arm. The correct choice was entrance of a repeated arm. Normal rats display a repetition lag effect, that is, memory performance improves with increasing number of items (lag) between repetitions, whereas lesioned animals perform at chance levels even at the highest lag. However, these studies confound temporal and spatial factors. There is a clear need to assess performance in rats using non-spatial procedures to establish unequivocally that deficits are due to an impairment in temporal ordering.

Brody and Pribram (1978) used both spatial and non-spatial tests of sequential memory in monkeys with large prefrontal lesions which included the sulcus principalis, superior and inferior convexities, and the frontal eye fields. The monkeys were impaired at learning both types of sequence. Pinto-Hamuy and Linck (1965) also found impairments in a self-ordered sequential task in monkeys with similar lesions. Passingham (1985) proposed that it was damage to the arcuate cortex (areas 8 and 6) that was responsible for the sequencing impairments as he found monkeys with lesions to the principal sulcus to be unimpaired in a spatial sequencing task but monkeys with lesions to arcuate cortex were slow to learn the task. The impairment, he suggests, may not be one of sequencing but an inability to direct attention to several points in space, as monkeys with lesions in area 8 are poor at searching for targets in an array and also tend to neglect targets.

Electrophysiological recordings of monkey prefrontal cortex during sequential tasks support the view held by Passingham (1985). Firing of cells in the arcuate area but not in the area of the principal sulcus are dependent upon the sequential order of presentation of stimuli and the correct performance by the animal (Barone & Joseph, 1989).

Animals with prefrontal cortex lesions display deficits primarily in delayed reaction tasks although the underlying cognitive impairment has not been established. Problems of attention appear to play some part with a possible impairment in spatial functioning. Immediate spatial perception is not in itself disrupted but circumstances in which spatial tasks include a delay are particularly affected. It has been proposed that both spatial and temporal factors are important determinants of behaviour in animals with prefrontal lobe lesions. Tasks directly assessing timing abilities of animals with such lesions do not suggest that prefrontal lesions have a deleterious affect but there is some evidence to suggest that prefrontal cortex and the hippocampal system play complementary roles in modulating timing behaviour. Although prefrontal cortex is defined by projection

from the mediodorsal nucleus of the thalamus there is direct projection from the hippocampus to prefrontal cortex (Ferino, Thierry & Glowinski, 1987; Swanson, 1981) which may be of functional importance in these tasks. There is more evidence, especially in the light of human data, for a role of the prefrontal cortex in sequential behaviour although this has not been established unequivocally in animals.

2.3. Amnesic Syndromes.

2.3.1. General characteristics of amnesia.

One of the problems encountered in considering the behavioural deficits exhibited by patients with amnesic syndromes is whether such a syndrome is a unitary disorder or whether amnesias of different aetiologies produce different patterns of mnemonic deficits. Coupled with this is the problem of identifying the critical lesion responsible for the amnesia.

In many cases there is incidental damage that may not be related to the amnesic symptoms. Also, lesion location in living patients lacks precision and post mortem analyses of patients that have undergone adequate neuropsychological assessment are relatively rare (Mayes, Meudell & Pickering, 1988). There are, however, a number of structures that have been implicated in memory processes producing considerable debate as to the minimal sufficient lesion necessary for the presence of an amnesic syndrome.

One of the most extensively studied cases is that of H.M. (Scoville & Milner, 1957) who underwent bilateral resection of portions of the hippocampus and hippocampal gyrus, as well as the uncus and amygdala for intractable epilepsy. The surgery resulted in a circumscribed amnesia for long term memories acquired post-operatively leaving remote memories and intellectual function intact. Based on operations on other patients which included the hippocampus and amygdala in varying degrees, Scoville & Milner (1957) concluded that removal of the hippocampus and not the amygdala was responsible for the amnesic syndrome. A number of other cases have been reported that implicate the hippocampus in mnestic processes (Cummings, Tomiyasu, Read & Benson, 1984; Muramato, Kuru, Sugishita & Toyokuru, 1979; Squire, Amaral & Press, 1990; Kneisley, 1982).

One of the few studies in which extensive neuropsychological and neuropathological analyses have been carried out concerns patient R.B. (Zola-Morgan, Squire, & Amaral, 1986). This patient developed an amnesia following an ischaemic episode. He exhibited

a marked anterograde amnesia with little, if any retrograde amnesia and no other cognitive impairments. On post mortem examination he was shown to have a circumscribed bilateral lesion involving the entire CA1 field of the hippocampus with only minor pathology elsewhere in the brain that was very unlikely to be associated with his memory deficit.

Further evidence for the involvement of medial temporal lobe structures in memorial processes comes from Viral Encephalitic patients who commonly develop a permanent amnesic syndrome. This disease, generally caused by the Herpes Simplex virus produces extensive lesions in the medial temporal lobe including the hippocampus, amygdala and uncus and frontal lobe. The lesions in these patients are often more widespread and diverse and difficult to interpret. At the least, the hippocampus is clearly implicated in long term information processing either on its own or in conjunction with other structures such as the amygdala (Mishkin, 1978) or the rhinal cortex (Gaffan & Murray, 1992). Recent work on monkeys has suggested that rhinal cortical lesions may produce more severe effects on short term memory than combined hippocampal and amygdalar lesions (Gaffan & Murray, 1992) although the *pattern* of impairments are very similar. Lesions to the hippocampus and the amygdala in monkeys sometimes result in encroachment on the posterior and anterior rhinal cortex respectively. Therefore, combined amygdala and hippocampal lesions will result in complete rhinal cortex ablation. This does question where the locus of the memory deficits does in actual fact lie. Attempts to model the human amnesic syndrome in non-human primates that have suggested combined hippocampal-amygdala as being the most likely regions responsible for memory impairments are confounded by effects of rhinal cortex damage. Further systematic study of rhinal cortex lesions in animals and the contribution of damage to this area to human amnesia is clearly needed to resolve these issues.

The role of the fornix, the main efferent pathway of the hippocampal formation, is more controversial in human amnesics. Garcia-Bengochea and Friedman (1987) reviewed the literature concerning the effects of fornix transection in man and reported 142 published cases in which the fornix had been transected bilaterally to relieve temporal lobe epilepsy with no evidence of memory dysfunction. However, only two of the studies reported complete transection of the fornix and no memory loss. The rest described cases that had undergone unilateral fornicotomy or had indeed shown evidence of some memory loss (see review by Gaffan & Gaffan, 1991). Of these remaining two studies one used stereotaxically guided heat lesions which could have resulted in substantial sparing of the fornix (Sugita, Doei, Matsuga & Takao, 1971) and in the other (Garcia-Bengochea, De La Torre, Esquivel Vieta & Fernandez, 1954) changes in memory were difficult to

establish as the majority of patients presented initially with more or less advanced psychotic syndromes. As Gaffan and Gaffan (1991) point out unilateral transection of a fornix which projects from a diseased hippocampus would not be expected to produce memory loss whereas bilateral fornicotomy should produce severe memory impairment. In cases of transection of the fornix, unilaterally, for removal of colloid cysts from the third ventricle one would expect a moderate memory impairment as the hippocampus is normal. Severe memory impairments have been reported after both unilateral and bilateral fornicotomy for removal of colloid cysts (Cameron & Archibald, 1981; Carmel, 1985; Christiansen, 1971; Sweet, Talland & Ervin, 1959).

A similar amnesic syndrome may also result from damage to diencephalic structures the largest group of such patients being those with alcoholic Korsakoff's syndrome. As with temporal lobe amnesia the intellect generally remains intact with a loss of memory for recent events. Disagreement exists as to the locus of the critical lesion with the mammillary bodies of the hypothalamus (MB) and the mediodorsal nucleus of the thalamus (MD) being the two most common sites implicated.

Some studies have demonstrated isolated mammillary body damage (Assal, Probst, Zander & Rabinowicz, 1976; Colmant, 1965; Delay, Brion & Elissalde, 1958; Dusoir, Kapur, Byrnes, McKinstry & Hoare, 1990) but damage often involves other structures including MD (Mair, 1979; Mayes, Meudell, Mann & Pickering. 1988) and the anterior thalamus (Cravioto, Korein & Silberman, 1961). Adams, Collins & Victor (1962) stressed the importance of MD in a large survey of 300 patients. In this survey they found severe lesions to the mammillary bodies but not MD in five patients who had no memory defects. Victor, Adams & Collins (1971) reported that although damage was present in MB in every one of 43 autopsied Korsakoffs it was only those that suffered damage in both MB and MD who suffered from memory impairment. Mair (1979) suggested that the two loci represent key stations of two memory circuits (cf Mishkin, 1978) and it is possible that for amnesia to result lesions must occur at some point in each of the two circuits. One of these projects via the fornix from the hippocampus to the mammillary bodies and from there to the anterior nucleus of the thalamus and then via the cingulate cortex back to the hippocampus. The other projects from the amygdala to medial thalamic nuclei and then to the orbitofrontal cortex before returning to the amygdala.

Work with monkeys supports this view in that Aggleton (1986) found that lesions which damage both the medial thalamus and the mammillary bodies produced a severe recognition memory deficit whereas lesions to either the anterior medial thalamus,

posterior medial thalamus or mammillary bodies alone produced a much milder impairment.

Hippocampal damage in Korsakoff patients is generally mild and inconsistent. Of two patients studied by Mayes et al. (1988) one had bilateral cell loss from the CA1 region of the hippocampus. Victor, Adams, & Collins (1971) reported that eight of twenty two Korsakoff subjects showed some involvement of the hippocampus. Also Jernigan, Schaffer, Butters, and Cermak (1989) found a small but significant reduction in volume of grey matter on MRI of a sector of medial and posterior-inferior cortex, which appeared to include the hippocampus and parahippocampal gyrus. Finally, Squire, Amaral and Press (1990), in a MRI study of four Korsakoff patients, reported normal sized temporal lobes, hippocampal formation and parahippocampal gyri for all but one patient. The findings from radiological techniques cannot rule out the possibility of more subtle abnormalities such as losses of cell fields in the hippocampus that do not alter substantially the area of the structure. The inconsistency of the damage to the hippocampus, however, would suggest that it is unlikely to be responsible for the memory impairment, although it may be contributory to mnemonic deficits in some subjects.

In addition to damage of subcortical structures many patients with Korsakoff's syndrome have been shown to have more diffuse cortical damage with a preponderance in the frontal lobe. Jacobson and Lishman (1990) assessed the brains of Korsakoff amnesics and non-Korsakoff alcoholics using computerised tomography (CT). Both groups showed evidence of frontal shrinkage, although this was greater in the Korsakoff patients. Mayes, Meudell, Mann and Pickering (1988) demonstrated reduced nucleolar volumes in layers III and V of the frontal cortex at post-mortem of two Korsakoff patients. Only one showed visible signs of cortical atrophy, this patient also having more marked neuronal loss. Frontal pathology appears to be a feature of chronic alcoholism rather than Korsakoff's syndrome per se. Shimamura, Jernigan and Squire (1988) also found significant frontal atrophy in alcoholics and patients with Korsakoff's syndrome on CT scan and Harper, Kril and Daly (1987) found the number of neurons in the frontal cortex to be markedly reduced in alcoholics with or without Korsakoff's syndrome.

Relevant to the MB/MD debate is the famous case of N.A. who sustained a restricted unilateral lesion of MD by penetration of the brain via the right nostril by a minature fencing foil (Cohen & Squire, 1980, 1981; Kaushall, Zetin & Squire, 1981; Squire & Moore, 1979). The deficit exhibited by N.A. is primarily an anterograde amnesia for verbal material. Although this case has been used as evidence of a lesion restricted to MD it is doubtful that the foil entered MD without damaging other structures en route

(Weiskrantz, 1985) and should be viewed with caution. A recent MRI revealed more extensive damage including the left diencephalaon, bilateral mammillary bodies and the right anterior temporal lobe (Squire et al., 1988).

Anatomically, then, there appears to be two forms of amnesia although it must be remembered that there is a substantial degree of interconnectivity between memory related structures directly and indirectly via cortical connections. For example, the major afferent of the mammillary bodies is the fornix which originates in the hippocampal formation and the main efferent terminates in the anterior nucleus of the thalamus. Damage to one structure, therefore, will alter input-output relations in both temporal lobe and diencephalic structures.

Behaviourally, temporal lobe amnesia and diencephalic amnesia exhibit a number of similarities and also a number of differences. Parkin (1984) ennumerated five general symptoms common to both - a) premorbid levels of intellectual functioning are maintained, b) immediate memory function remains intact, c) retrograde amnesia is present in varying degrees, d) a severe anterograde amnesia with performance on long term memory test at least two standard deviations below the norm, e) a degree of residual learning capacity is present (skill or procedural learning).

Lack of insight and confabulation have frequently been reported in cases of diencephalic amnesia particularly in Korsakoff's syndrome (Talland, 1965; Victor, Adams & Collins, 1971), although this does not appear necessarily to be a permanent feature of the illness. These characteristics can improve with time but Korsakoff patients do show, on the whole, a general lack of concern regarding their memory problems. Temporal lobe amnesics, on the other hand, rarely show lack of insight and confabulation.

Korsakoff patients typically have a retrograde amnesia that extends over several decades and shows a temporal gradient whereas both H.M.'s (Marslen-Wilson & Teuber, 1975) and R.B.'s premorbid memory does not differ from that of controls. There does not, however, appear to be a clear cut dissociation between temporal lobe and diencephalic amnesia in terms of retrograde amnesia. N.A. has very good premorbid recall which in fact was significantly better than that of controls (Cohen & Squire, 1981) and post encephalitic patients show great variability in retrograde amnesia, it often being as extensive as that exhibited by Korsakoffs'.

There are also differences in the pattern of anterograde amnesia shown by Korsakoff and temporal lobe patients. Korsakoff patients show greater sensitivity to interference

on short term memory tasks using the Peterson and Peterson (1959) paradigm (Cermak, 1976; Cermak & Butters, 1981).

These studies do point to functional differences between amnesias of varying aetiology, and as Parkin (1984) suggests this must be borne in mind when considering studies using heterogenous amnesic groups. It also suggests that in comparing performance of Korsakoff patients and Post Encephalitic patients on the same tasks useful information can be elicited concerning brain behaviour relations.

2.3.2. Amnesics' temporal processing.

It has long been noted that amnesics show disturbances in temporal judgments. Williams & Zangwill (1949) found Korsakoff and post-ECT patients often tend to overestimate how long ago recent events occurred, although the ECT patients also sometimes underestimated the time of occurrence of events. H.M.'s temporal judgments have been claimed to be normal up to intervals of 20 secs, after which he grossly underestimates time, (Richards, 1973) which points to involvement of medial temporal lobe structures in temporal judgment in humans. Oscar-Berman, Zola-Morgan, Oberg & Bonner (1982) suggested that temporal disturbances in Korsakoff patients are also due to limbic system damage although they do show deficits in tasks sensitive to frontal lobe damage in non-human primates. This study by Oscar-Berman et al. (1982) tested Korsakoffs, and alcoholic and normal controls on a DRL schedule. Korsakoff patients were impaired at all intervals (3, 6, 12 and 18 secs) compared to the controls.

There is a clear need to clarify the effects of frontal lobe dysfunction on amnesia, especially Korsakoffs amnesia. Patients with restricted frontal lobe lesions do not exhibit a full blown amnesic syndrome (Ghent, Mishkin & Teuber, 1962; Stuss, Kaplan, Benson, Weir, Chiulli & Sarazin, 1982), but prefrontal damage does result in cognitive impairments that influence the successful functioning of memory. For example, there are disorders of attention, planning, monitoring and use of feedback (Stuss, 1986).

In addition there appear to be deficits in the ordering and handling of sequential behaviours and the ability to discriminate items in memory temporally. Corsi (cited in Milner, 1971) presented frontal lobe patients with two lists of common words and required a two choice recognition task and a two choice recency judgement task. Patients with unilateral right and left frontal damage performed normally on the recognition task but patients with left frontal damage were impaired on the recency task. Lewinsohn, Zieler, Libet, Eyeberg & Neilson (1972) extended this finding to recency judgements of pictures as well as words.

In addition to deficits in temporal order memory patients with frontal damage also perform poorly on memory tasks requiring sequential organization (Milner, 1982). The frontal lobe, therefore, is thought to be involved in the sequential ordering of events and there is evidence to suggest that it is also involved in temporal estimations but in a qualitatively different way to the hippocampus. Using the discrete trial peak-interval procedure Meck, Church, Wenk & Olton (1987) showed that whereas fornix lesioned rats remembered the time of reinforcement as occurring earlier than it did, rats with frontal lesions remembered the time of reinforcement as occuring later. How far deficits in amnesics' temporal order judgements can be attributed to frontal dysfunction will be discussed later.

Amnesics generally show high levels of proactive interference. In Korsakoff subjects concurrent learning is consistently and significantly worse than individual pair learning even when the pairs had previously been acquired individually (Oscar-Berman & Zola-Morgan, 1980). When learning successive paired associate lists in which the same stimulus terms were paired with different response terms (AB-AC paradigm) amnesic patients show a tendency to intrude first list responses into second list recall (Kinsbourne & Wood, 1980; Mayes, Pickering & Fairbairn, 1987; Warrington & Weiskrantz, 1978). This has been interpreted as a possible deficit in 'time-tagging' or an impairment in the discrimination of contextual cues (Winocur & Weiskrantz 1976).

Winocur & Weiskrantz (1976) used a mixed group of amnesics in their paired associate AB-AC paradigm consisting of 3 Korsakoffs, 2 post-encephalitics and one of unknown aetiology. A similar study of Warrington & Weiskrantz (1978) also used amnesics of mixed aetiology in a procedure that cued recall in the two lists by the first three letters of the words e.g. cycle, cyclone. That temporal lobe patients with no evidence of frontal pathology also performed poorly in these interference tasks would suggest that this deficit is not due to frontal pathology in Korsakoff patients.

The contextual deficit hypothesis derives from the findings that distinctive context differentially aids Korsakoffs recall of paired associate learning and word list learning (Winocur & Kinsbourne, 1978; Winocur, Moscovitch and Witherspoon, 1987). This theory suggests that amnesics encode events but fail to discriminate among past events on the basis of spatial and temporal contextual cues but the term 'context' has not been clearly defined (Hirst, 1982; Mayes, Meudell, & Pickering, 1985). However, there is mounting evidence that amnesics of varying aetiology exhibit a larger impairment in source or temporal contextual memory than would be expected from their fact memory

ability. Shimamura and Squire (1987) tested seven Korsakoff amnesics, three amnesics who had suffered ischaemic episodes and N.A. on source memory. They all showed normal item memory and deficits in memory for the temporal context in which these items had been learned. Using the same procedure Janowsky, Shimamura and Squire (1989) reported a similar result with frontal lobe patients who showed no evidence of amnesia. This was taken as evidence that source memory deficits in Korsakoff patients is possibly due to frontal lobe pathology. Source memory deficits have been shown to correlate with performance on tests of frontal lobe dysfunction (Schacter, Harbluk, & McClachan, 1984). Other studies have found no correlation between temporal contextual memory and performance on frontal lobe tests (Parkin, Leng, & Hunkin, 1990; Pickering, Mayes, & Fairbairn, 1989) or frontal atrophy demonstrated by CT scan (Kopelman, 1989). In fact, both Pickering et al. (1989) and Kopelman (1989) found more evidence of a relation to severity of amnesia, findings which support the contextual deficit hypothesis.

Korsakoffs also do not show release from proactive interference (PI) in lists of words of varying taxonomic categories unless told to expect a category shift or the category shift is combined with contextual shift (Winocur, 1981). It has been suggested that Korsakoffs' failure to release from PI is due to frontal lobe damage (Moscovitch, 1982; Squire, 1982). Amnesics with no frontal damage do release normally from PI (Cermak, 1976; Moscovitch, 1982), whereas frontal patients do not (Moscovitch, 1982). However, Freedman & Cermak (1986) found this to be true only of patients with frontal lobe damage who also exhibited memory deficits. These patients are therefore quite likely to have additional damage to other structures.

Janowsky, Shimamura, Kritchevsky and Squire (1989) found that patients with frontal lobe damage performed similarly to controls and non-Korsakoff amnesics in a release from PI paradigm and suggested that release from PI in Korsakoffs was not due to frontal pathology. The debate is far from resolved as other studies have found strong correlations between interference phenomenon and frontal pathology but not severity of amnesia in Korsakoff patients (Leng & Parkin, 1989; Squire, 1982). In addition a study by Winocur, Oxbury, Roberts, Agnetti and Davis (1984) of patient, B.Y., who has bilateral lesions in the medial thalamus showed that he performed well relative to Korsakoffs in interference paradigms. N.A., whose lesion was smaller than B.Y.'s also exhibited normal release from PI (Squire, 1982). More recently Moscovitch, Osimani, Wortzman, Richards and Freedman (1990) reported a case study of a patient having amnesia as a result of bilateral haemorrhagic infarction of the dorsomedial nucleus who performed normally on a release from PI paradigm. These studies would suggest that inter-

ference deficits are not dependent solely on damage to the medial thalamus.

The temporal order hypothesis is a modified version of context theory that focuses on temporal relations. This theory proposes that amnesics recognise events but fail to encode the temporal relations between those events. Hirst and Volpe (1982) studied patients of mixed aetiology with focal and diffuse cerebral injury and found that although amnesics were inferior there was no significant difference from controls in event recognition whereas they performed at or below chance on order recognition. A similar procedure was followed using news events as stimuli with the same results.

Huppert & Piercy (1978) proposed that Korsakoff patients carried out recency judgements in a qualitatively different way to control subjects. Because the Korsakoffs were unable to discriminate between the effects of frequency of presentation and recency they concluded that their judgements were based solely on trace strength whereas normals based their judgements jointly on trace strength and specific information about time.

Squire, Nadel and Slater (1981) criticised the temporal order hypothesis by saying that loss of temporal order information could be predicted from loss of event information. They tested NA and post-ECT patients on a recency task but equated the controls' recognition score to the amnesics by increasing the interval between presentation of the material and the recognition test. After a 40 minute interval the recognition and temporal order scores of the controls were the same as those of the amnesics. Meudell, Mayes, Ostergaard and Pickering (1985), however, also manipulated retention intervals and learning opportunity to show that, using the recency/frequency procedure, normals with poor memory still use specific contextual memory to make temporal order judgements.

Mayes, Baddeley, Cockburn, Meudell, Pickering and Wilson (1989) examined the question of the contribution of frontal lobe pathology to the recency judgement performance of Korsakoffs amnesics. Using the Huppert and Piercy (1978) procedure they found that amnesics with medial temporal lobe damage showed a tendency to base recency judgements on trace strength whereas patients with frontal lobe lesions performed in a qualitatively similar way to normal controls. Furthermore, Shimamura, Janowsky and Squire (1990) found no correlation between tests of frontal lobe dysfunction and sequencing in Korsakoff, non-Korsakoff amnesics and frontal lobe patients.

Petrides and Milner (1982) also found temporal lobe deficits on a task that required the self-ordering of a sequence of pointing responses that was dependent upon involvement

of the hippocampus. Patients with unilateral temporal lobe lesions not extending beyond the pes of the hippocampus were unimpaired on these tasks whereas those with more radical hippocampal excisions exhibited material-specific deficits depending upon the side of the lesion. HM, however, who has damage to the hippocampus was unimpaired on tests of verbal and non-verbal recency (Sagar, Gabrieli, Sullivan, & Corkin, 1990).

Both medial temporal lobe amnesics and patients with diencephalic damage have deficits in timing and ordering tasks. That this is the fundamental impairment underlying the amnesia has not been proven, nor has the region responsible for the impairment been identified. Studies of Korsakoffs are confounded by frontal lobe damage although evidence does suggest that there may be qualitative differences between the pattern of deficits due to frontal pathology and subcortical timing deficits.

2.4. Conclusions.

Although there is an abundance of studies assessing the timing behaviour of lesioned animals, few studies have examined the performance of amnesics on temporal estimations. Those that have been carried out demonstrate an impairment in temporal perception. In particular, H.M.'s underestimation of temporal durations of more than 20 seconds corresponds with the findings from the animal literature that rats with hippocampal lesions exhibit a left shift in peak time. Korsakoff amnesics, like hippocampal lesioned rats but unlike rats with prefrontal cortex lesions, are impaired on DRL schedules. Deficits in DRL can arise not only because of problems in temporal processing but also because of a failure to inhibit responding. So in the light of only one study it is difficult to establish the nature of the DRL deficit in human amnesic subjects.

Animals with hippocampal lesions and human amnesics both show a differential sensitivity to contextual cues compared to normal intact subjects. This is true of amnesics of varying aetiology and has been proposed as the primary deficit in anterograde amnesia rather than a consequence of poor memory. This could be a result of an impairment in *time tagging* events and an increased sensitivity to temporal interference. It has been suggested that impairments in recognition memory tasks exhibited by animals with hippocampal lesions is a result of procedures that reduce the distinctiveness of stimuli, both in terms of stimulus features and their occurrence in the temporal domain, thus producing high levels of interference. Amnesics with both temporal lobe and diencephalic amnesia also perform poorly on interference tasks. Although this has been attributed, in some instances, to frontal lobe damage the evidence from the animal literature suggests that it can also result from damage to the limbic system. However, both

animals with prefrontal cortex lesions and humans with frontal lobe damage have attentional deficits which can result in an increased susceptibility to interference.

Amnesics generally are impaired at making recency judgements even under circumstances in which they display normal event recognition. Loss of recency memory and sequential organization is characteristic of frontal lobe damage in humans. A similar dissociation in item and order memory has been demonstrated in prefrontal lesioned rats. But whereas hippocampal rats are also disrupted in temporal order judgements, HM has been shown to have normal recency memory. It is difficult to ascertain, therefore, the contributions of cortical and subcortical structures to recency memory in human amnesics, and whether temporal order impairments in temporal lobe and diencephalic amnesia are a result of damage to the same or different systems.

Diencephalic impairments in temporal order judgements could be due to disconnection of the frontal lobe as a result of damage to MD or, alternatively, to interruption of the hippocampal-mammillary body pathway by damage to the mammillary bodies. The subiculum of the hippocampus and medial mammillary bodies are strongly connected by the major fibre projection of the fornix and it has been proposed that this pathway acts as a single functional unit subserving memory, and that amnesia can result from interruption of this pathway at any of its stages (Delay & Brion, 1969; Gaffan, 1991). Temporal lobe impairments, on the other hand, may be due to direct hippocampal damage. It is also possible, however, that such memory impairments may be due to damage to a combination of structures (Mishkin, 1978). In addition, in both diencephalic and temporal lobe amnesia the problem of establishing the critical area responsible for deficits in temporal processing is confounded in cases that also have direct frontal lobe damage.

2.5. Aims of the present study.

The present research aimed to investigate the temporal processing of diencephalic and temporal lobe amnesics in terms of both duration estimation and sequential ordering. The results of these tests were examined in relation to the following questions:-

1. Is memory for temporal order and the perception of time dependent upon the same neural substrate?

Temporal order impairments have been found after hippocampal system damage and prefrontal cortex damage in animals, whereas there is a dissociation between the effects of lesions to these two areas on timing tasks. Amnesic subjects generally are impaired in tests of sequential order but it is not known whether this is a result of damage to the

hippocampal-mammillary body pathway or to direct or indirect frontal cortex damage. Very little information is available concerning amnesics timing behaviour and subsequently the relationship of performance on tests of duration estimation and memory for temporal order and frontal cortex damage.

2. Are deficits in temporal processing a result of poor memory?

If temporal processing is dependent upon subcortical structures that are responsible for global amnesia, disorders of time perception may be a direct result of the memory impairment. This is related to question 1 in that severity of amnesia could show a relationship to time estimation, memory for order, both, or neither. A number of studies, both human and animal, have indicated that item and order information are dissociable but again there is little information concerning the relationship of duration estimation to memory impairment.

3. Is there a correspondence between tests used with animals and human subjects?

The evidence for timing deficits in animals with hippocampal system lesions is based on 'behavioural' tasks such as operant procedures. Therefore, performance of amnesic subjects was assessed on an analagous task using an automated fixed interval procedure as well as time estimation tasks using procedures based on experiments with intact human subjects. As such operant procedures are well documented in the animal literature this research concentrated upon recency judgements in animals. Tests requiring the judgement of relative recency in which the degree of interference was varied were given to human amnesics and rats having fornix or prefrontal cortex lesions in an attempt to establish whether temporal order impairments in amnesic subjects are in fact due to cortical or subcortical damage.

CHAPTER 3
Tests of duration estimation by amnesic subjects

3.1. Experiment 1: Time reproductions and estimations.
3.1.1. Introduction
This experiment examined the performance of both temporal lobe and diencephalic amnesics on a number of time estimation tasks. In order to compare the performance of amnesic subjects in this study with the performance of H.M., a time reproduction task similar to that used by Richards (1973) was carried out. In this task an interval of time is first of all demonstrated to the subject who is then required to duplicate this interval. Reproduction methods are considered to be more accurate and reliable than other methods of time estimation, such as production or verbal estimation (Clausen, 1950; Block, 1989). They also avoid the need to *translate* the duration into verbal time units but are heavily reliant on memory processes, requiring the ability to make a comparison with some stored representation of the sample interval.

To reduce the memory load two further time estimation tasks were carried out using the method of production. In this procedure the subject is given an interval of time in seconds and is then required to produce this interval. This method entails relating subjective time to clock time and is susceptible to distortions due to misperception of objective scales of time (Clausen, 1950). It does, however, involve only absolute judgments of the status of the ongoing duration whereas the reproduction method also requires a relative judgment of comparison of the reproduced and standard intervals. Productions were made with both *empty* and *filled* intervals. In the *filled* interval condition the subject carried out a distractor task (reading), in order to prevent counting (although instructed not to do so). During *empty* intervals the subject was asked to sit quietly and not to count.

From the evidence concerning the estimation of temporal duration by H.M. it would suggest that the post-encephalitic subjects, who are also likely to have hippocampal damage, should exhibit normal temporal estimation of intervals up to 20 seconds and thereafter show significant underestimation of time. Previous evidence (Williams & Zangwill, 1950) suggests that the Korsakoff subjects will also be impaired in making temporal estimations, specifically that they will underestimate the length of the duration. The patterns of performance of the two groups will be compared to assess if it is possible that any deficits are possibly due to common neurological substrates.

Because of the increased memory load in the reproduction task it would be expected

that amnesic subjects should perform worse on this task compared to the two tests of time estimation and that this impairment would be more pronounced with longer intervals. However, although the time estimation tasks do not require memory for a preceding event, an impairment in these tasks is not sufficient to establish that the deficit is in the timing mechanism. Such impairments may be secondary to the amnesia suggesting that, again, the deficit would be more pronounced with longer intervals. In this case, poor performance in temporal judgment would be correlated with measures of severity of amnesia.

The time estimations with filled intervals, as well as preventing strategies such as counting, also produce increased levels of interference, preventing attention being directed to the passage of time. Both temporal lobe and diencephalic amnesics show increased susceptibility to interference and should thus be differentially affected in this task compared to the time estimation with empty intervals and compared to the control group.

Finally, if temporal estimation is dependent upon the integrity of frontal lobe function as has been suggested of temporal order memory, performance on the time estimation tasks will correlate with performance on tests of frontal lobe function. Both the Korsakoff and post-encephalitic groups were heterogeneous in terms of degree of frontal lobe impairment which could provide useful information from the correlations between these measures and performance on the time estimation tasks.

3.1.2. Methods
3.1.2.1. Subjects
The diencephalic amnesic group (5 men and 2 women, mean age 57.7 years) had all been diagnosed as suffering from Korsakoff's syndrome due to alcohol abuse. They had been resident in hospitals or residential hostels for at least three years. The alcoholic control group for the Korsakoff subjects consisted of 7 men and 1 woman (mean age 48.4 years). All had a long term history of alcohol abuse but did not report memory difficulties and had abstained from heavy drinking for some weeks prior to testing. They were recruited through National Health Service and charitable organisation facilities for rehabilitation of alcoholics.

The temporal lobe amnesic group consisted of 3 men (mean age 40) diagnosed as suffering from viral encephalitis some 2 to 15 years prior to testing. All suffered memory problems that had forced them out of work. In none of the cases was there precise information regarding the location and extent of brain damage. The control group for

the post encephalitic subjects consisted of 11 men (mean age 46.6 years) all of whom were employees of the University of Durham.

3.1.2.2. Procedure
3.1.2.2.1. Psychometric Testing

Subjects in the Korsakoff group, the alcoholic controls and the temporal lobe amnesics were assessed with the Wechsler Adult Intelligence Scale (WAIS) and the National Adult Reading Test (NART) (Nelson, 1985) to evaluate IQ, and with the Wechsler Memory Scale (WMS), and the Warrington word and face recognition tests (Warrington, 1985) to assess memory function. One subject in the temporal lobe amnesic group had a speech impediment and so did not attempt the NART. Frontal lobe function was assessed using a number of tests which included the Wisconsin Card Sorting Test (WCST) (Heaton, 1981), Verbal Fluency (Benton, 1968), Design Fluency (Jones-Gotman & Milner, 1977), a revised version of the Cognitive Estimation test (Shallice & Evans, 1978) and the Picture Arrangement and Block Design subtests of the WAIS. The normal control subjects were assessed on all frontal lobe tests and the NART was used to evaluate IQ

Wisconsin Card Sorting Test

This is a test of problem solving ability in which the subject is required to sort 128 cards, matching each card to one of four key cards. The cards may be matched according to one of three principles - colour, form or number of symbols. The subject must ascertain the correct sorting principle from feedback indicating whether they are correct or incorrect on each response. After ten consecutive correct responses the sorting principle is changed by the examiner without warning. Testing is continued until each sorting category has been repeated twice or until all cards have been sorted. A high perseverative response score together with the achievement of fewer than the normal number of categories has been shown to be indicative of cerebral dysfunction and the presence of frontal involvement in cases with focal lesions (Heaton, 1981). The test does not distinguish between side of lesion and it is important to note that brain damage to areas other than the frontal lobes can impair performance on this test.

Verbal Fluency

In this test the subject is asked to produce as many words as they can, beginning with a certain letter (C, F and L), in one minute. The number of words are recorded and the resulting score scaled according to age and education. Subjects with both right and left frontal lobe lesions have depressed fluency scores (Miller, 1984), although this is more pronounced following lesions to the left hemisphere (Milner, 1964).

Design Fluency

This test is a non-verbal analogue of the verbal fluency test in which the subject is asked to produce as many novel abstract drawings as they can think of in five minutes. Subjects having right frontal or fronto-central damage are most impaired at this test, whilst subjects with left frontal and right temporal lobe damage show milder deficits. The most striking feature of the performance of subjects having right frontal lobe damage is a tendency to make many perseverative responses despite a low novel output (Jones-Gotman & Milner, 1977). Therefore, the number of perseverative responses as a percentage of total output was used as the measure to assess possible frontal lobe dysfunction in this study. The output from each subject was rated by an independent examiner for perseverative responding.

Cognitive Estimation

This was based on the cognitive estimation task devised by Shallice and Evans (1978). Ten questions were selected from this task which required estimations of sizes, heights and weights etc. of familiar objects (see Appendix 1). Subjects with frontal lobe lesions, irrespective of side of lesion, give a greater percentage of bizarre responses to such questions (Shallice & Evans, 1978). A response was scored according to its occurrence in terms of the number of standard deviations from the mean of the normal control group responses. If it fell within one standard deviation of the mean a score of 0 was given and the maximum score for each question was three. Therefore, the higher the score the more bizarre the responses. Shallice and Evans (1978) found that subjects with anterior hemisphere lesions made 66.4% abnormal responses and those with right anterior lesions made 54.9% abnormal responses. In this study, then, an abnormal response rate greater than 50% (i.e. a score of greater than 15) was considered indicative of frontal lobe damage.

Picture Arrangement

Picture arrangement is a subtest of the WAIS in which the subject is shown a number of pictures in a preset random order which must be rearranged to depict a logical story line. Subjects with right hemisphere lesions, particularly those with right temporal lobe lesions, obtain significantly lower scores, as measured by the age scaled scores used in the WAIS, than subjects with left hemisphere lesions (McFie & Thompson, 1972). However, when a qualitative analysis was carried out it was found that subjects with right frontal lobe lesions left significantly more cards in the presented order than those subjects with left hemisphere or right non-frontal damage. In the present study the picture arrangement test of the revised version of the WAIS was used and the measure obtained was the number of pairs of pictures left in the presented order which did not

comprise part of the potentially correct order. This gives a fairly conservative estimate of number of pictures left in the presented order as many of the pictures are in fact presented in the correct order by the experimenter. McFie and Thompson (1972) found that subjects with right frontal lesions left, on average, 2.75 pairs in the presented order, and those with left frontal lesions left .68 pairs in order, and those with right temporal lesions 1.37 pairs. Therefore, a score of greater than 3 was considered abnormal.

Block Design

A subtest of the WAIS-R was used to assess constructional ability. Damage to the right frontal lobe and bilateral frontal lobe damage has been associated with impairments in constructional abilities such as block design tasks, subjects frequently displaying inertia i.e. the blocks are not examined for alternative design possibilities, and a tendency to focus on only one salient feature of the design (Benton, 1968; Goodglass & Kaplan, 1979). The measure used was the scaled score derived from the WAIS-R.

One subject in the Korsakoff group was not available to carry out the Verbal Fluency, Design Fluency, Cognitive Estimation and Picture Arrangement tests and two subjects in the alcoholic control group did not carry out the Design Fluency and Cognitive Estimation tasks, one of these also did not complete the picture arrangement test.

3.1.2.2.2. Experimental procedure

The experiment took place over three sessions at weekly intervals. All subjects received the time reproduction condition during the first session, followed by the time estimations with filled and empty intervals presented in a counterbalanced order during the following two sessions. The time intervals for all conditions were 3, 6, 12, 24, 48, and 96 seconds. Each interval was presented twice per session, once at the beginning of the session and once following performance of another task (psychometric tests or other experimental tasks). There was an interval, therefore, of approximately 20 minutes between each of the two presentations. The intervals were presented in random order for all subjects and were measured using a digital stop watch.

In the time reproduction condition the experimenter demonstrated an interval of time by saying *'start'* and *'stop'*. The subject was then asked to reproduce that interval by also saying *'start'* and *'stop'*. The subject was asked to try not to count during any of the intervals and care was taken that no clocks or watches could be seen or heard by the subject. The subject was not told the length of the interval but a notice with the words *'I am timing'* was displayed whilst the interval was being demonstrated and when the subject was reproducing the interval *'Tell me when to stop'* was displayed.

For the time estimation conditions the subject was given the time in seconds and asked to produce this interval. The experimenter told the subject to 'start' and the subject was then required to say 'stop' when the interval had elapsed. The 'Tell me when to stop' notice was displayed along with the length of the required interval in seconds. During filled intervals the subject started reading a printed passage as soon as the start of the interval had been indicated by the experimenter and continued reading throughout the interval. A different prose passage of varying type face was used for each trial. Again the subject was asked not to count and all watches and clocks removed from sight.

3.1.3 Results
3.1.3.1 Psychometric Testing

Table 3.1 shows the results of the psychometric test scores for the Korsakoff and the Alcoholic control groups. The groups were matched according to verbal, performance and full scale IQ as measured by the WAIS and NART. The Korsakoff group, however, were significantly impaired on tests of memory function. t-tests revealed a significant effect for both the WMS [$t(13) = 6.81, p<.001$] and the Warrington word and face recognition memory test [*words*, $t(13) = 7.93, p<.001$; *faces*, $t(13) = 5.57, p<.001$].

Table 3.1: Group means (standard deviations) for psychometric test scores of Korsakoff subjects and alcoholic control subjects.

	Korsakoff (n = 7)	Alcoholic Controls (n = 8)	t	df	p
WAIS					
Verbal IQ	95.0 (9.9)	100.3 (9.2)	1.0	13	NS
Performance IQ	93.6 (8.1)	96.8 (10.5)	0.6	13	NS
Full Scale IQ	95.1 (9.2)	98.5 (8.8)	0.72	13	NS
NART					
Verbal IQ	102.9 (9.3)	107.6 (7.7)	1.09	13	NS
Performance IQ	105.1 (6.3)	108.5 (5.2)	1.13	13	NS
Full Scale IQ	104.0 (8.5)	108.2 (6.9)	1.07	13	NS
WMS					
Memory Quotient	75.7 (6.0)	101.3 (8.2)	6.81	13	<0.001
Warrington Recognition Test					
No. correct:- Words	28.3 (2.2)	45.4 (5.3)	7.93	13	<0.001
Faces	31.7 (5.2)	45.3 (4.2)	5.57	13	<0.001

NS = Not Significant
All probabilities two tailed

The psychometric test results for the post-encephalitic subjects and normal control subjects are shown in table 3.2a and b. There was no significant difference between the groups on the NART verbal, performance and full scale IQ. One post-encephalitic subject did not carry out the NART but his WAIS verbal, performance and full scale IQ fell within the range of that of the normal control subjects as measured by the NART. The post-encephalitic group were comparable to the Korsakoff group in all measures of memory function and memory loss.

Table 3.2a: Group means (standard deviations) for psychomentric test scores of post-encephalitic subjects and normal control subjects.

	Post-Encephalitic Subjects (n = 3)	Normal Controls (n = 11)
WAIS		
Verbal IQ	99.7 (8.1)	
Performance IQ	97.3 (6.5)	
Full Scale IQ	98.0 (6.6)	
NART		
Verbal IQ	*107.5 (3.5)	110.3 (6.3)
Performance IQ	*106.5 (3.5)	110.5 (4.6)
Full Scale IQ	*107.5 (2.1)	111.0 (5.5)
WMS		
Memory Quotient	84.3 (11.2)	
Warrington Recognition Test		
No. Correct:- Words	32.7 (0.6)	
Faces	31.3 (5.1)	

* N = 2

Table 3.2b: Psychometric test scores for post-encephalitic subjects.

Subject	WAIS			NART			WMS	WARRINGTON	
	FSIQ	VIQ	PIQ	FSIQ	VIQ	PIQ		words	faces
BT	91	91	91	105	104	106	76	33	37
BD	104	107	104	110	109	109	97	32	30
GH	99	101	97				80	27	35

FSIQ - Full scale IQ
VIQ - Verbal IQ
PIQ - Performance IQ

Table 3.3 and 3.4 show the results of the frontal lobe tests for the Korsakoff and alcoholic control groups. The Korsakoff group achieved significantly fewer categories in the WCST than the alcoholics [$t(13) = 2.5\ p <.05$] and made significantly more perseverative responses [$t(13) = 2.7\ p <.05$]. There was, however, a great deal of variability of scores within the groups. Using a cutoff of 46 as indicating a severe level of perseverative responding and hence a strong likelihood of frontal lobe damage, four of the Korsakoff subjects and only one of the alcoholic controls were impaired according to this criterion. Five of the alcoholic controls made very few perseverative responses falling well within the normal range and one showed a moderate degree of perseveration. The other three Korsakoff subjects displayed a mild degree of perseveration but their scores fell within the range of the normal control subjects tested in this study (5 - 31).

The Korsakoff subjects produced significantly fewer words on the verbal fluency test than the alcoholic controls [$t(12) = 2.8\ p <.05$]. All the Korsakoff scores, however, fell within the normal range, except one (T.C.) which was borderline. The alcoholic control scores were all within the normal to superior range except one, which again was borderline (T.H.). In the design fluency test the Korsakoff subjects made significantly more perseverative responses than their control group [$t(10) = 2.35\ p<.05$]. Using 25% perseverative responding as the cutoff (Jones-Gotman and Milner, 1977) three of the Korsakoffs and only one of the alcoholic controls fell outside the normal range.

There was a significant difference between the Korsakoff subjects and their controls in the number of pictures left in the presented order in the picture arrangement test [$t(12) = 2.26\ p<.05$]. Using the criterion of a score greater than 3 being abnormal, four of the Korsakoff subjects and two of the alcoholic controls produced scores outside the normal range.

There was no significant difference between the Korsakoff and alcoholic control groups on test scores for the block design and cognitive estimation tests. All scores in both of the groups for these two tests fell within the normal range.

Table 3.3: Group means (standard deviations) for frontal lobe test scores of Korsakoff and alcoholic control subjects.

	Korsakoff		Alcoholic Controls				
	n	Mean (SD)	n	Mean (SD)	t	df	p
WCST Categories	7	2.6 (1.6)	8	4.8 (1.8)	2.5	13	.027
Perseverative responses	7	48.6 (22.8)	8	20.3 (17.7)	2.7	13	.022
Verbal Fluency Scaled score	6	31.2 (6.3)	8	48.4 (13.8)	2.8	12	.015
Design Fluency % Preseverative responses	6	27.7 (19.6)	6	6.1 (11.1)	2.35	10	.04
Picture Arrangement No. left in order	6	6.2 (3.97)	8	2.6 (1.8)	2.26	12	.043
Block design Scaled score	7	8.1 (1.2)	8	8.4 (1.9)	0.27	13	NS
Cognitive Estimation	6	6.5 (3.6)	6	4.5 (2.2)	1.17	10	NS

NS Not Significant
All probabilities two tailed

Table 3.4: Frontal lobe function for Korsakoff and alcoholic control subjects.

Korsakoff
Subjects

	WCST		Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
	Cats.	Persev. Resps.					
HKK	2	28	31	6.7	5*	7	6
BJ	3	66*	32	15.8	7*	8	6
SM	2	57*	34	37.5	6*	9	12
RS	5	30	26	28.6*	5*	9	9
TC	2	23	23*	61.1*	2	6	2
JB	4	51*				9	
HK	0	85*	41	16.7	2	9	4

Alcoholic
Control Subjects

DM	2	42	40	0	5*	6	6
FB	6	9	52	2			
GD	3	49*	64	9.1	5*	7	1
BS	6	16	51	27.6*	2	9	3
SC	6	5	63	0	0	12	5
TH	6	4	24*	0	1	10	5
JR	3	21	56			8	
RD	6	12	37	0	3	8	7

* Scores falling outside of the normal range

Cats. - Categories achieved in the WCST
Persev. Resps. - No. of perseverative responses

Table 3.5 shows the results of the tests assessing frontal lobe function for the post-encephalitic and normal control groups. The post-encephalitic subjects achieved significantly fewer categories on the WCST [$t(12) = 2.51 p<.05$] and made significantly more perseverative responses [$t(12) = 2.89 p<.05$] than their control group. As shown in table 6, two of the three post-encephalitics made a moderate number of perseverative responses, being just below the cutoff of 46 and the remaining subject made only 15 perseverative responses, this being within the normal range. There were no significant differences between the groups on any of the other frontal lobe tests. Two of the post encephalitic subjects produced well below normal scores on the verbal fluency test, being within the defective range and one of these subjects also scored very highly on perseverative responding in the design fluency test.

Table 3.5: Group means (standard deviations) for frontal lobe test scores of post-encephalitic and normal control subjects.

	Post-Encephalitic Subjects (n = 3)		Normal Controls (n = 11)		t	df	p
	Mean	(SD)	Mean	(SD)			
WCST Categories	3.3	(0.6)	5.3	(1.3)	2.51	12	.027
Perseverative responses	32.7	(15.3)	13.2	(9.0)	2.89	12	.013
Verbal Fluency Scaled Score	26.0	(14.8)	39.7	(9.4)	2.00	12	NS
Design fluency % Persverative Responses	29.8	(44.0)	8.2	(13.4)	1.53	12	NS
Picture Arrangement No. left in order	1.7	(1.5)	1.6	(2.4)	0.02	12	NS
Block Design Scaled Score	11.3	(2.1)	11.3	(2.7)	0.04	12	NS

NS Not significant
All probabilities two tailed

Table 3.6: Frontal lobe test scores for the post-encephalitic subjects.

SUBJECT	WCST		Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
	Cats.	Persev. Resps.					
BT	3	41	16*	0	2	12	2
BD	3	42	43	9.1	0	9	9
GH	4	15	19*	80.4*	3	13	7

* Scores falling outside of the normal range

Cats. - Categories achieved in the WCST
Persev. Resps. - No. of perseverative responses

3.1.3.2. Experimental Results

Figures 3.1, 3.2 and 3.3 show the means of the time estimates for each group in relation to actual time. If estimated time is equal to true time the data should lie on a line at 45 degrees. In all three conditions the data for both control groups lie at or very close to the diagonal, whereas the post encephalitic group and the Korsakoffs appear to be fairly accurate up to 20 seconds, after which they underestimate the intervals. This is more pronounced in the Korsakoff group except for the filled interval condition in which the post-encephalitics and the Korsakoffs appear to perform very similarly.

The data was analysed in terms of the mean error from target for each time interval irrespective of sign. Figures 3.4, 3.5 and 3.6 depict the mean error from target for the Korsakoff and alcoholic control groups. These show that the Korsakoff subjects do, in fact, make greater errors than the alcoholic controls at all time intervals, although this is more pronounced for the longer intervals. Analysis of variance with the factors group, condition and bins was carried out using a reciprocal transformation of the data to uphold the homogeneity of variance assumption. This confirmed the finding that the Korsakoff group made greater errors than their controls particularly at longer intervals with a significant main effect of group $[F(1,13) = 19.51 \ p = .001]$ and a significant group x length of duration interaction $[F(5,65) = 2.58 \ p = .035]$. As would be expected all subjects made larger errors at longer intervals as shown by a significant effect of length of duration $[F(5,65) = 51.51 \ p < .001]$. The groups did not perform similarly in all the experimental conditions shown by a main effect of condition i.e. type of time estimation $[F(1,13) = 3.52 \ p = .022]$. The differences between the conditions tended to be more pronounced at the longer intervals but the interaction of condition X time just failed to reach significance $[F(10,130) = 1.89 \ p = .052]$. The Korsakoff subjects, however, were not differentially affected by experimental condition even at the longer intervals as there were no group X condition or group X condition X time interactions.

The differences between the experimental conditions proved to be due to the reproduction condition producing smaller errors than either the filled and empty conditions for both groups. When comparing the reproduction task to the filled interval task the main effect of condition was significant $[F(1,13 = 6.6, p = .023]$ but in the reproduction versus empty interval conditions the effect of condition just failed to reach significance $[F(1,13 = 3.52, p = .083]$. When comparing the filled and empty interval conditions there was no significant difference between these two tasks.

Figures 3.7, 3.8, and 3.9 show the mean error from target for each interval for the post-encephalitic and normal control groups. In the reproduction task the two groups appear

Figure 3.1: Mean time estimates for each group in the time reproduction condition in relation to the length of the demonstrated interval.

Time Reproduction

Estimated Time (secs)

Alcoholic Controls
Normal controls
Encephalitics
Korsakoffs

Real Time (secs)
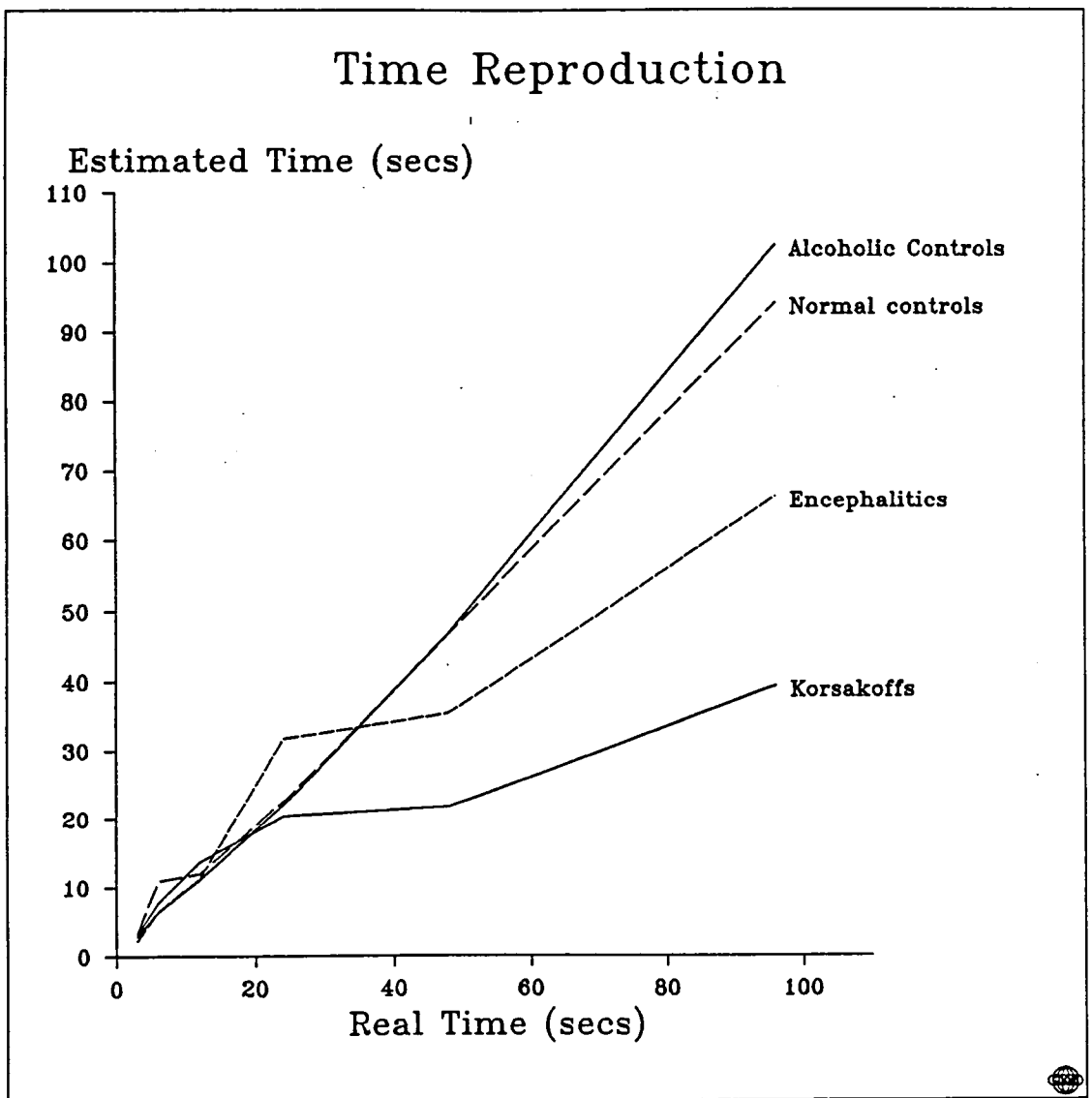
Figure 3.2: Mean time estimates for each group in the time estimation - empty interval condition in relation to the length of the interval to be estimated.

Time Estimation – Empty Interval

Estimated Time (secs)

Real Time (secs)

Normal Controls
Alcoholic Controls

Encephalitics
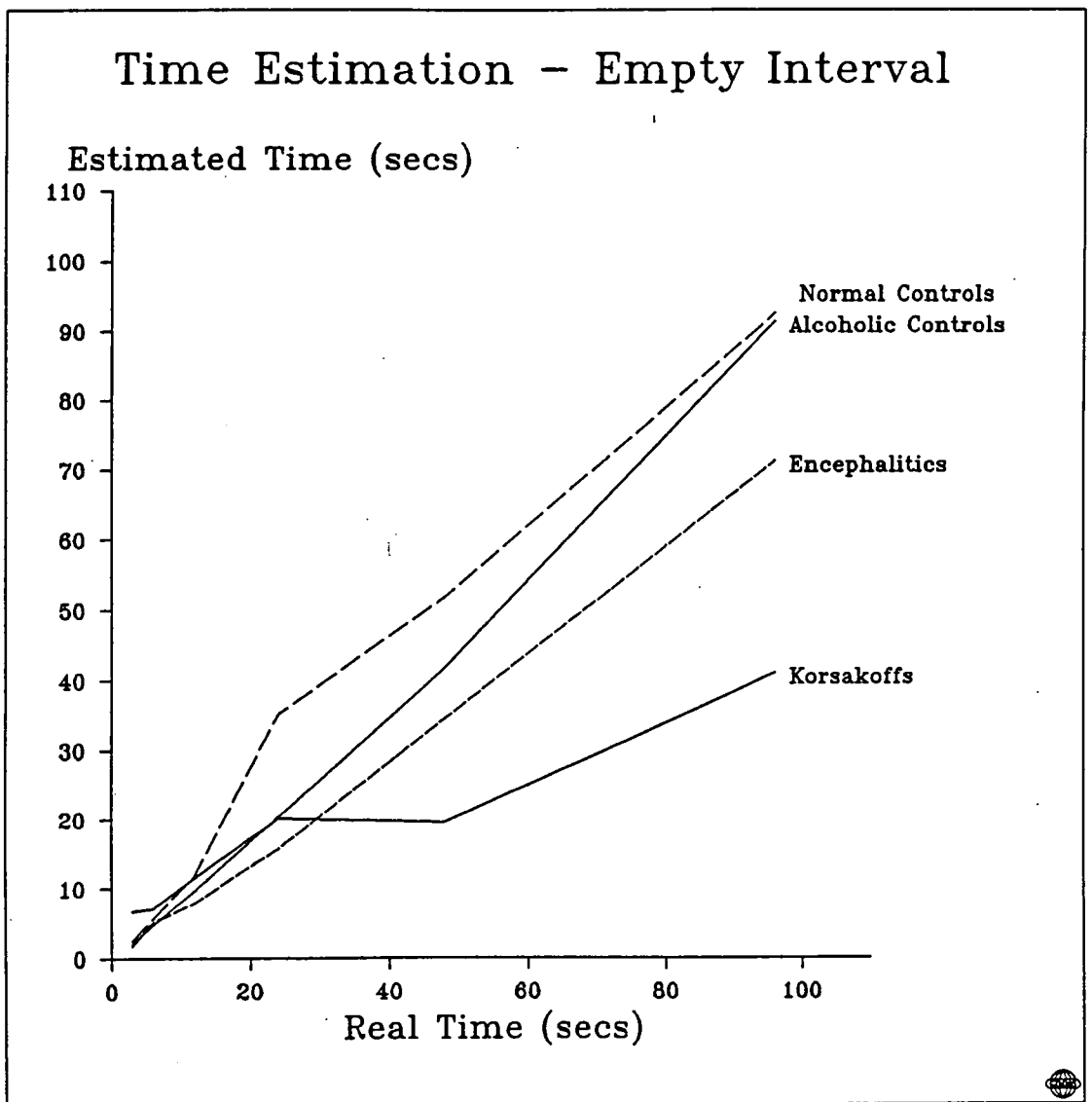
Korsakoffs

Figure 3.3: Mean time estimates for each group in the time estimation - filled interval condition in relation to the length of the interval to be estimated.

Time Estimation – Filled Interval

Estimated Time (secs)

Real Time (secs)
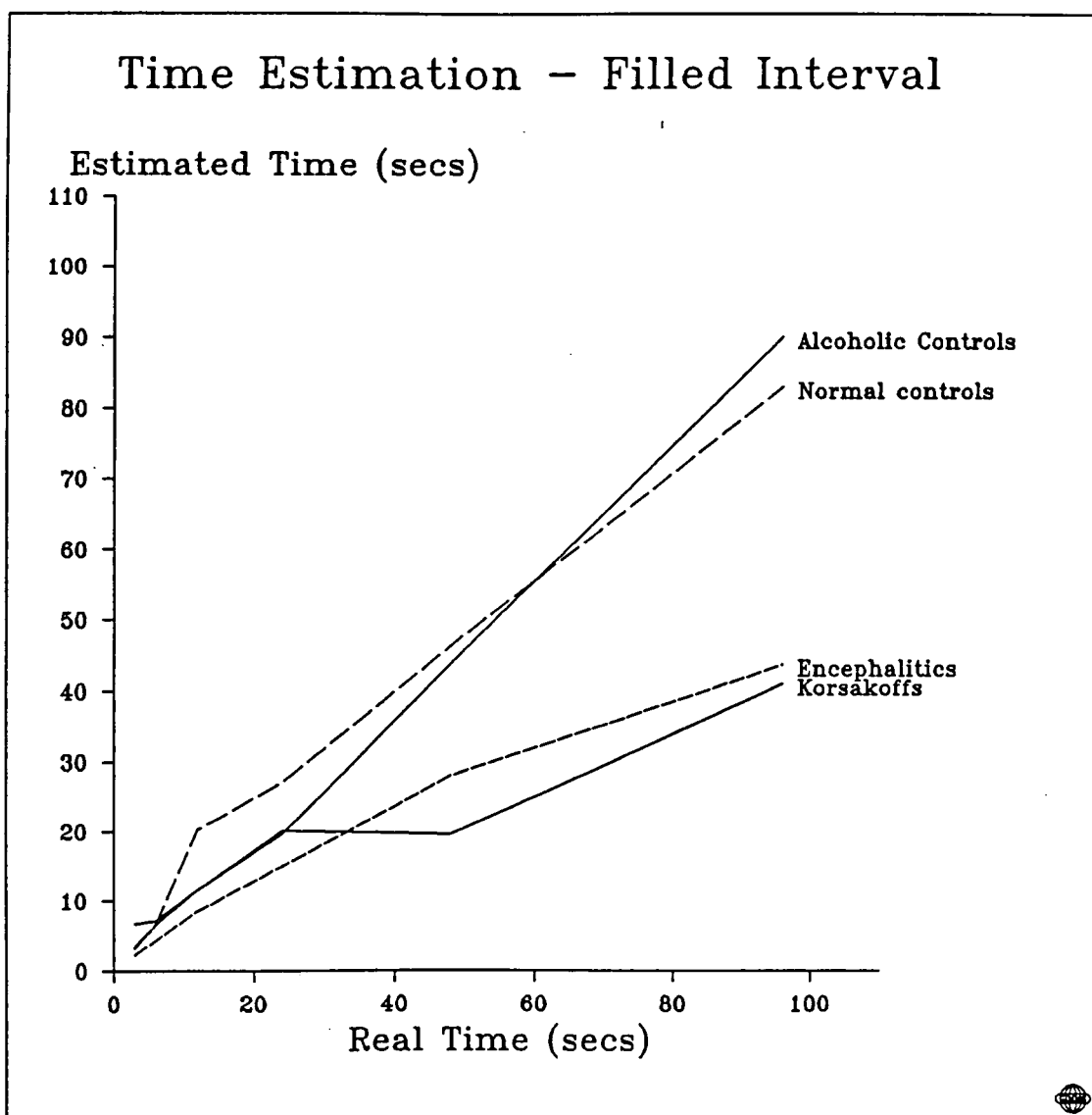
Figure 3.4: Mean error from target in the time reproduction condition for the Korsakoff and alcoholic control groups.

Time Reproduction

Mean Error (secs)

[Graph showing Mean Error (secs) on the y-axis ranging from 0 to 80, and Time Intervals (secs) on the x-axis ranging from 0 to 100. Two curves are plotted: "Korsakoffs" rising to about 62 at 95 seconds, and "Alcoholic Controls" rising to about 19 at 95 seconds.]

Time Intervals (secs)
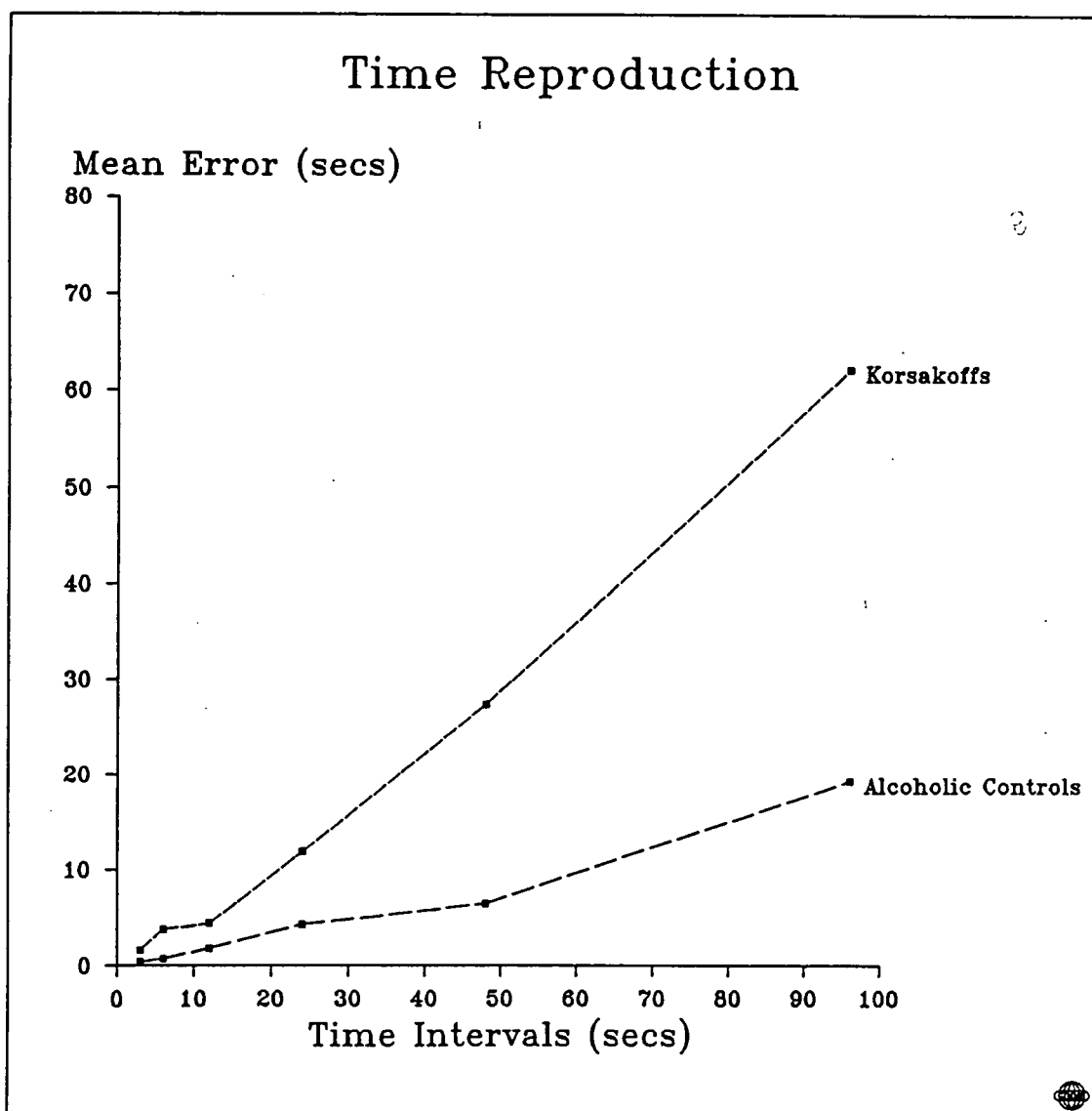
Figure 3.5: Mean error from target in the time estimation with empty intervals condition for the Korsakoff and alcohlic control groups.

Time Estimation – Empty Interval

Mean Error (secs)

Korsakoffs

Alcoholic Controls

Time Intervals (secs)
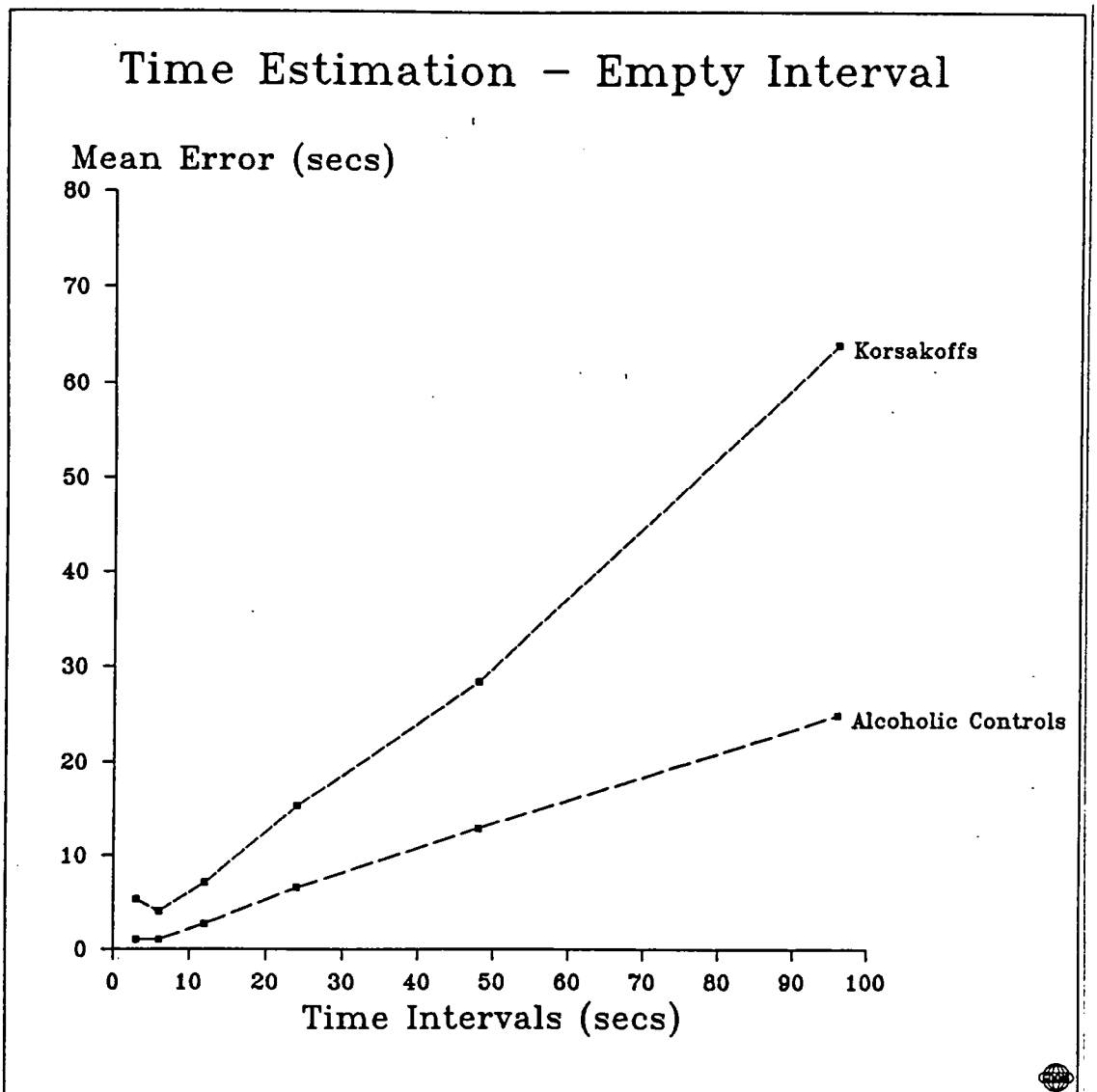
Figure 3.6: Mean error from target in the time estimation with filled intervals condition for the Korsakoff and alcoholic control groups.
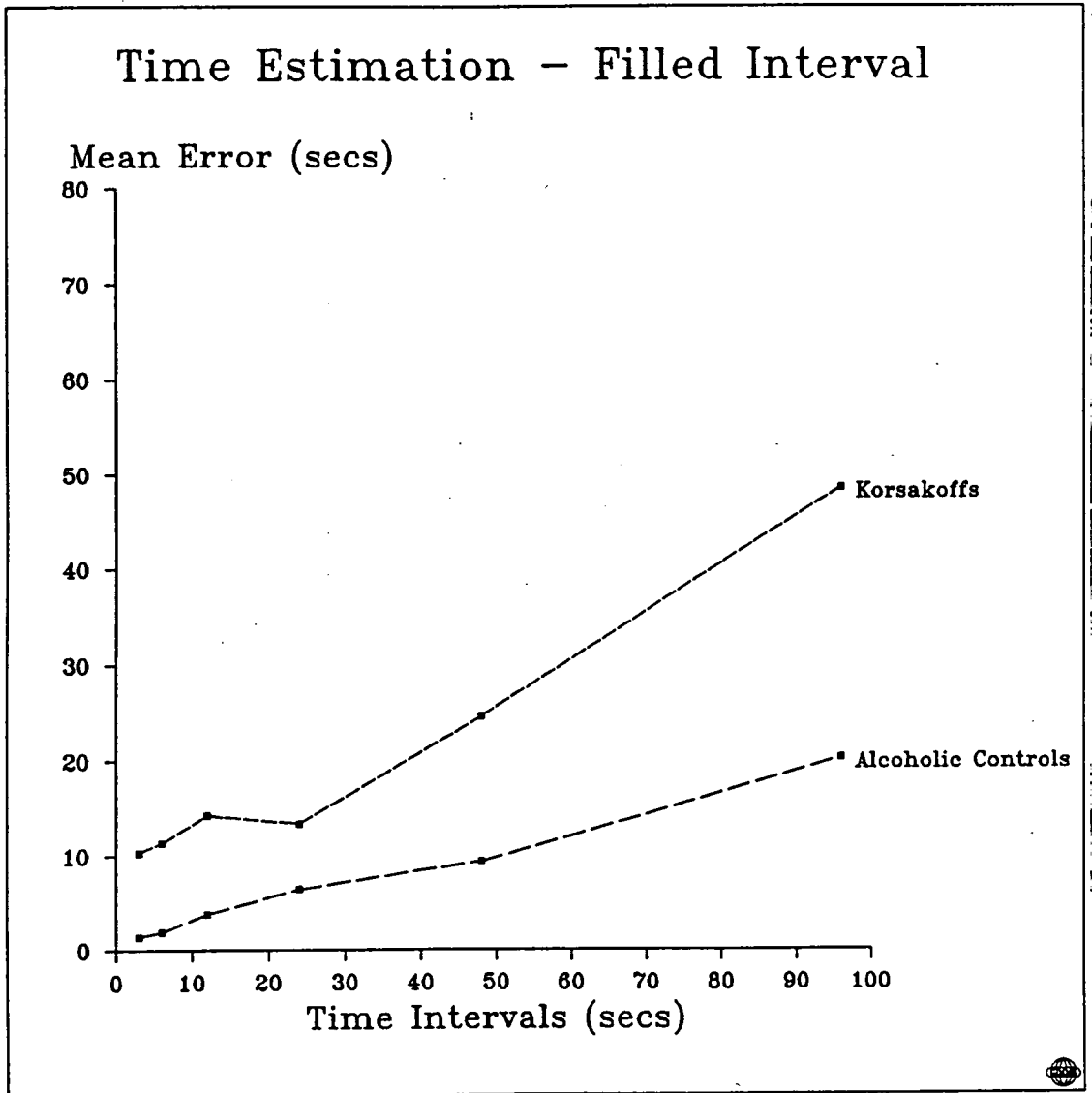
Figure 3.7: Mean error from target in the time reproduction condition for the normal control and post-encephalitic groups.

Time Reproduction

Mean Error (secs)

Encephalitics

Normal Controls

Time Intervals (secs)

Figure 3.8: Mean error from target in the time estimation with empty intervals condition for the post-encephalitic and normal control groups.

Time Estimation – Empty Interval

Mean Error (secs)

Encephalitics

Normal Controls

Time Intervals (secs)

Figure 3.9: Mean error from target in the time estimation with filled intervals condition for the post-encephalitic and normal control groups.

Time Estimation — Filled Interval

Mean Error (secs)

Encephalitics

Normal Controls

Time Intervals (secs)

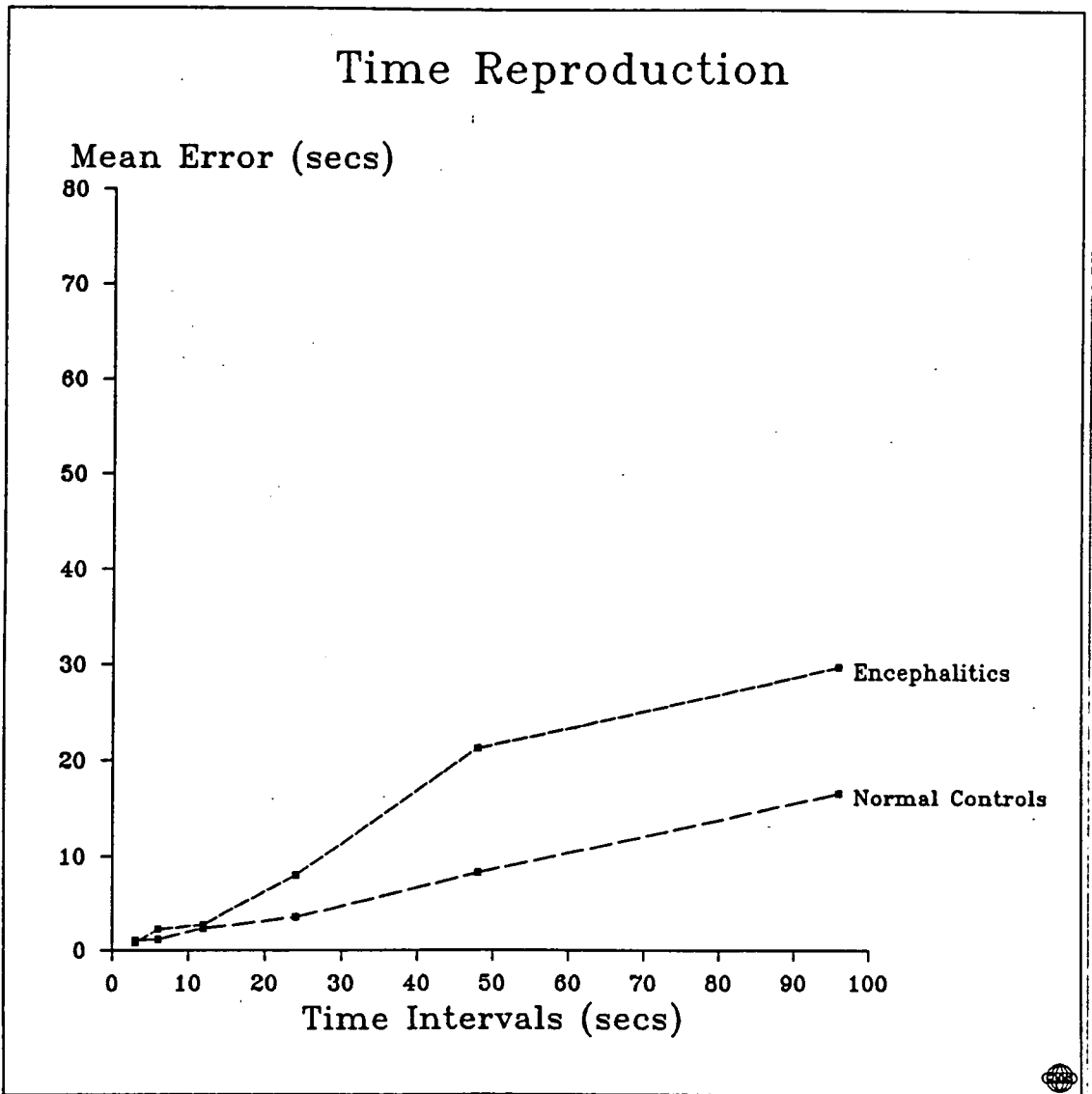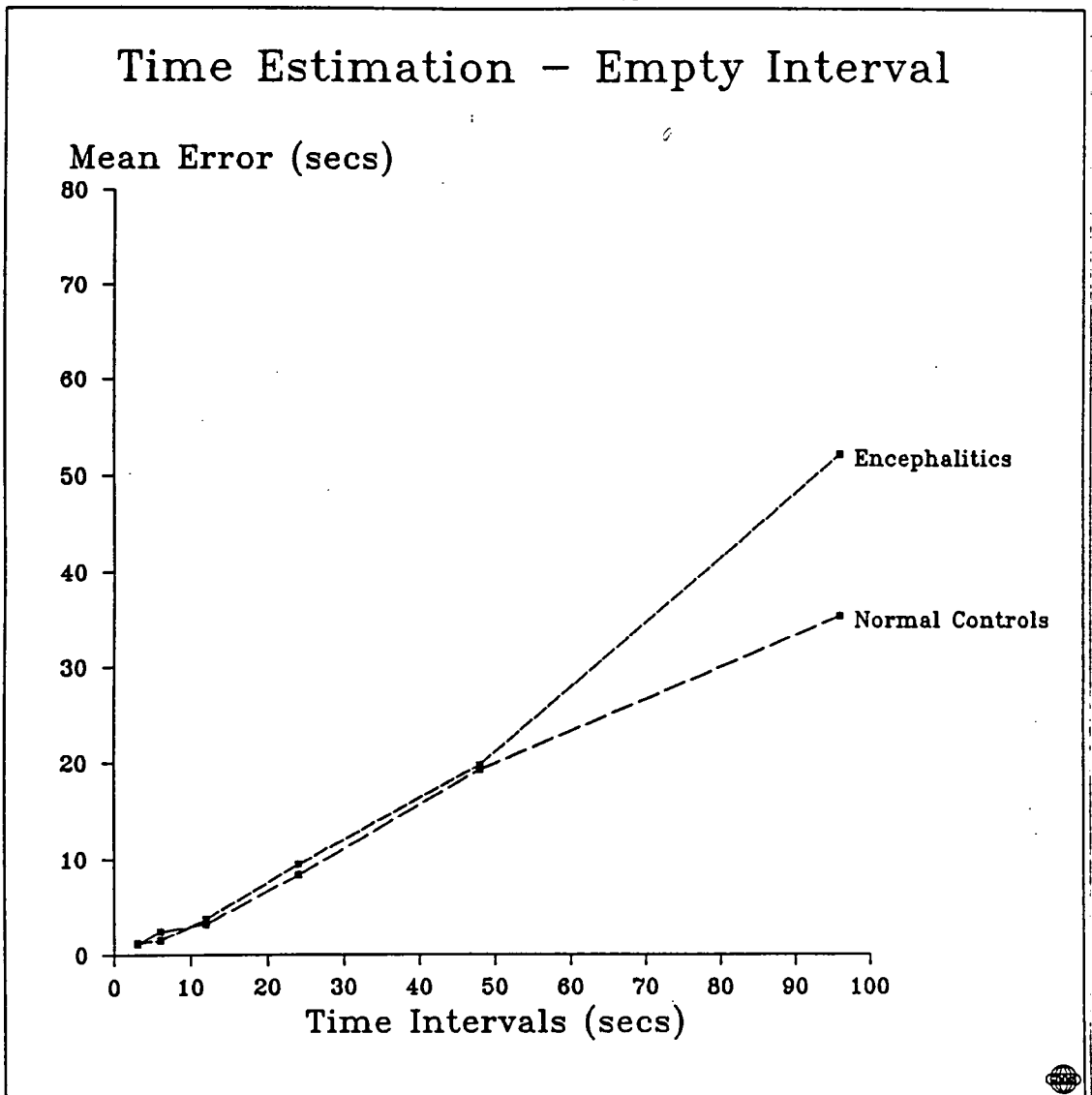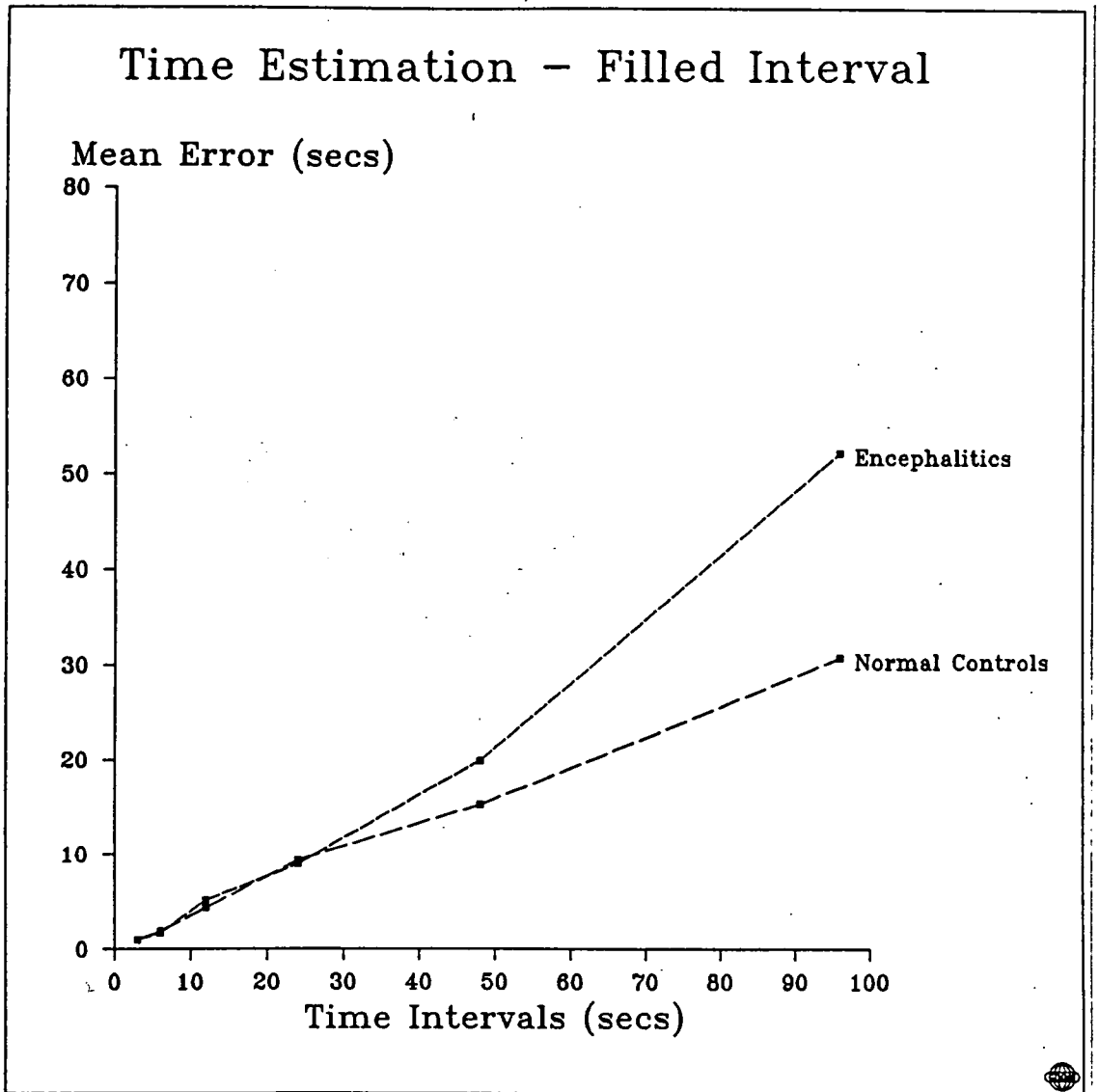to make similar errors up to 12 seconds and thereafter the post-encephalitics make greater errors. In the time estimation tasks the two groups appear to perform similarly except on the longest interval of 96 seconds in the empty interval condition and at 48 and 96 seconds in the filled interval condition.

Again the data was analysed using analysis of variance with reciprocal transformation of the data. There was no difference in the size of overall error between the two groups as the main effect of group was not significant. Neither was there any difference in error from target in the different experimental conditions. Both groups made larger errors with longer intervals as shown by a significant effect of length of duration [$F(5,60) = 46.88, p < .001$]. The encephalitic group, however, was not differentially affected by the type of task or the length of the duration as the interactions of group X condition, group X time and group X time X condition were not significant.

To compare the level of performance of the two amnesic groups in relation to their control groups an analysis of variance was carried out with two between subjects factors, that is group (amnesic vs control) and study (Korsakoff and alcoholic control subjects vs post-encephalitic and normal controls) as well as the between subjects factors of condition and length of duration used in the foregoing analyses. As would be expected the amnesic subjects in general performed worse than the control subjects with a main effect of group [$F(1,25) = 15.14, p=.001$]. The interaction of study X group, however, just failed to reach significance [$F(1,25) = 3.02, p=.095$]. A more direct comparison of the performance of the amnesic groups could only be assessed by increasing the size of the post-encephalitic group but a conservative analysis using just three subjects does suggest that this may yield a significant difference.

The total error from target made by individual subjects in each of the three conditions was correlated with performance on tests of frontal lobe function and tests of severity of amnesia and intellectual function for each group. Tables 3.7 and 3.8 show the results of the Spearman rank order correlations for the Korsakoff group. The measures of severity of amnesia (table 3.8) comprised the memory quotient derived from the WMS, the total score on the Warrington Recognition tests for words and faces, the full scale WAIS IQ minus MQ, the full scale NART IQ minus MQ, and a test of short term memory - the digit span subtest of the WMS. The tests of intellectual function were the WAIS full scale IQ and the NART full scale IQ. All correlations represent the relationship between poor performance on the time estimation tasks and poor performance on the other tests.

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Correlations between tests of frontal lobe function and performance on the time estimation tasks for the Korsakoff group showed a tendency for positive correlations between both the Cognitive Estimation and Picture Arrangement tests and the time estimation whereas Block Design correlated negatively with the temporal estimation. Poor performance on the Block Design test correlated negatively with the error from target in the filled interval condition ($r_s = -.90, p=.007$) and just failed to reach significance with the total error ($r_s = -73, p=.063$). Significant positive correlations were found between the Cognitive Estimation test and the filled interval condition and total errors ($r_s = +.82$, $p=.044;$ $r_s = +.90, p=.015$). There was a tendency for the picture arrangement to have a positive relationship with the filled condition and total errors but this did not reach statistical significance.

Table 3.7: Spearman rank order correlations between poor performance on the time estimation tasks and impairment on tests of frontal lobe function for the Korsakoff group.

Type of Time Estimation	Tests of Frontal Lobe Function					
	WCST	Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
Reproduction	-.21	-.09	+.26	-.12	-.16	+.20
Estimation Empty Intervals	-.11	-.26	-.43	+.44	-.32	+.67
Estimation Filled Intervals	+.47	-.52	+.12	+.68	-.90 p=.007	+.82 p=.044
Total Error on all 3 conditions	+.11	-.31	+.03	+.73	-.73 p=.063	+.90 p=.015

All probabilities two tailed

Table 3.8: Spearman rank order correlations of error on time estimation tasks, tests of memory function and tests of intellectual function for the Korsakoff subjects.

Type of time Estimation	Tests of Memory and Intellectual Function						
	WMS	Warrington Recognition	WAIS IQ-MQ	NART IQ-MQ	Digit Span	WAIS IQ	NART
Reproduction	+.06	-.21	-.31	-.64	-.34	+.61	-.54
Estimation Empty Intervals	-.55	-.84 p=.018	+.26	+.19	-.27	+.02	+.36
Estimation Filled Intervals	-.88 p=.008	-.77 p=.042	+.26	-.45	-.83 p=.022	-.52	-.23
Total error on all 3 conditions	-.71 p=.06	-.88 p=.010	.18	-.71 p=.072	-.61	-.27	+.20

All probabilities two tailed

The correlations between severity of amnesia and time estimation showed a negative correlation between impairment on the tests of memory function and impairment on the time estimation tasks with the WMS, Warrington recognition tests, and digit span tests all producing statistically significant correlations with temporal estimation. The WMS memory quotient (table 3.8) correlated negatively with the filled interval condition and just failed to reach significance with the overall total for the three experimental conditions (r_s =-.88, p=.008; r_s=-.71, p=.06). The Warrington Recognition test (table 3.8) correlated negatively with the empty and filled interval conditions and the total error score (r_s=-.84, p=.018; r_s =-.77, p=.042; r_s=-.88, p=.01) whilst the negative correlation between the NART IQ - MQ difference and the total errors fell just short of significance (r_s=-.71, p=.072). The digit span test correlated negatively with the the filled interval condition (r_s=-.83, p=.022).There were no statistically significant correlations between tests of intellectual function and the temporal estimation tasks.

Tables 3.9 and 3.10 give the results of Spearman rank order correlations for the alcoholic control subjects. Only that between the cognitive estimation test and the time estimation with empty intervals reached near statistical significance (r_s=+.75, p=.084). Of the tests of memory function performance on the WMS, and WAIS IQ - MQ show a positive relationship with performance on the time estimation. The Memory Quotient of the WMS was positively correlated with the empty interval condition (r_s=+.86, p=.006).

The WAIS IQ - MQ difference correlated positively with reproduction ($r_s=+.95$, $p<.001$). Only the filled interval condition showed any relationship with intellectual function with a statistically significant positive correlation between the errors on this task and lower scores on the NART ($r =+.71, p=.046$).

As there were only three subjects in the post-encephalitic group rank order correlations were not carried out. But the only frontal lobe test to show any signs of a possible relationship with performance on time estimation was the cognitive estimation task. B.T., who made fewest errors on the time estimation made the fewest abnormal responses on the cognitive estimation, G.H., similarly the next fewest on both tasks and finally B.D. who performed the worst on both tasks.

There appeared to be no relationship between the post-encephalitic errors on the time estimations and tests of memory function except for the WMS. This presented as a negative relationship, the subject scoring highest on the WMS making the largest error on temporal estimation and similarly the subject scoring lowest on the WMS achieved the least error over all the time estimations.

Table 3.9: Spearman rank order correlations of errors on time estimation tasks and tests of frontal lobe function for the alcoholic control group.

Type of time Estimation		Tests of Frontal Lobe Function				
	WCST	Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
Reproduction	-.02	-.19	-.27	-.13	-.41	-.35
Estimation Empty Interval	+.31	+.36	-.30	+.35	+.06	+.75 p=.084
Estimation Filled Interval	+.05	-.14	-.14	-.09	-.29	+.35
Total Error on all 3 conditions	+.23	.00	-.43	+.13	-.12	+.59

All probabilities two tailed

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Table 3.10: Spearman rank order correlations of errors on time estimation tasks, tests of memory function and tests of intellectual function for the alcoholic control group.

Type of Time Estimation			Tests of Memory and Intellectual Function				
	WMS	Warrington Recognition	WAIS IQ-MQ	NART IQ-MQ	Digit Span	WAIS IQ	NART
Reproduction	+.36	-.26	+.95 p<.001	+.38	+.20	-.41	-.19
Estimation Empty Intervals	-.86 p=.006	+.60	+.26	+.19	-.25	+.66 p=.076	+.57
Estimation Filled Intervals	+.02	+.08	-.19	-.55	+.25	+.25	+.71 p=.046
Total error on all 3 conditions	+.64 p=.09	+.26	+.37	+.08	-.04	+.36	+.54

All probabilities two tailed

3.1.4. Discussion

The Korsakoff amnesics were impaired relative to the alcoholic controls in all three tasks, reproduction, time estimation with filled and empty intervals. As predicted the impairment was one of underestimation which was more pronounced as the length of the interval increased. The post-encephalitics, on the other hand, were unimpaired relative to the normal controls in all aspects of temporal estimation.

Although figures 1, 2 and 3 suggest that estimation of duration was normal up to 20 seconds for both amnesic groups this method of presenting the results, as used by Richards (1973), averages out direction of error. When mean error from target is plotted, regardless of the direction of the error, the post encephalitic subjects do perform very similarly to the controls up to 24 to 48 seconds, thereafter producing greater error, although the group X length of duration interaction was not statistically significant. The Korsakoff group, however, produced greater errors than their controls at all time intervals. In this respect there appears to be little similarity between the pattern of results produced by the Korsakoff subjects and that exhibited by H.M. There was no evidence of a cutoff at the 20 sec interval before which the Korsakoff amnesics performed normally. The post-encephalitic group produced a similar pattern to that of H.M., being unimpaired at the shorter intervals but producing greater errors in the direction of

underestimation at longer intervals although they were not significantly impaired relative to their control group. It is, however, difficult to make definitive statements on the ability of post-encephalitic subjects in view of the small group size in this experiment.

Both the Korsakoff and alcoholic control groups performed better on the reproduction task compared to the two time estimation tasks. The post-encephalitics and the normal controls also made fewer errors in this condition although this was not statistically significant. Therefore, the prediction that the amnesic groups would be differentially impaired by the increased memory load in this task was not borne out. Rather, the data is consistent with previous findings that reproduction tasks tend to be more accurate than other methods of time estimation (Clausen, 1950; Block, 1989).

The proposal that deficits in time estimation could be secondary to the amnesia is consistent with the finding that impairments in the Korsakoff group increase with the length of the interval but not with the finding that, unlike H.M., they are also impaired at the shorter intervals. It was expected that if temporal estimation is secondary to the amnesia performance on the time estimations would correlate with tests of memory function. In the Korsakoff group, however, measures of memory function tended to correlate negatively with ability on the time estimation tasks. The only exception to this was the WAIS IQ - MQ difference although the NART IQ - MQ difference did show a negative correlation. Measures of IQ per se did not correlate with performance on the temporal estimations. The task most likely to show a correlation with severity of amnesia, the reproduction task, did not produce any significant correlation but the Korsakoffs performed better in this task than the estimation tasks. The post-encephalitic data also suggested a tendency for a negative relationship between memory ability, as measured by the WMS, and overall performance on time estimations. The alcoholic control group, on the contrary, tend to show a more positive relationship between ability on memory tests and the ability to carry out time estimation tasks and also a positive correlation between intellectual ability and estimations measured with empty intervals.

Clearly, memory is not the critical factor involved in the ability to make temporal estimations as the post-encephalitics were unimpaired even though they exhibited comparable severity of amnesia to that of the Korsakoff subjects. The alcoholics did not show a consistent relationship between memory and time estimation but their results do suggest that memory can be utilised in making such estimations. However, this relationship could be a result of general intellectual ability as the WAIS full scale IQ also proved to have a statistically significant correlation with time estimation. It would appear that the Korsakoff subjects make temporal estimations in a qualitatively different

way to the controls which is not dependent upon memory function but using a mechanism that is detrimentally affected by memory ability. This mechanism would also appear to be involved in the making of numerical estimations of a more general nature as measured by the cognitive estimation task, for performance on this task showed a consistent relationship with time estimation in all three groups, that is the Korsakoff, post-encephalitic and alcoholic control groups. None of the other frontal lobe tests produced any relationships with time estimation except the picture arrangement and block design tests in the Korsakoff group. Poor performance on the picture arrangement test showed a positive relationship with overall errors and error on the filled interval condition, although this was not statistically significant, whereas poor performance on the block design showed a negative relationship with these two measures.

Impairments in performance on cognitive estimation tasks has been attributed to a deficit in the formation and utilization of cognitive plans or strategies for problem solving (Shallice & Evans, 1978; Smith & Milner, 1984) which is a function attributed to the frontal lobes. The reason for the cognitive deficit underlying impairments in the picture arrangement test is uncertain but has been suggested to be the inability to correct an error in the face of contradictory information (McFie & Thompson, 1972). Impairments in temporal estimation could be the result of the inability to plan and utilize appropriate strategies, and, if memory could be utilised to make time estimations, which is a possibility suggested by the alcoholic control data, better preserved memory function would not assist the subject to make an estimation if there is an additional inability to correct error in the face of contradictory information.

If the impairment is one of a difficulty in the formation of appropriate strategies and use of contradictory feedback, it must be of a fairly specific nature as many of the frontal lobe tests require such an ability. For example, the WCST requires a logical strategy for its solution which depends upon the correct use of feedback. But performance on this test showed no relationship to performance of temporal judgments. Disorders of temporal estimation cannot be attributed to general frontal lobe dysfunction but a specific process that may be partly served by the frontal lobes.

Finally, the prediction that the amnesic subjects would be differentially affected by interference in the filled interval condition was also not borne out by the results. There was no difference in the pattern of results for the filled interval condition compared to the empty interval condition for either of the amnesic groups and neither of the control groups found this task more difficult. This prediction is based on the assumption that processing of temporal information is not automatic and should, therefore, compete

with other cognitive processing for capacity. However, the empty intervals cannot be assumed to be cognitively 'empty' as the processing carried out by subjects cannot be controlled. It is also possible that the task used in the filled condition served to structure time in a constructive way. It does suggest, however, that subjects were not 'cheating' by counting in the other experimental conditions although it is possible that other time structuring strategies may have been used such as thinking of musical rhythms or reciting poetry.

In conclusion, the Korsakoff group but not the post-encephalitics were impaired at making temporal judgments, particularly as the length of the intervals to be measured increased. With the longer intervals the impairment was one of underestimating the length of the duration, in a similar manner to that of H.M., but there was no evidence to suggest that a cut-off point of 20 secs delineated a transfer from normal to abnormal estimations. The pattern of results for the encephalitic subjects were similar to the pattern displayed by H.M., although they were not significantly impaired compared to their control group. It appeared that the Korsakoff subjects were making temporal estimations in a qualitatively different manner to that of the controls as negative correlations were found between tests of memory function and performance on the time estimation tasks as opposed to a positive correlation in the alcoholic control group. This negative relationship was also observed in the post-encephalitic data. Correlations were also found between performance on time estimation and performance on certain but not all tests of frontal lobe function in all three groups. It is possible that specific cognitive functions such as the formation and utilization of problem solving strategies and use of feedback may be a factor in the temporal judgment impairment, these functions being carried out by the frontal lobe. The results did not support the hypothesis that deficits in temporal estimation occur as a result of the amnesia nor are an inevitable consequence of anterograde amnesia.

3.2 Experiment 2: Time estimations by amnesic subjects using a fixed interval procedure.

3.2.1. Introduction

This experiment investigated the performance of amnesic subjects' time estimation using a fixed interval (FI) procedure. On a FI schedule the first response after a set interval is reinforced. Animal performance of FI schedules is characterized by a pause in responding at the start of the interval followed by an accelerated rate of responding terminating in the reinforcement. This post-reinforcement pause gives a measure of temporal discrimination. However, human studies have generally failed to replicate the pattern of responding produced by animals. In the conventional human experimental procedure, responding on a button is reinforced by the additition of counter points which may be later exchanged for money. The pattern of responding exhibited by human subjects has been reported to be either high-rate which consists of a constant rate of responding throughout the schedule showing no temporal discrimination, or a low-rate of one or two responses at the end of the interval (Leander, Lippman & Meyer, 1968; Lippman & Meyer, 1967). This low-rate responding, although it does not resemble the pause-respond pattern of animal performance, does show temporal differentiation as the pattern of responses varies directly with the reinforcement contingency.

In animal experiments reinforcers typically require a consummatory behaviour, the important feature of which is that it interrupts operant responding (Matthews, Shimhoff, Catania, & Sagvolden, 1977). In human experiments this means that a two-chain response is used. That is, responding on the FI schedule is carried out on one button and reinforcement is acquired by the pressing of another button. This two-chain response has been shown to produce similar patterns of performance to those observed in animal operant experiments when the FI response button is used as an observing response. For example, Lowe, Harzem and Hughes (1978) devised a procedure in which a response on one button gave access to a clock and response on another button delivered reinforcement. They proposed that subjects in this experiment relied upon the temporal stimuli provided by the clock, rather than using strategies such as counting or constant key pressing, thus producing a pause-respond pattern with increasing acceleration as the end of the interval approached. The present study utilised the two-chain response procedure by requiring subjects to respond on one button to gain information as to whether the interval had elapsed and on another to acquire the reinforcement.

A number of factors have been identified which are important determinants of temporal discrimination in human operant studies. Explicit experimental instructions as to the

nature of the schedule can determine whether a subject produces a response based approach, with a corresponding high-rate pattern of responding, or an interval based approach with a low-rate response pattern (Lippman & Meyer, 1967). Accordingly in this study the subjects were given explicit instructions as to the temporal nature of the schedule but without stating the actual length of the interval.

A variant of the FI procedure is the peak interval procedure. A number of trials are interspersed in a fixed interval session in which no reinforcement is given and the trial continues for an extended period of time. In these probe trials the response rate peaks at the time that reward is expected, and then declines over time. This gives a more accurate measure of the subjects timing ability as temporal discrimination is not essential in acquiring reinforcement in FI schedules. This has been used to assess the temporal discrimination performance of brain lesioned animals, and, as mentioned in chapter 2, has shown that rats with hippocampal lesions exhibit a left shift in peak time whereas rats with frontal cortex lesions exhibit a right shift. An analogue of this variant of the FI schedule was devised in which a number of probe trials were incorporated into the FI session in which the reinforcement was delayed by two thirds of the length of the fixed interval.

In order to examine further the suggestion made by Richards (1973) that temporal estimation is normal up to intervals of twenty seconds in amnesic subjects, two intervals were used of fifteen and thirty seconds. The FI bears some similarity with the reproduction procedure used in the previous experiment as it avoids the need to make a translation of a verbal time unit into duration measurement. This method was found to produce more accurate temporal estimation. It also allows many more trials to be carried out in a session at each time interval. In addition, salient feedback is given as to accuracy of responding by the delivery of coin reward for each correct response, whereas in the previous experiment no feedback was given. It was expected that control subjects would utilise this feedback in order to adjust responding to acquire better temporal discrimination. The amnesic subjects, however, if they suffer from a deficit in modifying responding in response to contradictory information, would not be aided by such information (See section 3.1.4). It would be expected, then, that the amnesic subjects would not improve across a session and would not show any sensitivity to the extended probe trials. As the probe trials are longer than other trials the control subjects should show a sensitivity to this contradictory information by producing longer latencies to respond on subsequent trials. Again correlations were carried out between performance on the fixed interval task and measures of memory function and frontal lobe function.

3.2.2. Methods

3.2.2.1. Subjects

The Korsakoff group was the same as that in experiment 1 except for one subject (J.B.) who was unavailable for testing. This left a group of four men and two women, mean age 57.3 years. The alcoholic control group was also the same as that in experiment 1 with the addition of a further male subject. The mean age for this group was 48.4 years. The post-encephalitic group remained unchanged and one subject was excluded from the normal control group as he was familiar with the computer programme used to run the experiment. The mean age, therefore, of the post-encephalitic group was 40 years and the normal control group was 49.2. These changes to the groups did not appreciably alter the overall patterns of the psychometric test scores.

Scores for individual subjects on the tests of frontal lobe damage can be found in experiment 1 (table 3.4). The additional subject in the alcoholic control group achieved 2 categories in the WCST and made 46 perseverative responses which is suggestive of frontal lobe damage. He also scored within the defective range on the verbal fluency test achieving a score of 22. For the block design he scored 9, picture arrangement 2, design fluency 16.7, and cognitive estimation 4, which were all within normal limits.

3.2.2.2. Apparatus

The experiment was run using a Toshiba T1000 portable computer linked to an external monitor (screen size 20 x 15 cms), an electronic coin dispenser, and two single key pads (7.5 x 5 cms) (buttons A and B) which were operated by the subject. A notice was attached to button A on which the words, *'press this button to find out when the time is up'* was displayed, and attached to key B was a notice showing the words *'press this button to get a 2p.'*

3.2.2.3. Procedure

Each subject took part in two sessions at weekly intervals, one session consisting of a FI of 15s and the other a FI of 30s. The order of the FI conditions was counterbalanced across subjects.

The subjects sat facing the monitor screen with the coin dispenser immediately to the right of it. Button A was placed in front of the screen and Button B in front of the coin dispenser. Subjects were then instructed that they would be given a number of intervals of time, all of the same length, and that the interval commenced when a box (white rectangle 4 x 7 cm on a black background) appeared on the screen and a short tone was heard from the computer. They were not informed of the length of the interval but were

asked to try and find out when the interval had elapsed by pressing button A. They were instructed that a press to button A prior to the end of the interval would produce the words 'Not Yet' on the screen (for 0.5s), but if the interval had elapsed they would see the word 'Now' appear. On seeing the word 'Now' a press to button B would produce a coin (2p sterling) from the coin dispenser which could be collected at the end of the session. They were told that they could press button A as often as they liked, but that they should press button B only once, and that they should aim to earn as many coins as possible. In addition to the coin reward, a successful press to button B produced a short cheerful tune from the computer, and the word 'Correct' appeared on the screen. If Button B had not been pressed by the end of a predetermined time limit (limited hold), the words 'Sorry, Too late' appeared on the screen accompanied by a deep tone from the computer. At the termination of the trial either by a correct response on button B or a time-out indication, the rectangle disappeared from the screen and was followed by a preset inter-trial interval.

A short practice session was given with an inter-trial interval of 2s and a limited hold of 8s for each FI condition. Once the subject had received two coins this session was terminated and the experiment proper commenced. Seventy trials were given with an inter-trial interval of 2s and a limited hold of 5s for each condition. During the second half of the session eight probe trials occurred in the same predetermined random order for each subject on both conditions. In the probe trials the intervals were extended by 10s in the FI15 and 20s in the FI30. The limited hold period was the same as for normal trials.

3.2.3. Results

Figure 3.10 shows the mean number of responses in each 2.5 sec. bin of the FI15 condition for all the groups. Both control groups exhibit an increasing number of responses as the end of the interval approaches with very few responses up to 10 seconds. Both the Korsakoff group and the post-encephalitic group also show an increasing rate of responding but the 'scalloping' is not as marked, as there are more responses in the first half of the interval. One subject in the post-encephalitic group adopted a strategy of a constant high rate of responding which does not reveal temporal discrimination. When this subject is excluded from the post-encephalitic data (figure 3.11) the post-encephalitics appear to perform very similarly if not better than their control group.

An analysis of variance was carried out on the number of responses in each 2.5s bin with log transformation of the data to uphold the homogeneity of variance assumption. This confirmed that the Korsakoff subjects made more responses overall than the alcoholic control subjects, and that both groups' responses increased as the interval progressed, as the main effects of group [$F(1,13) = 9.48, p=.009$] and bins [$F(7,81) = 30.38, p<.001$] were significant. This increase in responding with progression of the interval was greater in the alcoholic control subjects as the group X bins interaction also proved to be significant [$F(7,81) = 5.23, p<.001$]. The post-encephalitic and normal control subjects also showed greater responding as the end of the interval approached as confirmed by a main effect of bins [$F(7,77) = 16.43, p<.001$] but there was no significant difference between these two groups either in terms of overall response rate or in rate of increase in responding as the interval progressed.

Figures 3.12 and 3.13 show the mean number of responses in each 2.5 second bin for all trials in the FI30 condition except the probe trials. Again the control groups show a steady increase in the rate of responding as the interval progresses, showing sensitivity to the temporal nature of the task. The amnesic groups show a steadier response rate throughout the interval with some increase as the end of the interval approaches. Again a log transformation of the data was used to carry out an analysis of variance. The increase in responding with the length of the interval in the Korsakoff and alcoholic control groups was confirmed by a main effect of bins [$F(13,169) = 31.48, p<.001$] and that this was more pronounced in the alcoholic group by a group X bins interaction [$F(13,169) = 6.49, p<.001$]. The Korsakoff group also made significantly more responses than their controls overall [$F(1,13) = 8.50, p=.012$].

Figure 3.10: Mean number of responses in each 2.5s bin of the interval in the FI 15 task for all trials (excluding probe trials) for all the groups.

FI 15S TRIALS 1–70 (excluding probe trials)

KORSAKOFFS
N=6

ALCOHOLIC CONTROLS
N=9

2.5s BINS

ENCEPHALITICS
N=3

NORMAL CONTROLS
N=10

2.5s BINS

Figure 3.11: Mean number of responses in each 2.5s bin of the interval for all trials (excluding probe trials) in the FI 15 task for all the groups excluding A.P. from the normal control group and G.H. from the post-encephalitic group

FI 15S TRIALS 1–70 (excluding probe trials)

KORSAKOFFS
N=6

ALCOHOLIC CONTROLS
N=9

2.5s BINS

ENCEPHALITICS
N=2

NORMAL CONTROLS
N=9

2.5s BINS

93

Figure 3.12: Mean number of responses in each 2.5s bin of the interval for all trials (excluding probe trials) in the FI 30 task for the Korsakoff and alcoholic control groups.

FI 30S TRIALS 1–70 (excluding probe trials)

KORSAKOFFS
N=6

ALCOHOLIC CONTROLS
N=9

Figure 3.13: Mean number of responses in each 2.5 bin of the interval for all trials (excluding probe trials) in the FI 30 task for the post-encephalitic and normal control groups.

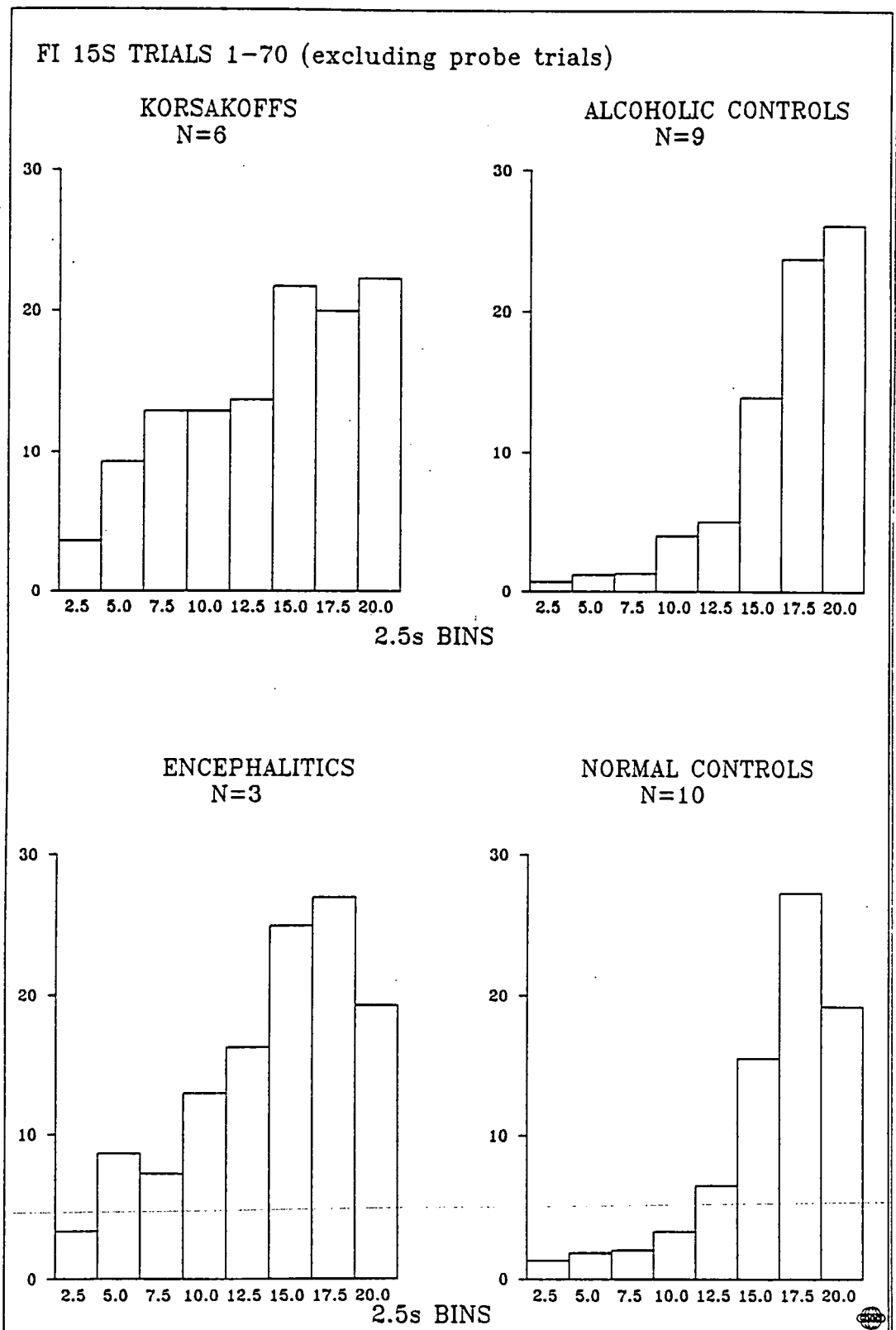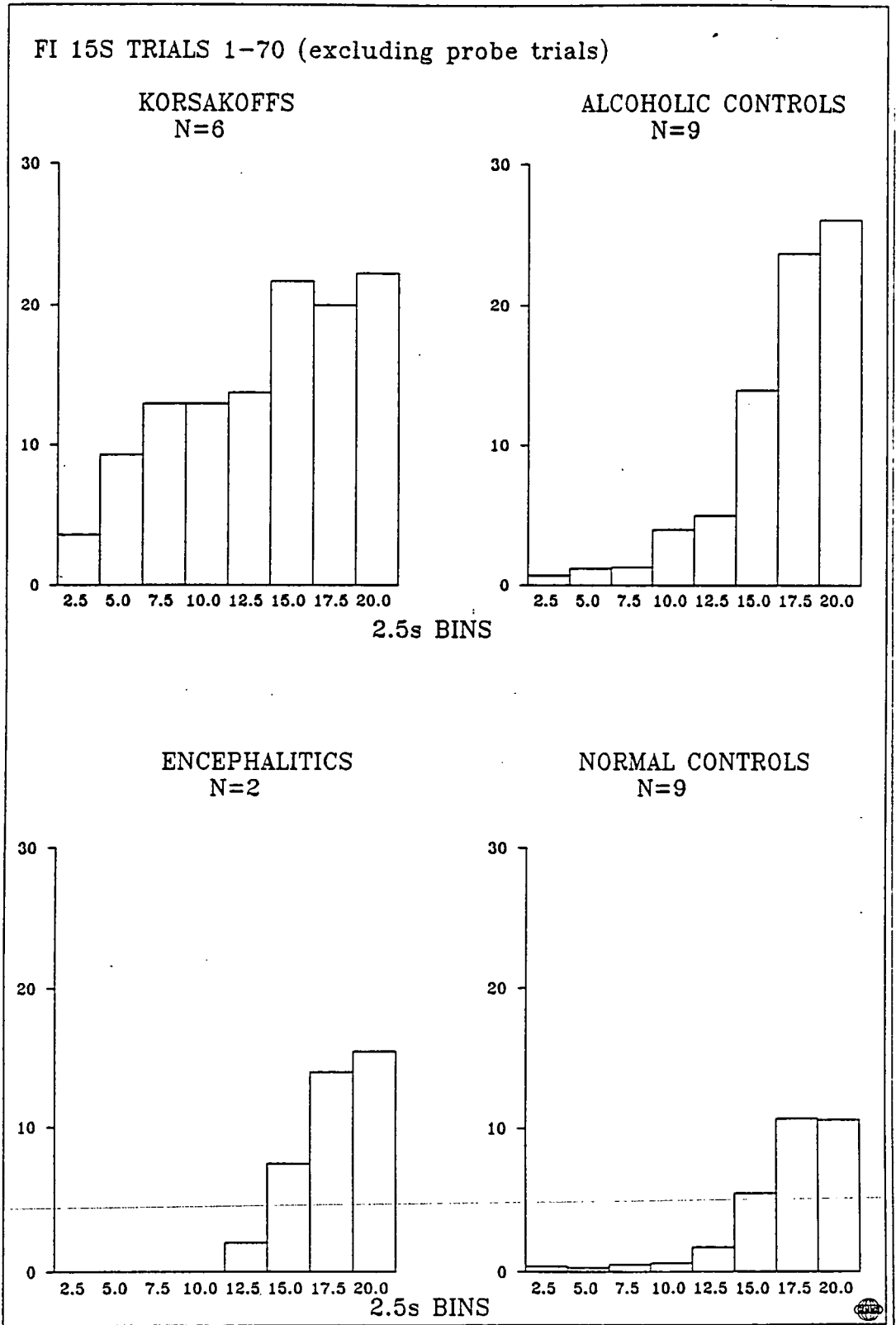FI 30S TRIALS 1-70 (excluding probe trials)
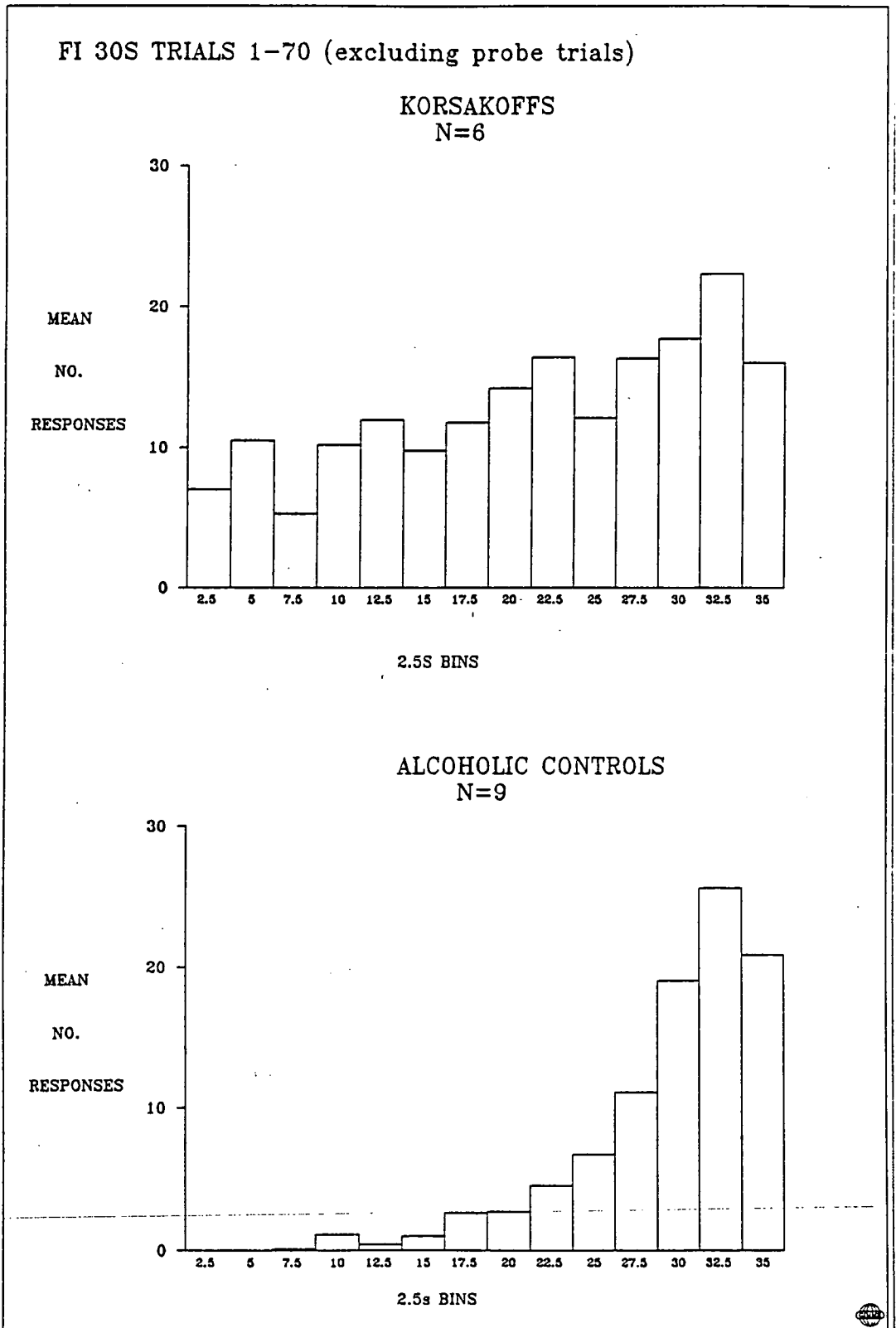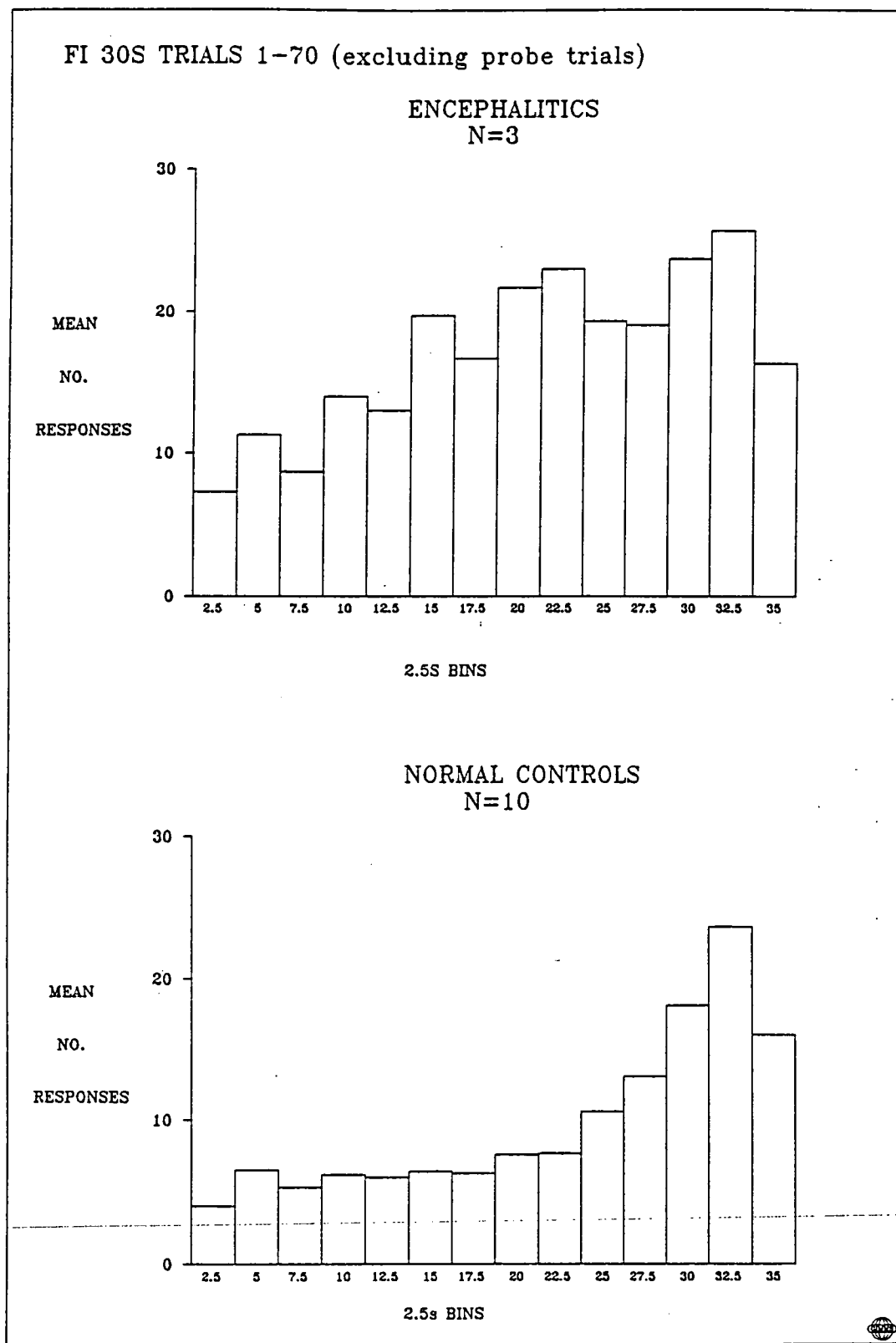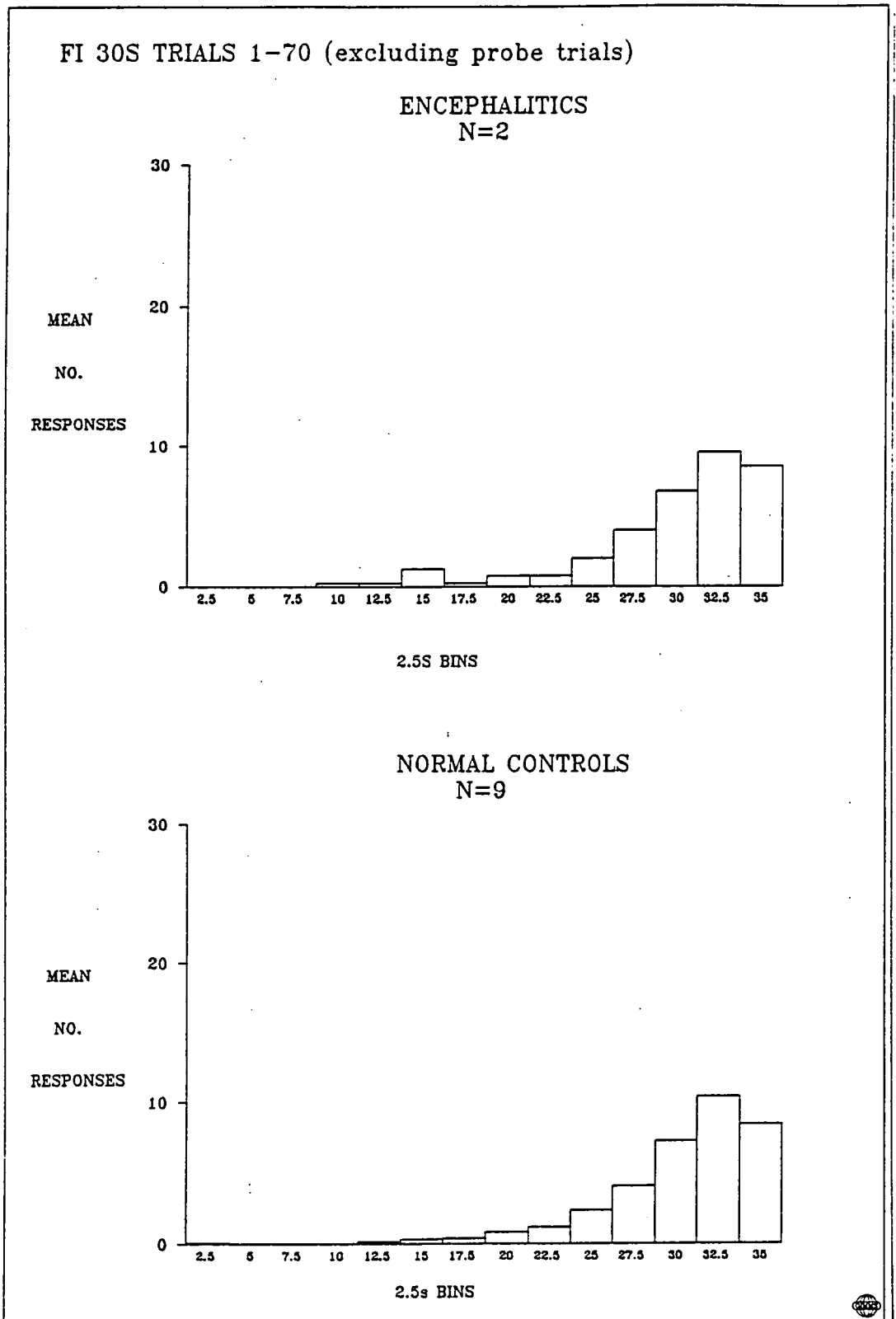
ENCEPHALITICS
N=3

NORMAL CONTROLS
N=10

Figure 3.14: Mean number of responses in each 2.5 bin of the interval for all trials (excluding probe trials) in the FI 30 task for the post-encephaltic and normal control groups excluding subjects A.P. and G.H.

FI 30S TRIALS 1-70 (excluding probe trials)

ENCEPHALITICS
N=2

NORMAL CONTROLS
N=9

The apparent poor performance of the post-encephalitic group in this task can, again, be attributed to one subject adopting a steady high rate of responding. Figure 3.14 shows the results of the remaining two post-encephalitic subjects. The graph also shows the pattern of responding of the normal control group excluding subject A.P. who also adopted a high response rate strategy. This demonstrates the accuracy of the subjects in both groups who were using a temporally based strategy for responding and also the similarity between the two groups pattern of responses. The data was analysed for all three encephalitic subjects and all normal control subjects using a log transformation. There was a significant main effect of bins [$F(13,143) = 16.89, p<.001$] confirming the increase in rate of responding at the termination of the interval but there was no significant difference between the two groups in number of responses or the increase in rate of responding.

To compare the performance of the two amnesic groups in each of the FI conditions analyses of variance were carried out with the between subjects factors of group (amnesic vs controls) and study (Korsakoff and alcoholic control vs post-encephalitic and normal control). The interaction of study X group failed to reach significance in both instances suggesting that there was no difference in comparative performance of each of the amnesic groups and their control groups. This is probably a result of there being only three subjects in the post-encephalitic group and one of these subjects adopting a response based strategy thus producing a large variance. Again it would be necessary to increase group size of the post-encephalitic subjects to make it possible to compare performance between the amnesic groups more directly.

The time to the median response on each trial, averaged across a session (excluding probe trials), was taken as a measure of temporal differentiation. Figures 3.15 and 3.16 shows the mean time to the median response for each subject and the mean median response time for each group. The mean median response time for the Korsakoff group was 12.82 seconds (*SD=2.48*) compared to 16.47 (*SD=1.38*) for the alcoholic controls in the FI15 condition , and 23.03 (*SD=3.90*) compared to 29.92 (*SD=1.76*) in the FI30 condition, showing a tendency for the Korsakoff subjects to underestimate the interval. The post-encephalitic amnesics produced a mean median response time of 15.53 seconds (*SD=2.57*) in the FI15 and 26.13 seconds (*SD=6.32*) in the FI30 which were slightly lower than the normal control group mean times of 16.50 (*SD=1.29*) and 29.05 (*SD=4.39*) seconds. Most of the control subjects performed very similarly except for A.P. in the normal control group who adopted a constant high rate of response strategy, particularly in the FI30 condition. This is reflected in the low median response time for this subject, as for G.H. in the post-encephalitic group, who adopted a similar strategy.

Figure 3.15: The mean time to the median response on each trial (excluding probe trials) for each subject in the Korsakoff and alcoholic control groups in the FI 15 and FI 30 conditions.

TIME TO MEDIAN RESPONSE–TRIALS 1–70 (excluding probe trials)

KORSAKOFFS FI 15S

ALCOHOLIC CONTROLS FI 15S

KORSAKOFFS FI 30S

ALCOHOLIC CONTROLS FI 30S
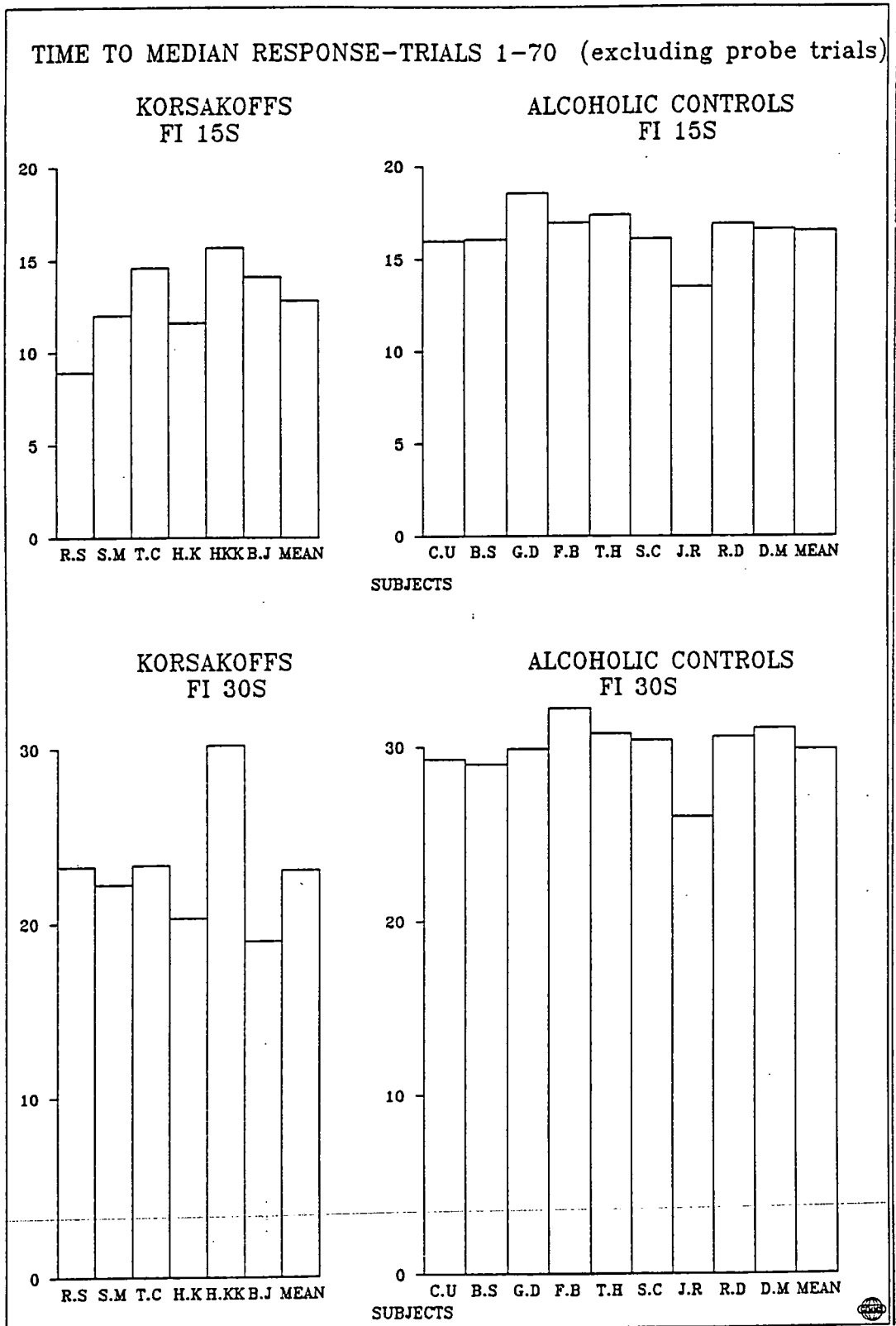
Figure 3.16: The mean time to the median response on each trial (excluding probe trials) for each subject in the post-encephaltic and normal control groups in the FI 15 and FI 30 conditions.

TIME TO MEDIAN RESPONSE–TRIALS 1–70 (excluding probe trials)

99
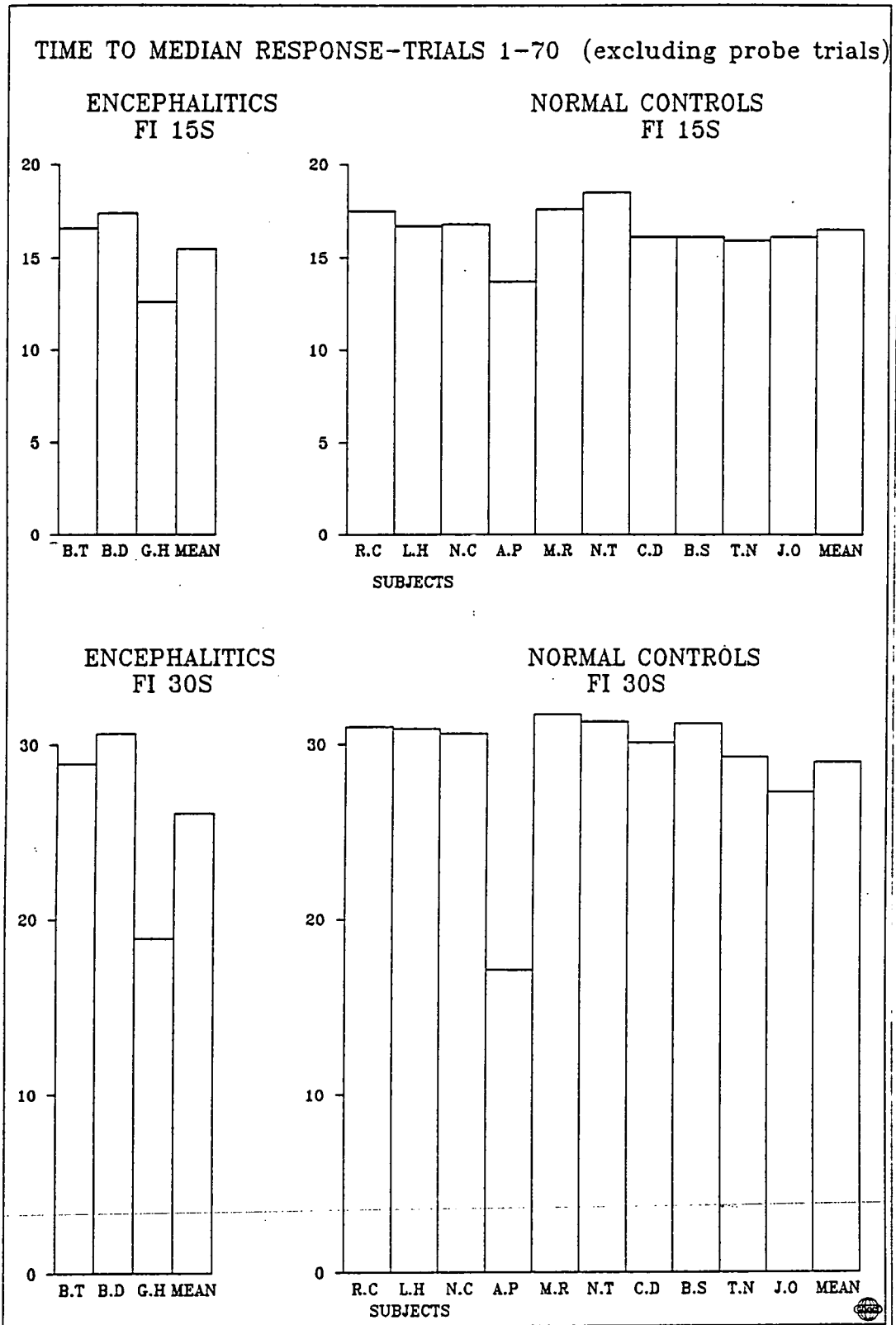
Figure 3.17: The mean error from target for each group on the FI 15. The target was designated as the mid-point of the interval during which a reward could be obtained i.e. 17.5s, and the error was calculated as the target minus the median response time on trials 1-35 and 36-70, excluding probe trials. Direction of error i.e. over or under-estimation was not taken into account.

FI 15S

Error from Target (secs)

Figure 3.18: The mean error from target for each group on the FI 30. The target was designated as the mid-point of the interval during which a reward could be obtained i.e. 32.5s, and the error was calculated as the target minus the median response time on trials 1-35 and 36-70, excluding probe trials. Direction of error i.e. over or under-estimation was no taken into account.

FI 30S

Error from Target (secs)

Korsakoffs

Encephalitics

Normal Controls

Alcoholic Control

1-35   36-70

TRIALS

One subject in the Korsakoff group performed particularly well (H.K.K.), having median response times of 15.7 seconds and 30.2 seconds in the FI15 and FI30 conditions respectively.

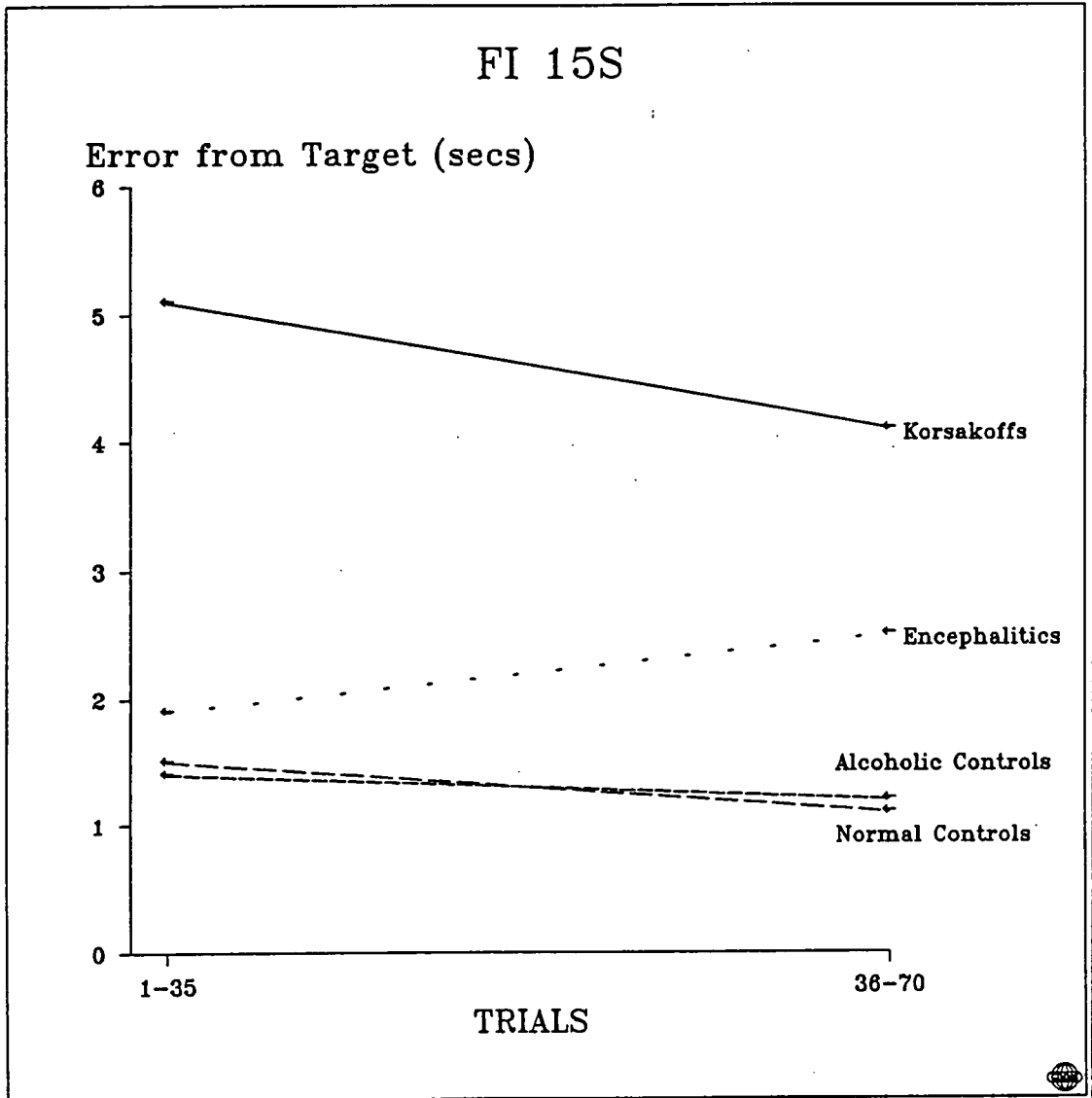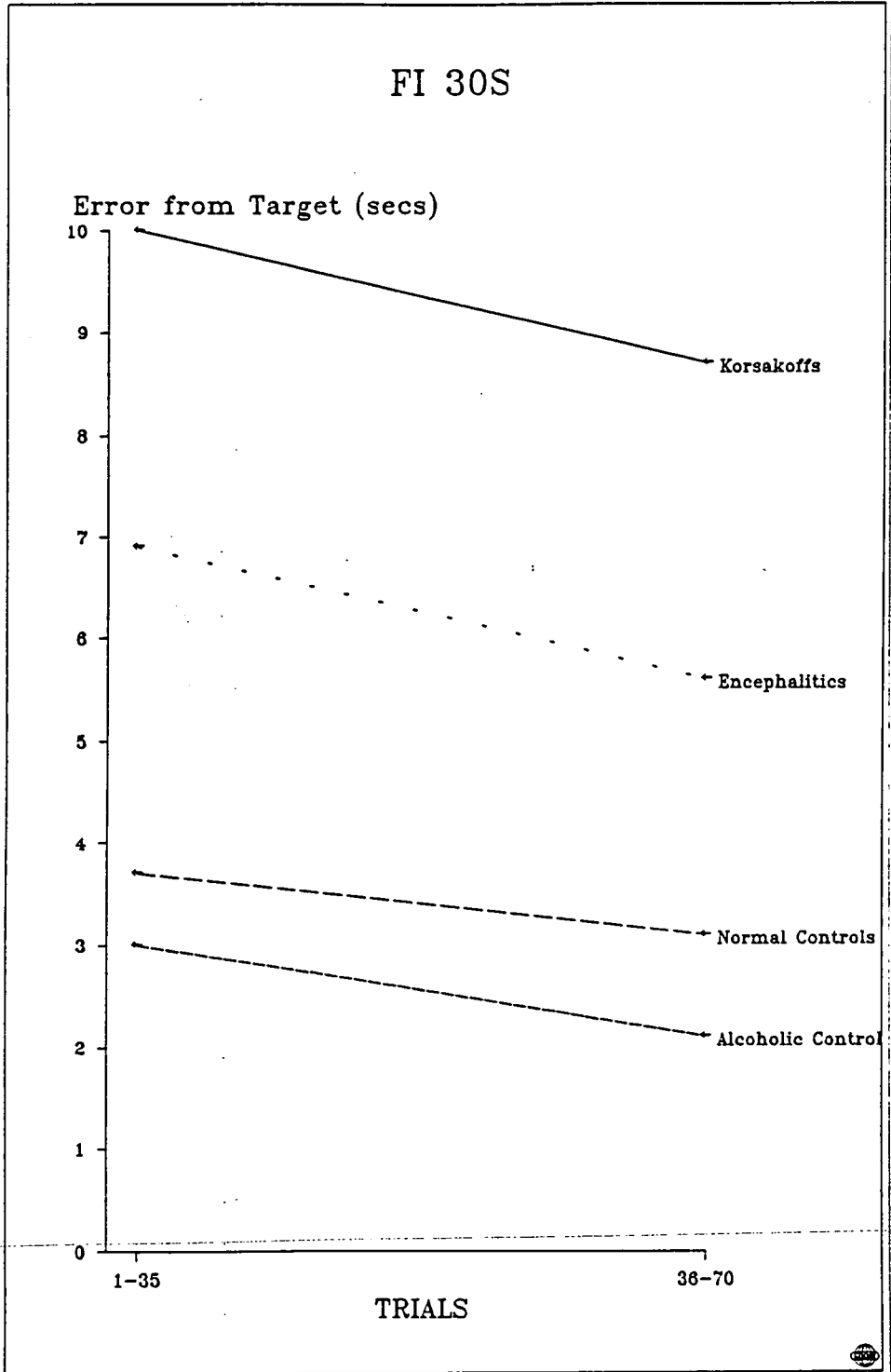The times to median response were analysed in terms of the error from target, the target being designated as the mid-point of the interval during which a reward could be obtained i.e. 17.5 seconds in the FI15 and 32.5 seconds in the FI30 conditions. In addition, errors on trials 1 - 35 were compared to errors on trials 36 - 70 to assess if the amnesics were aided by feedback and hence improved across a session. Figures 3.17 and 3.18 shows the mean error from target for all groups on the FI15 and FI30 conditions. On both the FI15 and FI30 the Korsakoff group made greater errors than the alcoholics as confirmed by analysis of variance main effects of group [$F(1,13) = 12.32, p=.004; F(1,13) = 20.88, p=.001$]. Both groups made fewer errors in the second half of the session in both conditions although this just failed to reach significance in the FI30 [**FI15** $F(1,13) = 14.29, p=.002;$ **FI30** $F(1,13) = 4.46, p=.055$]. The Korsakoff subjects improved to a greater extent than the alcoholics in the FI15 condition as shown by a significant group X half interaction [$F(1,13) = 4.75, p=.048$] but not in the FI30 condition. This, however, is probably due to a floor effect in the alcoholic control data. They were making very few errors and so apparently made little improvement in error across the session.

There was no significant difference between the encephalitic group and the normal control group in the extent of the error in either condition. Both groups made smaller error in the second half of the session in the FI30 [$F(1,10) = 4.85, p=.05$] but there was no significant difference between the groups in extent of the improvement in performance. In the FI15, however, the post-encephalitic group made greater error in the second half of the session whilst the normal controls made smaller errors. This produced a significant group X half interaction [$F(1,10) = 6.87, p=.026$] and a non-significant main effect of half.

A further measure of efficiency on the FI schedule is the number of rewards obtained divided by the number of responses made in a session. The highest level of efficiency would be 1 i.e. one reward per response and the lowest 0. Efficiency was compared in the first half of the session (trials 1 - 35) to the second half of the session (trials 36 - 70 excluding probe trials). Figure 3.19 shows the mean efficiency ratio for all groups on both the FI15 and FI30. In both conditions all groups improved efficiency over the session except the normal control group in the FI15. The alcoholic control group also improved only minimally over the session in this condition. Analysis of variance was carried out comparing the Korsakoff and alcoholic control groups and the post-encephalitic and normal control groups. There was a significant difference between the Korsakoff and alcoholic control subjects in overall efficiency in both the FI15 and FI30 [*FI15 $F(1,13) = 14.82$, $p=.002$; FI30 $F(1,13) = 8.08$, $p=.014$*]. The improvement over the session failed to reach significance in both cases and there was no difference between the pattern of performance of the two groups in the two halves of the sessions. There was no significant difference between the post-encephalitic and normal control groups in overall efficiency in either condition. Performance in the two halves of the sessions again just failed to reach signifcance but the greater improvement of the encephaltic in the second half of the FI15 session was confirmed by a group X half interaction [*$F(1,11) = 6.51$, $p=.027$*].

Figure 3.19: The mean ratio of rewards to responses for each group on the FI 15 and the FI 30.
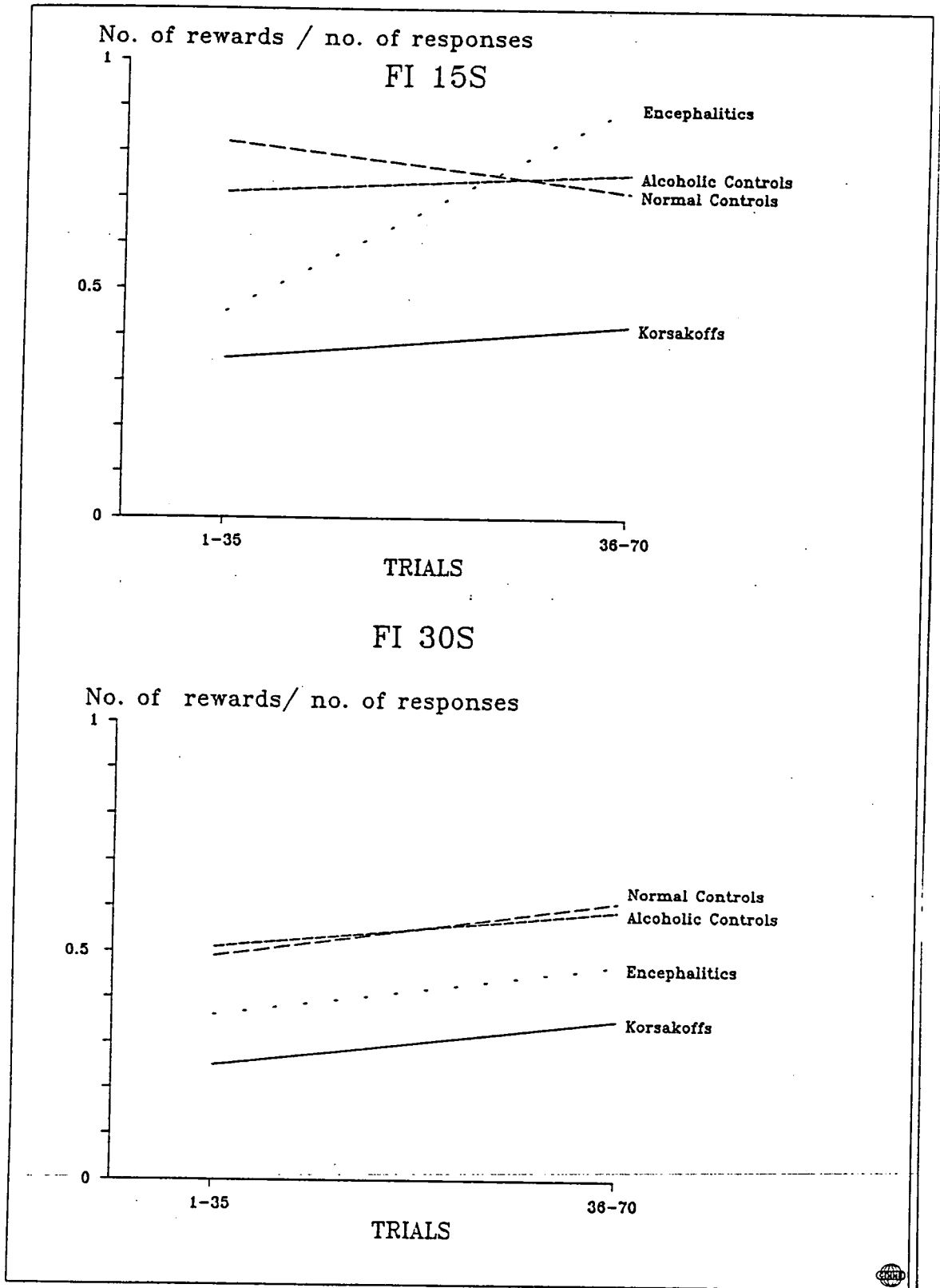
Figure 3.20 shows the mean number of responses in each 2.5 second bin of the probe trials for all the groups on the FI15 condition. All the groups, except the Korsakoff group, show a pronounced peak in response rate. The Korsakoff group show a steadier rate of responding throughout the interval but response rate is highest between 15 and 25 seconds. The mean number of responses in the 15 - 17.5 and the 20 - 22.5 second bins was 3.5, the highest response rate throughout the interval, suggesting that reward was most expected at 15 to 22.5 seconds. The alcoholic controls' peak response time was between 25 and 27.5 seconds with a mean of 5.1 responses, the encephalitics' at 20 - 25 seconds with a mean of 8 responses in each of these two bins, and the normal controls' at 17.5 - 22.5 with a mean of 5.5 responses in each of these two bins.

Figures 3.21 and 3.22 depict the mean number of responses in each 2.5 second bin in the probe trials for all groups in the FI30 condition. Both control groups show an increase in rate of responding as the interval progresses with a peak response time of between 40 and 47.5 seconds for the alcoholic controls (mean responses 4.9 in each bin) and between 42.5 and 52.5 seconds for the normal controls (mean number of responses 4.1 - 4.2). The Korsakoff and encephalitic groups show a steady response rate throughout the interval with no pronounced peak response time. The post-encephalitic pattern of responding again is due to subject G.H. adopting a high response rate strategy. When this subject is excluded the remaining two encephalitic subjects show a peak response time of 42 - 42.5 seconds.

Sensitivity to the extended interval in the probe trials was measured by comparing the time to the median response on the trials immediately preceding and following a probe trial. Figure 3.23 shows the mean median response times for the probe -1 and +1 trials for the Korsakoff and alcoholic control groups. In the FI15 both groups show an increased latency to respond on the probe +1 trial as confirmed by an analysis of variance main effect of type of trial [$F(1,13) = 5.87, p=.031$]. In the FI30, however, the alcoholics show an increased latency to respond whereas the Korsakoff subjects show a decreased latency on the probe +1 trial producing a non-significant main effect of type of trial and a near significant group X type of trial interraction [$F(1,13) = 3.29, .093$]. The Korskoff subjects median response generally occurred earlier in the interval on both conditions but this was not significant in either condition, although just short of significance in the FI15 [$F(1,13) = 4.14, P=.063$].

Figure 3.20: Mean number of responses in each 2.5s bin of the probe trials in the FI 15 for each group.

FI 15S PROBE TRIALS

KORSAKOFFS
N=6

ALCOHOLIC CONTROLS
N=9

2.5s BINS

ENCEPHALITICS
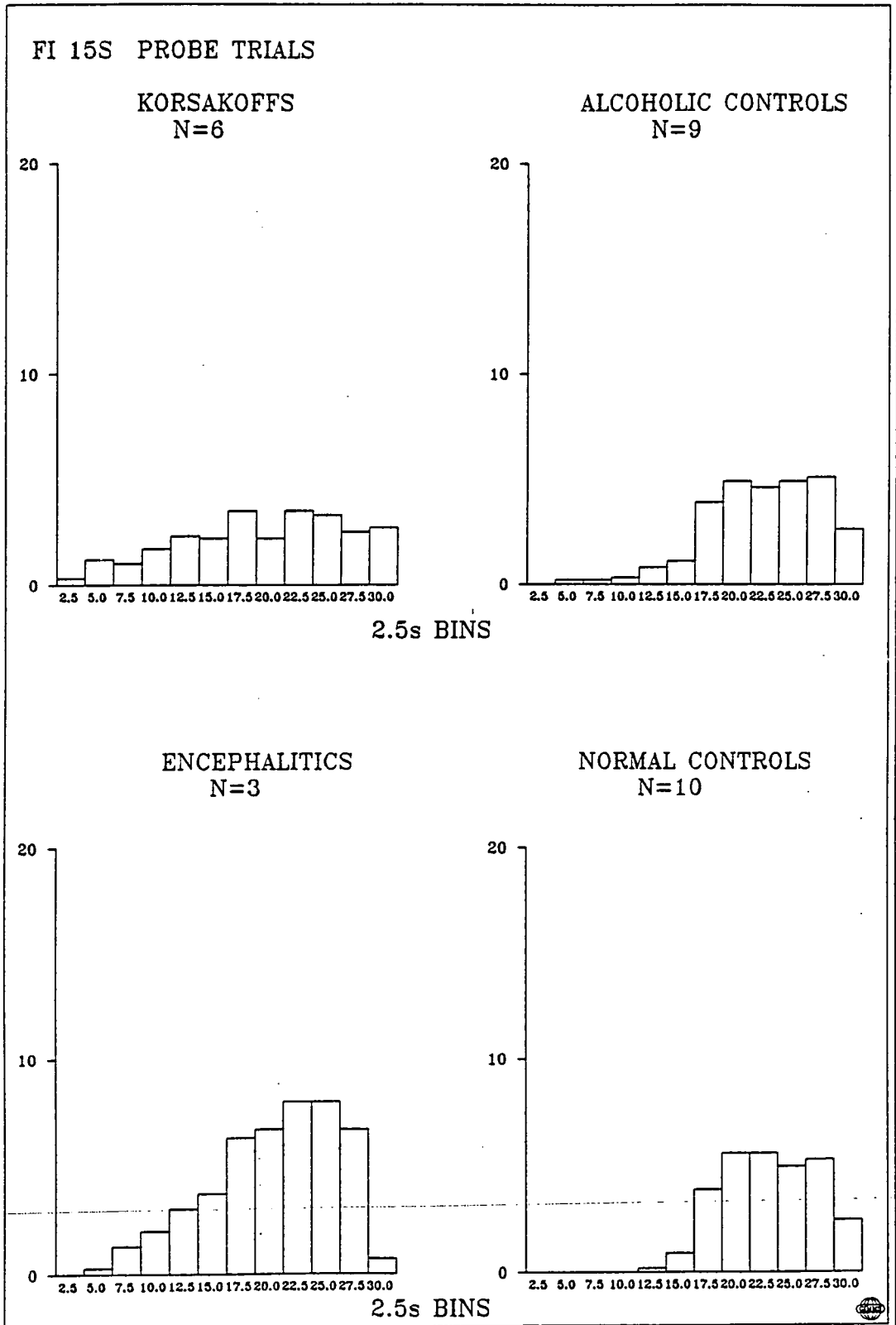N=3

NORMAL CONTROLS
N=10

2.5s BINS

106

Figure 3.21: Mean number of responses in each 2.5s bin of the probe trials in the FI 30 for the Korsakoff and alcoholic control groups.
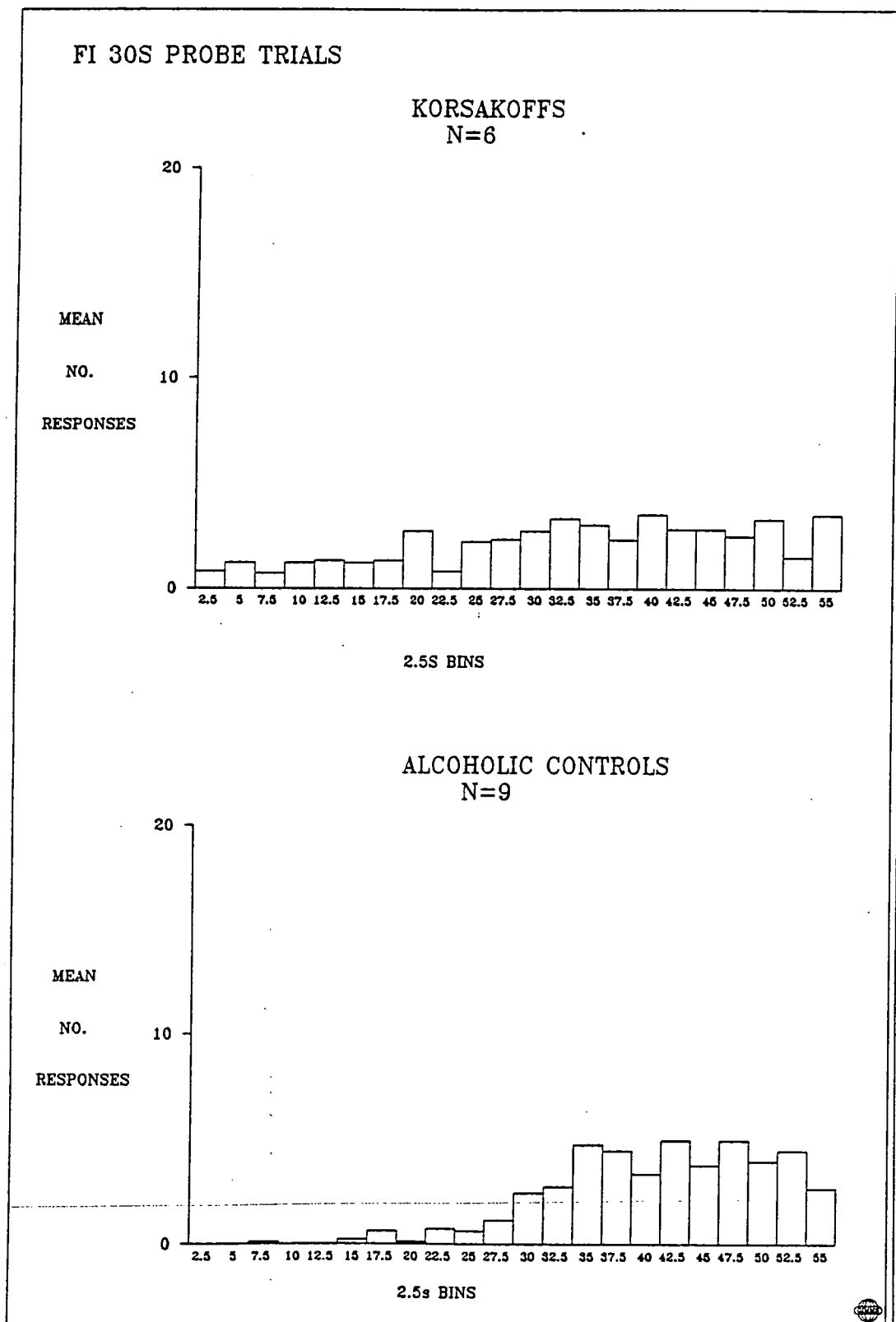
Figure 3.22: Mean number of responses in each 2.5s bin of the probe trials in the FI 30 for the post-encephalitic and normal control groups.

FI 30S PROBE TRIALS

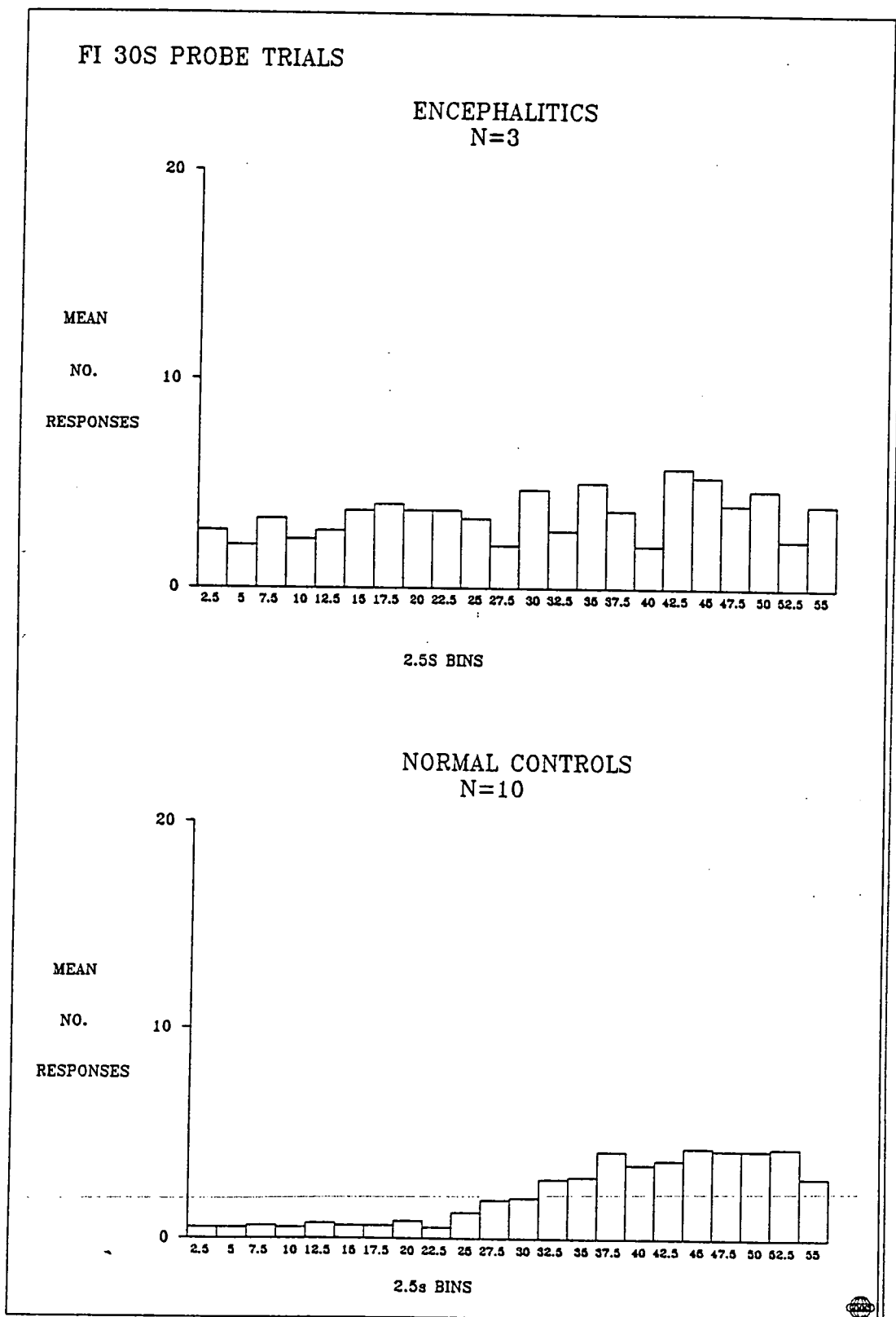ENCEPHALITICS
N=3

NORMAL CONTROLS
N=10

Figure 3.24 shows the mean median response times for probe trials + and - 1 for the post-encephalitic and normal control groups. A similar pattern of results are seen as produced by the Korsakoff and alcoholic control subjects. Analysis of variance revealed that, although the encephalitic subjects were responding earlier in the interval, this was not statistically significant in either condition. That responding occured later on the probe + 1 trial in the FI15 was confirmed by a main effect of type of trial [$F(1,11)$ = $12.6, p=..005$] but as would be expected the main effect of type of trial in the FI30 condition was not significant as the encephalitic subjects showed a decreased latency to respond whereas the controls showed an increased latency to respond.

Sensitivity to probe trials was further examined by comparing the number of '*time outs*' (trials in which no response is made before the end of the interval) that occurred on the trials immediately preceding and following a probe trial (Figure 3.25). A '*time out*' indicates overestimation of the interval. Both control groups and the encephalitic group obtained more '*time outs*' in the probe +1 trial than the probe -1 in both conditions whereas the Korsakoff group obtained more time outs on probe +1 in the FI15 but less in the FI30. Analysis of variance was carried out using a log transformation of the data to uphold the homogeneity of variance assumption comparing each amnesic group with their control group. The only significant results obtained were main effects of type of trial (*i.e. probe - and +1*) confirming the tendency to overestimate the intervals following a probe trial [**Korsakoff vs alcoholic control groups**, $F(1,13)$ = $5.09, p=.042;$ **post-encephalitic vs normal control groups**, $F(1,11)$ = $19.88, p=.001$]. The group X FI interaction just failed to reach significance in the Korsakoff vs alcoholic control groups [$F(1,13)$ = $3.55, p=.082$].

The mean error from target i.e. from *17.5* secs in the FI15 and from *32.5* secs in the FI30 was correlated with performance on tests of frontal lobe function, memory function, and intellectual function for each group using Spearman rank order correlations. All correlations represent the relationship between poor performance on the FI tasks and poor performance on the other tests i.e a positive correlation represents a correlation between poor performance on the FI in terms of greater error from target with poor

Figure 3.23: Mean time to median response on trials immediately preceding and following a probe trial in the FI 15 and FI 30 for the Korsakoff and alcoholic control groups.

FI 15S

Time in secs

Alcoholic Controls

Korsakoffs

PROBE-1   PROBE+1
Trials preceding and following a probe trial

FI 30S

Time in secs

Alcoholic Controls

Korsakoffs

PROBE-1   PROBE+1
Trials preceding and following a probe trial
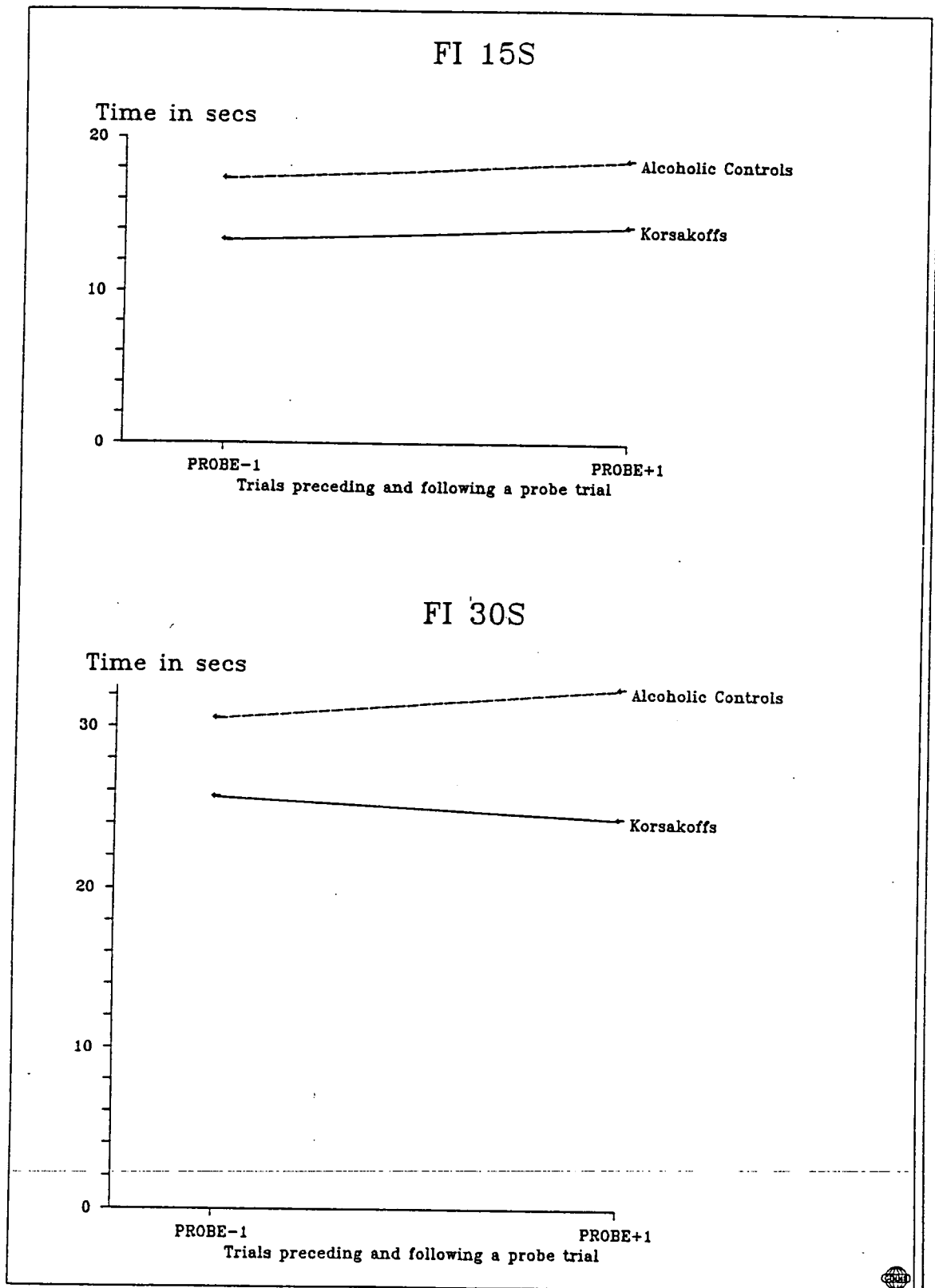
Figure 3.24: Mean time to median response on trials immediately preceding and following a probe trial in the FI 15 and FI 30 for the post-encephalitic and normal control groups.

FI 15S

Time in secs

Trials preceding and following a probe trial

FI 30S

Time in secs

Trials preceding and following a probe trial

111
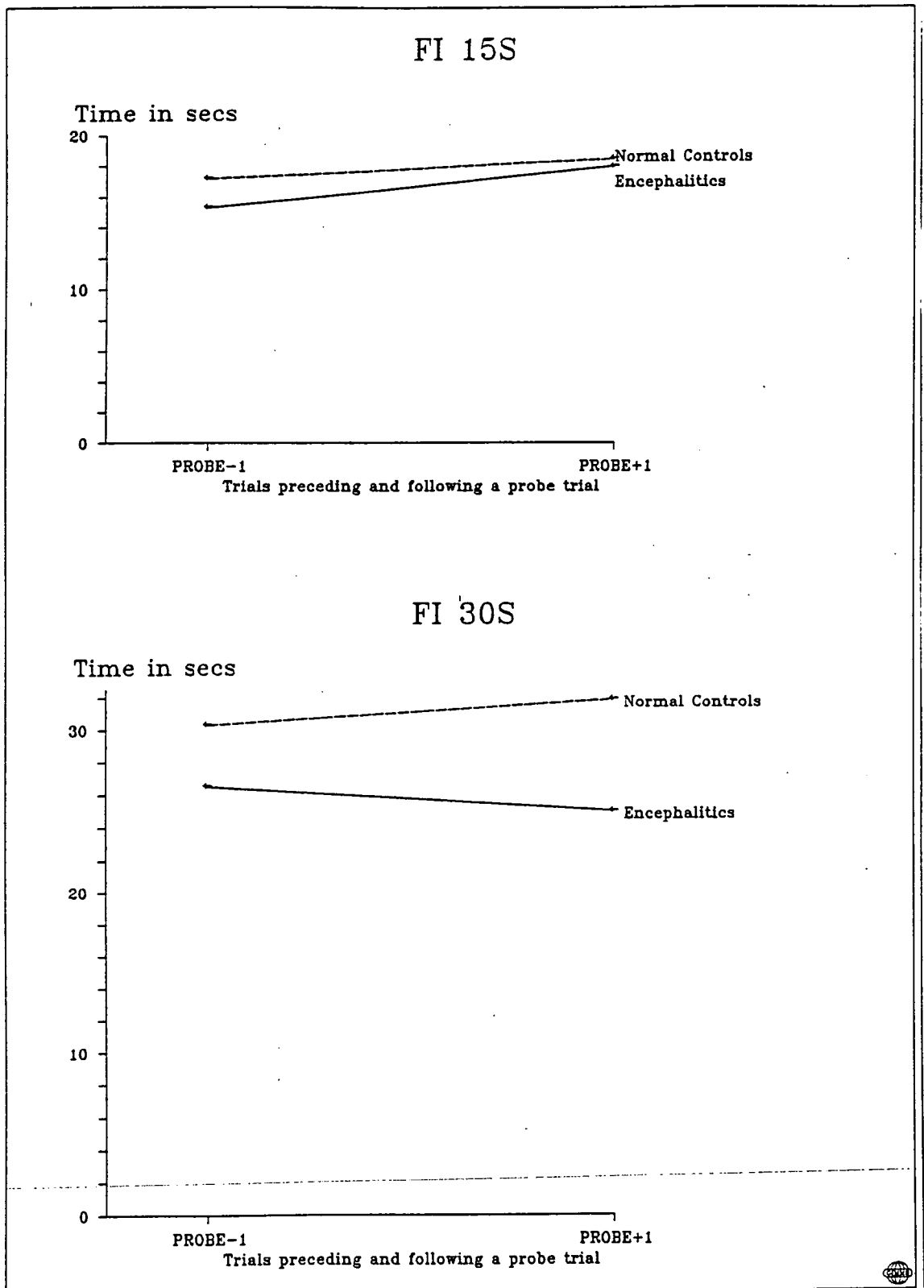
Figure 3.25: Mean number of time-outs on the trials immediately preceding and following a probe trial in the FI 15 and FI 30 for all the groups.

No. of Time Outs

Alcoholic Controls FI15
Alcoholic Controls FI30
Korsakoffs FI30
Korsakoffs FI15

PROBE−1
PROBE+1
Trials preceding and following a probe trial

No. of Time Outs

Normal Controls FI30
Encephalitics FI30
Normal Controls FI15
Encephalitics FI15

PROBE−1
PROBE+1
Trials preceding and following a probe trial
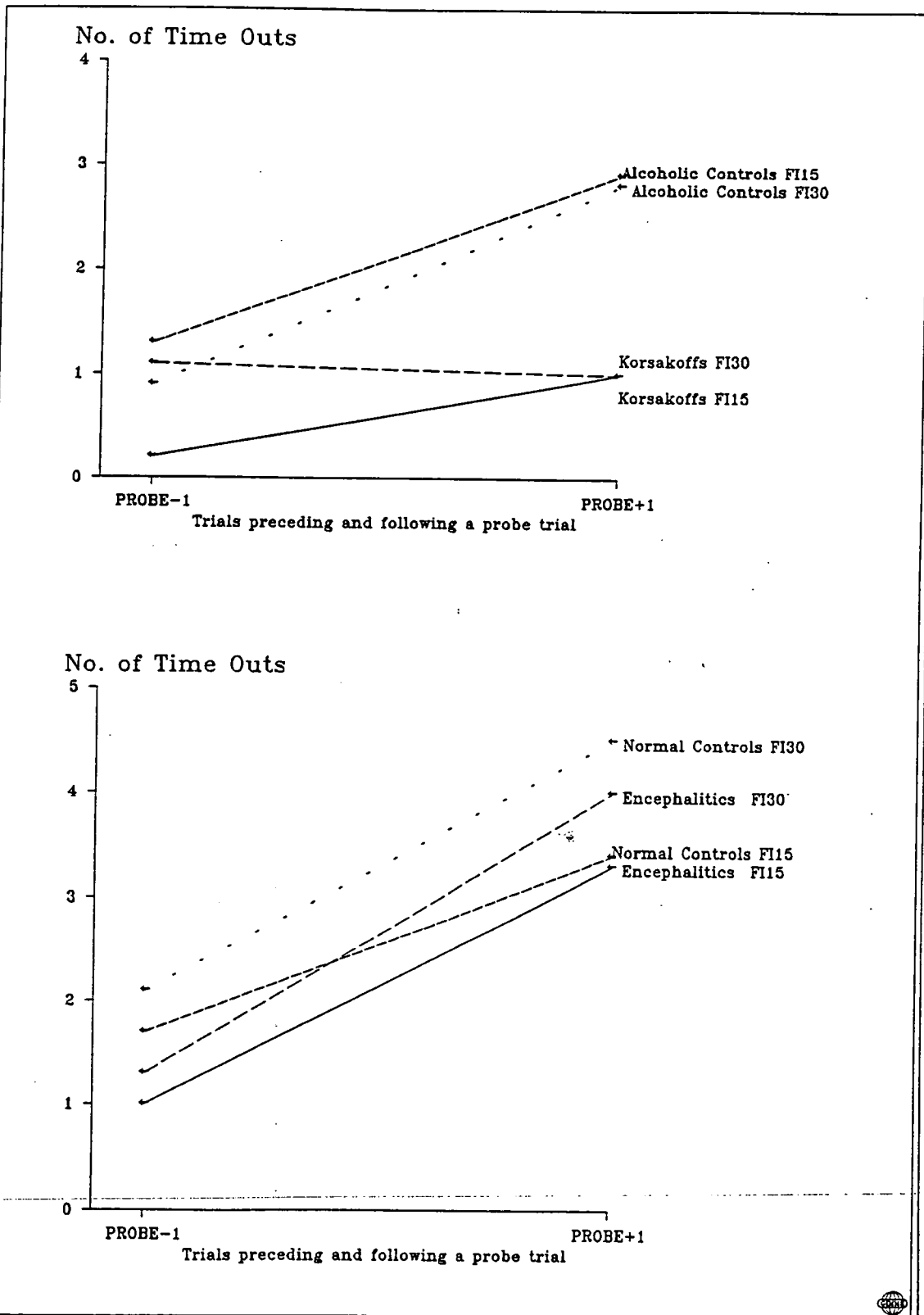
performance on the psychometric tests and a negative correlation represents a correlation between poor performance on the FI and and good performance on the psychometric tests.

Table 3.15 shows the results of the correlations between FI and tests of frontal lobe function for the Korsakoff subjects. This shows a tendency for performance on the FI to correlate negatively with performance on the block design and positively with performance on the WCST.

TABLE 3.15 **Spearman rank order correlations of error from target on FI15 and FI30 and tests of frontal lobe function for the Korsakoff group.**

FI Condition			Tests of Frontal Lobe Function			
	WCST	Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
FI15	+.54	-.31	+.26	+.46	-.88 p=.02	+.38
FI30	+.89 p=.018	-.66	-.09	+.12	-.52	+.12

All probabilities two tailed

Table 3.16: **Spearman rank order correlations of error from target on FI15 and FI30, tests of memory function and tests of intellectual function for the Korsakoff subjects.**

FI Condition			Tests of Memory and Intellectual Function				
	WMS	Warrington Recognition	WAIS IQ-MQ	NART IQ-MQ	Digit Span	WAIS IQ	NART
FI15	-.80 p=.06	-.44	+.78 p=.06	+.14	-.64	-.84 p=.036	-.75 p=.084
FI30	-.27	+.08	+.61	-.03	-.64	-.58	-.32

All probabilities two tailed

Table 3.16 shows the rank order correlations of mean error from target on FI15 and 30 and tests of memory and intellectual function in the Korsakoff group. This shows a tendency for a negative correlation between FI performance and performance on the memory tests. However, there was a positive correlation between WAIS IQ-MQ and performance on the FI 15. Performance on the IQ tests also correlated negatively with performance on the FI 15.

TABLE 3.17: Spearman rank order correlations of error from target on FI15, FI30, and the time estimation tasks for the Korsakoff subjects.

FI Condition			Time Estimation Tasks		
	FI30	Reproduction	Estimation Empty	Estimation Filled	Estimation Total Error
FI15	+.49	-.37	-.03	+.73	+.43
FI30		-.54	-.37	+.29	-.09

Table 3.17 shows the rank order correlations of error from target on the FI and error on the time estimation tasks carried out in experiment 1. None of the correlations was statistically significant.

The correlations between error on the FI and tests of frontal lobe function for the alcoholic control group are shown in table 3.18. This shows a correlation between poor performance on the FI and poor performance on the design fluency test in both FI conditions, although this fails to reach significance in the FI15. Also, contrary to that found in the time estimation experiment, there was a correlation between poor performance on the FI 30 and good performance on the cognitive estimation test. There were no statistically significant correlations between error on the FI and tests of memory and intellectual function (table 3.19).

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TABLE 3.18: Spearman rank order correlations of error from target in FI15 and FI30 and tests of frontal lobe function for the alcoholic control group.

FI Condition			Tests of Frontal Lobe Function			
	WCST	Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
FI15	+.48	-.24	+.69 p=.088	+.07	-.20	-.54
FI30	+.38	-.18	+.91 p=.004	+.04	-.33	-.76 p=.048

All probabilities two tailed

Table 3.19: Spearman rank order correlations of error from target on FI15 and FI30, tests of memory function and tests of intellectual function for the alcoholic control group.

FI Condition			Tests of Memory and Intellectual Function				
	WMS	Warrington Recognition	WAIS IQ-MQ	NART IQ-MQ	Digit Span	WAIS IQ	NART
FI15	+.33	+.36	+.25	-.22	+.37	+.14	+.14
FI30	+.25	+.38	+.30	+.07	+.38	+.04	+.43

There were no statistically significant correlations between the FI and the other time estimation tasks but the two FI conditions correlated positively with each other (table 3.20).

Table 3.20: Spearman rank order correlations of error from target on FI15, FI30, and the time estimation tasks for the alcoholic control subjects.

FI Condition			Time Estimation Tasks		
	FI30	Reproduction	Estimation Empty	Estimation Filled	Estimation Total error
FI15	+.86 p=.002	+.40	+.38	+.53	+.65
FI30		+.50	+.36	+.31	+.42

All probabilities two tailed

In the normal control group none of the tests of frontal lobe function correlated significantly with performance on the FI (see table 3.21). The error on the two FI conditions correlated positively with each other (r_s =.69, p=.026) and the error FI30 correlated with total error on the three time estimation conditions (r_s =.62, p=.054), whilst that between the FI15 and the time estimation just failed to reach significance (r_s = .58, p=.076). Of the three time estimation conditions only the error on the time estimation with empty intervals correlated significantly with error on the FI30 (r_s =.69, p=.028).

Table 3.21: Spearman rank order correlations of error from target on FI15 and FI30 and tests of frontal lobe function for the normal control group.

FI Condition		Tests of Frontal Lobe Function			
	WCST	Verbal Fluency	Design Fluency	Picture Arrangement	Block Design
FI15	-.13	-.01	-.03	+.35	+.19
FI30	-.12	+.01	+.36	+.46	-.01

3.2.4. Discussion

The experiment was successful in producing temporally based strategies as all groups displayed an increased rate of responding as the interval progressed, which can be compared to the scalloped pattern of responses exhibited in animal experiments. This allows assessment of the temporal discrimination of the subjects by examination of the pause-respond pattern. Only two subjects, one post-encephalitic and one normal control, appeared to use a response based strategy of a high rate of responding throughout the interval. Many of the control subjects displayed a low response rate of only one or two key presses in each interval but this type of responding is sensitive to the temporal contingencies of the schedule.

The Korsakoff subjects were impaired at both the FI15 and FI30 conditions in terms of the overall number of responses made, the pattern of responding, the efficiency ratio and the error from target. The post-encephalitic subjects, on the other hand, were not impaired relative to their control subjects on any of these measures. The Korsakoff impairment was one of underestimation of the intervals as shown by their mean time to median response which is in accordance with the underestimations exhibited in the previous time estimation experiment. Although the post-encephalitic subjects responded slightly earlier in the interval their temporal estimation of the interval did not differ significantly from that of the normal control group. These findings again fail to support the hypothesis that amnesic subjects time estimations will be normal at intervals below 20 seconds although the data does suggest that the Korsakoff subjects carried out estimation of the 30 second interval in a qualitatively different way to the 15 second interval. This will be discussed later.

The Korsakoff subjects generally made more responses than their controls in both conditions and on observing their responses it was noted that they often responded early in the interval even though they indicated that they knew that reward would not be available. This suggests that the Korsakoff subjects were failing to inhibit responding which may have contributed to their impairment. The post-encephalitic group's responses did not differ significantly from the control group's and thus did not exhibit a failure to inhibit responding even though one subject had adopted a response based strategy. However, in spite of the Korsakoff subjects failure to inhibit responding they still exhibited a scalloped pattern of responses which allows an assessment of their temporal discrimination.

The scalloping effect appeared to be more pronounced in the FI15 than the FI30 for the Korsakoff group. It is possible that the Korsakoff subjects were using a temporally

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based strategy in the shorter interval but depended upon a response based strategy in the longer interval. Experiment 1 demonstrated the Korsakoff group's increasing impairment with increasing length of interval which could result in them adopting a strategy in the longer FI condition that does not rely so heavily on temporal processing. Support for this comes from the finding that the Korsakoff subjects failed to show sensitivity to the probe trials in the 30 second but not in the 15 second interval. Awareness of the temporal nature of the schedule should result in a longer delay in responding on the trial following an extended probe trial compared to the trial preceding it. The Korsakoff group, however, responded earlier rather than later on the probe +1 trials in the FI30 whereas in the FI15 they responded later on these trials.

This lack of sensitivity to the extended duration of the probe trials is reflected in the number of 'time outs' acheived on the probe - and +1 trials by the Korsakoff group. A *'time out'* occurred when no response was made before the end of the interval indicating overestimation of the duration. It would be expected that more overestimations would occur following an extended probe trial than on other trials. All the groups produced this pattern of responding on the FI15 condition but the Korsakoff group achieved fewer *'time outs'* on the probe +1 trials in the FI30 condition, although this failed to reach statistical significance. In addition, there was no correlation between error from target in the FI15 and FI30, again supporting the notion that the two conditions were performed in a qualitatively different manner.

There was no clear evidence that the post-encephalitic subjects were performing the two temporal estimations in qualitatively different ways although their pattern of responses were in some respects similar to that of the Korsakoff subjects. The scalloping effect seemed more pronounced in the FI15 compared to the FI30 in the post-encephalitic group, but their response rate did not differ significantly from that of their control group. Like the Korsakoff group, they failed to show sensitivity to the probe trials in the 30 second but not the 15 second interval in terms of latency to respond on the trials preceding and following a probe trial, but did not exhibit a similar lack of sensitivity in the number of time outs achieved on the probe - and +1 trials. It seems unlikely that the post-encephalitics were responding differently in the two conditions, particularly as performance in the two conditions showed a positive relationship. However, because of the small group size such a correlation was not tested statistically.

Because of the Korsakoffs failure to inhibit responding at the beginning of the interval the measure of accuracy of the temporal discrimination was taken as the time to the median response on each trial. Although this gives a more realistic assessment of the

pause-respond pattern and hence their temporal estimation than time to first response, over-responding will also affect median response time. This showed the Korsakoff group to be impaired at both intervals compared to the alcoholic controls. They made significantly greater error from target and this appeared to be in the direction of under-estimation, as their mean response times were lower than the controls' in both conditions. The post-encephalitic subjects, on the other hand, responded only slightly earlier than the normal controls and showed no significant difference in error from target in either condition.

It was predicted that, if the Korsakoff group's impairment in making time estimations was partly due to an inability to use contradictory feedback, they would not improve their temporal discrimination across a session. They did, however, improve in error from median response in the second half of the session in both conditions. The post-encephalitics showed a similar improvement across a session as their controls in the FI30 but produced an increase in error in the latter half of the session in the FI15 condition.

The temdemcy for a relationship between the time estimations in experiment 1 and the picture arrangement test suggested that impairment in temporal estimation may be due to an inability to use feedback. However, there was no correlation between performance on the FI and the picture arrangement test in either the Korsakoff or the alcoholic control groups, although there was a suggestion of a positive relationship between these two measures in the post-encephalitic and normal control groups. The nature of the feedback in the two experiments is, however, different. In experiment 1 the subjects had to rely upon internal feedback as to the status of the ongoing duration and to make a judgement based upon this as to whether the interval had elapsed. Internal feedback was of lesser importance in this experiment as the subject could obtain external information as to the status of the ongoing duration by pressing the button to find out if the interval had elapsed. The Korsakoff group's failure to inhibit responding at the beginning of an interval even though they were aware that the interval had not elapsed is evidence that they could not alter responses in the light of such contradictory 'internal' feedback. The temporal judgement was, therefore, not crucially dependent upon this internal monitoring.

Neither was there a positive correlation between the temporal estimations and the cognitive estimation task as had been found in experiment 1. The alcoholic control group exhibited a negative correlation between performance on the FI30 and performance on the cognitive estimations. Performance of this task, therefore, did not rely upon

the ability to form and utilise plans and strategies in the same way as the time estimation tasks in experiment 1. This type of cognitive planning may be required for the internal monitoring required by this type of time estimation but not for the externally controlled estimations of the FI procedure.

There were no consistent correlations between tests of frontal lobe function and performance on the FI tasks across the groups. In the Korsakoff group the WCST correlated positively with the FI30 but not the FI15. As the Korsakoff group were relying upon a response based strategy in the FI30 it may be that frontal lobe function as measured by the WCST and verbal fluency is related to such a response based task but not the making of temporal estimations. Indeed, perseverative tendencies shown by poor performance on the WCST would contribute to a deficit in such a response based task. However, perseverative responding on the design fluency test correlated with poor performance on the FI in the alcoholic control group suggesting that frontal lobe perseveration could be involved in the estimation of temporal duration in this type of task.

There were also no consistent correlations between tests of memory function and performance on the FI, apart from the finding that performance on both FI conditions were tending to a negative correlation with the test of short term memory function, the digit span test, in the Korsakoff group. This is in accordance with the results of experiment 1 which showed a tendency to a negative relationship between tests of short term memory and performance on all the time estimation tasks in the Korsakoff group. There was also a tendency for MQ to correlate negatively with the FI tasks in this group. These results provide further evidence that temporal estimation is not primarily dependent upon memory, particularly as the post-encephalitic subjects exhibited comparable levels of memory loss to the Korsakoff group and yet performed as well as control subjects on the FI tasks.

The Korsakoff group, therefore, were impaired at both the FI15 and the FI30 whereas the post-encepalitic group were unimpaired at both intervals. The findings from experiment 1 and 2 suggest that the temporal judgments of H.M. are not representative of amnesic subjects in general. The Korsakoff group did not show normal temporal discrimination of intervals less than 20 seconds but the evidence shows that their impairments are greater with longer intervals for in the present experiment they appeared to use a response based strategy in the longer interval rather than a temporally based strategy. Their impairment in this experiment may, in part, be due to a failure to inhibit responding. They did, however, show evidence of sensitivity to the temporal contingencies of the schedule and a slight improvement in efficiency ratio across the sessions

although this was not statistically significant. Improvement in efficiency would suggest greater inhibition of responding and more reliance upon temporal factors as the session progresses. From the pattern of responding on this and the previous experiment it seems likely that the impairment was also one of temporal discrimination. The nature of the FI task required different strategies than the time estimations of experiment 1 which was reflected in the different pattern of correlations exhibited between the experimental task and certain frontal lobe tests such as the cognitive estimation task. The time estimations were dependent upon internal monitoring which required the correct use of internal feedback systems. The FI task was dependent upon external monitoring and feedback which the Korsakoff subjects demonstrated they could use efficiently. There was no consistent evidence of a relationship between the FI temporal estimations and frontal lobe function and neither was there any evidence that the FI was dependent upon intact memory function. This was consistent with the findings from experiment 1 and further emphasises the suggestion that impairment in temporal estimation is not a result of poor memory.

CHAPTER 4
Temporal order memory in amnesic subjects

4.1. Experiment 3: Object recency in amnesic subjects

4.1.1. Introduction

This experiment examined an alternative aspect of temporal processing to that of the previous experiments, that is memory for temporal order. The relationship between estimation of duration and memory for the sequence of events within the environment is not clear. Many cognitive psychologists believe that the perception of duration is dependent upon the perception of the number, type and sequential order of events occurring in that duration (Block, 1986; Michon, 1990). Michon (1990) suggested that time is merely the 'conscious product of processes that enable us to cope with the sequential contingencies of reality'. Others, however, believe that a clear distinction should be drawn between the two processes and that these two aspects of temporal processing have been confounded in many experiments (Crowder & Green, 1987). Block (1986) carried out a series of experiments that suggested that time estimation may be independent of temporal order memory. If the processing of temporal duration and order are products of a single cognitive process they will presumably be served by the same neurological system. This question was addressed by assessing amnesic subjects on a test of recency memory. If the two types of temporal judgement are, in fact, two aspects of a single process, impairment on the recency task should correlate with performance on the time estimation tasks carried out in experiments 1 and 2.

Both Korsakoff and temporal lobe amnesics have been found to be impaired on tests of recency memory (Hirst & Volpe, 1982; Huppert & Piercy, 1978; Squire, Nadel & Slater, 1981). Amnesics also exhibit a larger impairment in source or temporal contextual memory than would be expected from their fact memory ability (Shimamura & Squire, 1987). These findings have led to theories proposing that the amnesia results from the inability to utilise the temporal relationship between events to form meaningful memory structures, rather than the temporal order deficit being a result of poor memory (Hirst & Volpe, 1982; Winocur & Kinsbourne, 1978). An alternative view is that impairment in temporal order memory is a result of brain damage additional to that which is sufficient to cause an amnesia, specifically anterior cortical damage. Frontal cortex damage typically produces an impairment in sequential behaviours and recency memory (Corsi, cited in Milner, 1971). The present experiment, therefore, examined the relationship between performance on the recency task and performance on tests of frontal

lobe function and standard tests of memory function. It was expected that the amnesics would be impaired on this task and, if the recency impairment is a result of frontal lobe damage, poor performance on the experimental task should correlate with measures of frontal lobe damage. On the other hand, if the amnesia results from a deficit in utilising the temporal relationships between events, performance on the recency task should correlate with measures of memory function. However, such a correlation may also occur if the recency memory deficit is secondary to the amnesia.

Subjects were tested on a recency memory task using objects that could not easily be verbally labeled. This avoidance of verbal labels was designed to optimise comparability with animal experiments. The task was carried out under two conditions; one using a large set of objects, each object being presented once per session, and the other using a small set of objects which were presented repeatedly. Presenting an object repeatedly within a session taxes the subject's ability to place that object in its temporal context to a much greater extent than an object being presented only once in a session. It was expected that all subjects would perform worse on this condition compared to the large set size condition because of the higher levels of interference. It was also expected that the amnesic subjects would be differentially impaired in this condition relative to the control groups as they generally show high levels of proactive interference (Kinsbourne & Wood, 1980; Mayes, Pickering & Fairbairn, 1987), which has been proposed to be due to a deficit in *'time-tagging'* events (Winocur & Weiskrantz, 1976).

The number of intervening items in the study list between the two items presented for recency judgement (lag) was varied systematically so that there were 0, 1, 4 or 5 intervening items. It has been found that, in normal subjects, the smaller the lag the more inaccurate the recency judgement (Estes, 1985; Jackson, 1990). Therefore, it was expected that the control groups would exhibit this lag effect of increasing number correct with increasing lag. However, if the amnesic subjects suffer from a deficit in time tagging events it was expected that they would be impaired at all lags and not exhibit the pronounced lag effect expected of the controls.

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4.1.2. Methods

4.1.2.1. Subjects

The Korsakoff group in the present experiment was the same as that in experiment 1 i.e. 5 men and 2 women, mean age 57.7 years. The alcoholic control group was the same as that in experiment 2 and consisted of 8 men and 1 woman with a mean age of 48.4 years. The post-encephalitic group remained unchanged and the normal control group was the same as in experiment 1 (11 men, mean age 46.6 years).

Table 4.1: Group means (standard deviations) for psychometric test scores of Korsakoff and alcoholic control subjects.

	Korsakoff (n = 7)	Alcoholic Controls (n = 9)	t	df	p
WAIS					
Verbal IQ	95.0 (9.9)	98.8 (9.7)	0.77	14	NS
Performance IQ	93.6 (8.1)	97.4 (10.0)	0.83	14	NS
Full Scale IQ	95.1 (9.2)	97.6 (8.7)	0.54	14	NS
NART					
Verbal IQ	102.9 (9.3)	107.6 (7.7)	1.09	13	NS
Performance IQ	105.1 (6.3)	108.5 (5.2)	1.13	13	NS
Full Scale IQ	104.0 (8.5)	108.2 (6.9)	1.07	13	NS
WMS					
Memory Quotient	75.7 (6.02)	99.2 (9.8)	5.58	14	<0.001
Warrington Recognition Test					
No. correct:- Words	28.3 (2.2)	44.8 (5.3)	7.73	14	<0.001
Faces	31.7 (5.2)	44.1 (5.2)	4.72	13	<0.001

NS = Not Significant
All probabilities two tailed

The psychometric data for the Korsakoff and alcoholic control groups are shown in table 4.1. Although the composition of these two groups were slightly different than in previous experiments the psychometric profile was very similar. Table 4.2 show the results of tests of frontal lobe function for the Korsakoff and alcoholic control groups. The post-encephalitic psychometric data and frontal lobe test scores can be found in tables 3.2a, 3.2b, 3.5 and 3.6 of experiment 1.

Table 4.2: Group means (standard deviations) for frontal lobe test scores of Korsakoff and alcoholic control subjects.

	Korsakoff		Alcoholic Controls				
	n	Mean (SD)	n	Mean (SD)	t	df	p
WCST							
Categories	7	2.6 (1.6)	9	4.4 (1.9)	2.10	14	.055
Perseverative responses	7	48.6 (22.8)	9	23.1 (18.7)	2.46	14	.028
Verbal Fluency							
Scaled score	6	31.2 (6.3)	9	45.4 (15.6)	2.1	13	.055
Design Fluency							
% Preseverative responses	6	27.7 (19.6)	7	7.6 (10.9)	2.34	11	.039
Picture Arrangement							
No. left in order	6	6.2 (3.97)	9	2.6 (1.7)	2.46	13	.029
Block design							
Scaled score	7	8.1 (1.2)	9	8.4 (1.8)	0.38	14	NS
Cognitive Estimation	6	6.5 (3.6)	7	4.4 (1.99)	1.32	11	NS

NS Not Significant
All probabilities two tailed

4.1.2.2. Apparatus

Seventy two junk objects consisting of small items of electronic and laboratory equipment were used as stimuli. Unusual objects were chosen that were presumed to be difficult to label verbally without specialist knowledge. These objects were randomly divided into nine sets of eight objects, one set being designated as stimuli for the small set size (SS) condition and the remaining eight sets for the large set size (LS) condition.

The subject sat in front of a black curtain screen 51 cms high and 62 cms wide which could be retracted to reveal the stimulus placed 20 cms behind the curtain and immediately in front of a white backboard 20 cms high and 52 cms wide. When not being presented, the stimuli were placed behind the backboard out of view of the subject.

4.1.2.3. Procedure

The experiment took place over two sessions at weekly intervals. One session consisted of the SS condition and the other the LS condition. Order of presentation of the two conditions was counterbalanced across subjects. A series of time estimation tasks was given prior to and after each object recency session.

The subject sat in front of the screen and it was explained that a number of objects would be shown one at a time and that following this he/she would be shown two of the objects and asked to identify the one they had seen most recently.

The stimuli were presented for 1.5 seconds at a rate of one every 5 seconds by placing them behind the curtain and then opening and closing the curtain. As soon as a set of eight objects had been presented individually they were presented in pairs in the same way and the subject asked to point to the one seen most recently. The subject was allowed as much time as he/she required to make a choice. The presentation of one complete set for learning and recall is termed a run.

In the LS condition, once all eight objects of a set had been presented for recency recall, they were removed from behind the backboard and replaced by the next set of stimuli, thus giving a short interval of about 30s between the end of one run and the beginning of the next. All eight sets of eight stimuli were presented for learning and recall in the same manner.

The SS condition was carried out in exactly the same way but the same set of eight objects was presented in a different predetermined random order for all eight runs, with a 30s interval between each run.

The combinations of the stimuli for recall were arranged so that the number of intervening items between each object of the pair at study (lag) was 0, 1, 4 and 5 items on each run. The spatial position of each correct item appeared in a pseudorandom order such that an equal number of correct right and left responses occurred and that there were no more than two the same in succession.

4.1.3. Results

Figures 4.1 and 4.2 show the mean number correct on the object recency at each list length for the large set size (figure 4.1) and small set size (figure 4.2) for all groups. In both conditions the control groups performance improved as the lag increased whereas neither of the amnesic groups showed this consistent steady increase in number correct

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Figure 4.1: Mean number correct at each lag for all groups in the large set size condition.

Object Recency – Large Set

No. Correct

Normal Controls

Alcoholic Controls

Encephalitics

Korsakoffs

I– Standard Error of the Mean
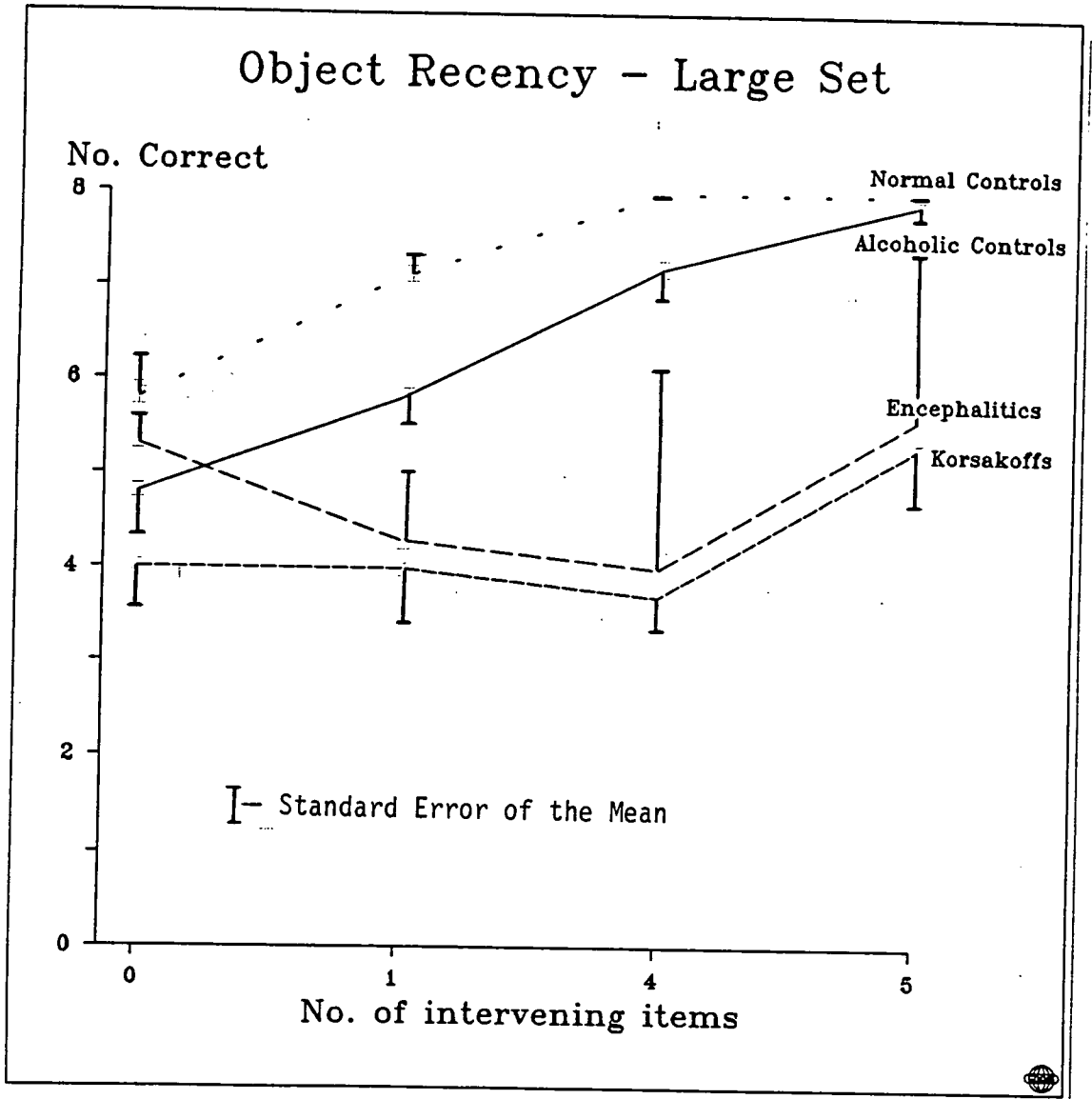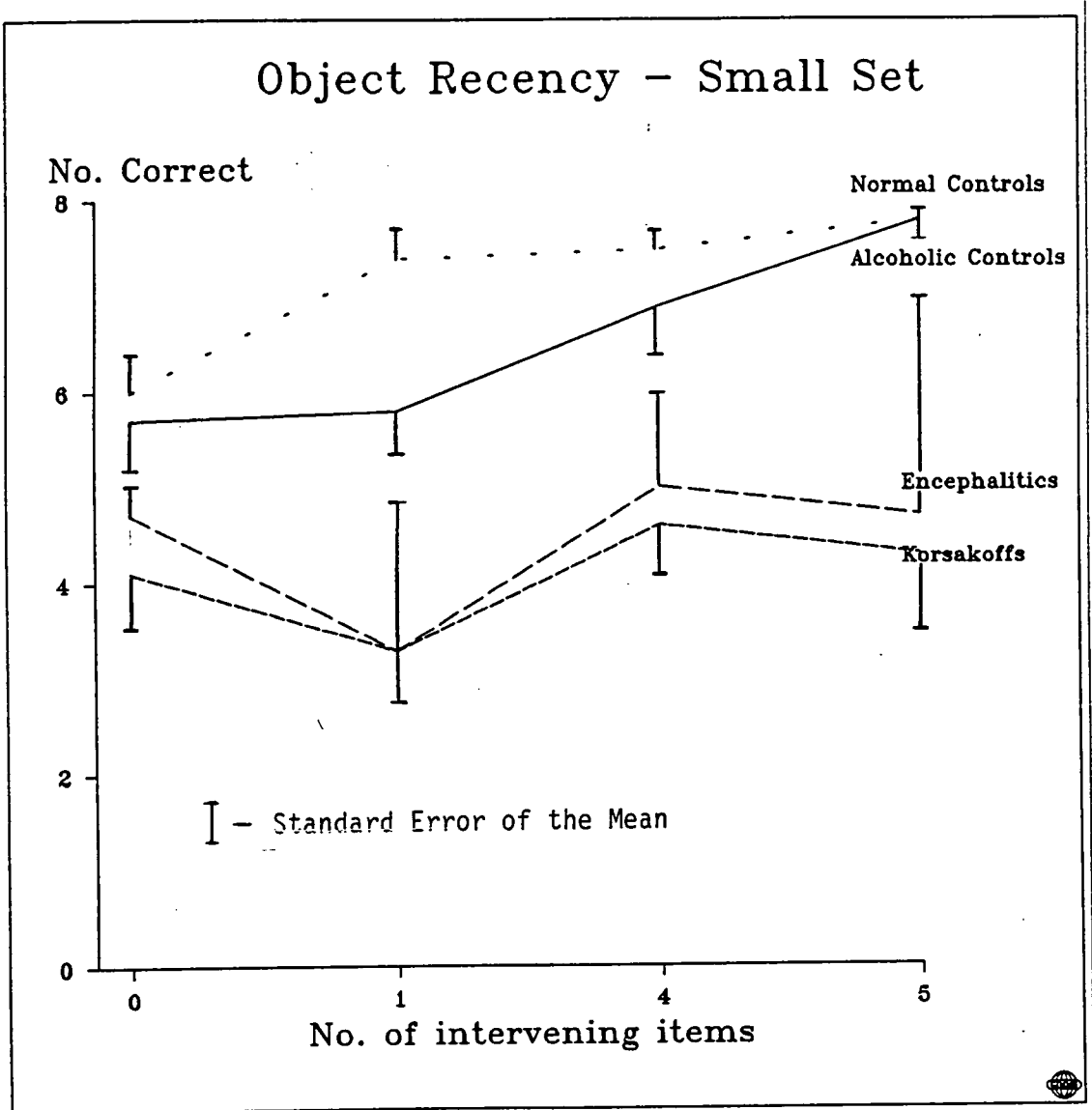
No. of intervening items

Figure 4.2: Mean number correct at each lag for all groups in the small set size condition.

with increasing lag. This improvement in performance with increasing lag appeared more pronounced in the LS condition. Both amnesic groups achieved lower scores compared to the controls across all lags although the encephalitic subjects performed similarly to the controls on the lag of 0 in the LS condition. With this single exception the performance of the post-encephalitic group appeared very similar to that of the Korsakoff subjects achieving only slightly higher scores.

Analysis of variance was carried out comparing the Korsakoff and alcoholic control groups with the factors group, set size and lag. This confirmed that the Korsakoff subjects were impaired relative to their control subjects with a significant effect of group $[F(1,14) = 49.93, p<.001]$. There was no difference in performance by the two groups on the different set size conditions and the Korsakoff group was not differentially affected by set size, as the main effect of set size and the group X set size interaction was not significant. That performance improved with increasing lag was confirmed by a main effect of lag $[F(3,42) = 7.76, p<.001]$ and that this was more pronounced in the control subjects by a significant group X lag interaction $[F(3,42) = 4.28, p = .01]$. Although it appeared that the improvement in performance with increasing lag was more pronounced in the LS condition the set size X lag interaction just failed to reach significance $[F(3,42) = 2.60, p=.064]$. There was no difference in performance between the two groups at the different lags in the two set size conditions as shown by a non-significant group X set size X lag interaction.

Analysis of variance comparing the post-encephalitic and normal control groups found the post-encephalitic subjects to be impaired with a main effect of group $[F(1,12) = 23.66, p<.001]$. There was no difference in performance of the two groups on the two set size conditions and the post-encephalitic group was not differentially impaired on either of the experimental conditions as the main effect of set size and the group X set size interaction proved not to be significant. Again the improvement across the lags was confirmed with a main effect of lag $[F(3,36) = 4.25, p=.011]$ and that the control group improved across the lags to a greater extent than the amnesic group by a group X lag interaction $[F(3,36) = 5.26, p=.004]$. The performance at each lag did not differ in the two experimental conditions as the set size X lag interaction was not significant but the two groups did differ at each lag in the two experimental conditions as the group X set size X lag interaction was significant $[F(3,36) = 3.90, p=.016]$.

Table 4.3 shows the correlations between object recency (total number correct on both conditions) and tests of frontal lobe function for the Korsakoff, alcoholic control and normal control groups. The correlations reported represent the correlation between poor

performance on the object recency and poor performance on the other tests. There were no significant correlations produced by any of the groups.

Table 4.3: Spearman rank order correlations of performance on the object recency and performance on tests of frontal lobe function for all groups except the post-encephalitic group.

			Tests of Frontal Lobe Function			
	WCST	Verbal Fluency	Design Fluency	Picture Arrange.	Block Design	Cognitive Estimation
Korsakoff Group	-.21	+.31	+.71	+.67	-.34	+.50
Alcoholic Controls	-.20	+.48	+.08	-.04	-.28	+.39
Normal Control Group	+.08	+.44	-.30	-.08	-.11	-.43

Table 4.4 shows the Spearman rank order correlations for all groups except the post-encephalitic group between the object recency and tests of memory and intellectual function. No significant correlations were found in the Korsakoff group. The alcoholic control group produced a positive correlation between poor performance on the NART and the object recency ($r_s = .83, p = .012$). Table 4.5 shows that none of the correlations between the object recency and estimation of duration proved to be statistically significant for any of the groups, except for a positive correlation in the alcoholic control group between estimation of empty intervals and object recency.

Table 4.4: Spearman rank order correlations of performance on the object recency task and performance on tests of memory and intellectual function for all groups except the post- encephalitic group.

Tests of Memory and Intellectual Function

	WMS	Warrington Recognition	WAIS IQ-MQ	NART IQ-MQ	Digit Span	WAIS IQ	NART
Korsakoff Group	-.35	-.36	+.34	-.04	-.14	-.20	-.23
Alcoholic Controls	+.32	+.57	-.008	-.13	-.07	+.45	+.83 $p=.012$
Normal Control Group							+.02

All probabilities two tailed

Table 4.5: Spearman rank order correlations of performance on the object recency task and performance on the time estimation tasks for all groups except the post-encephalitic group.

	Fixed Intervals		Time Estimations			
Object Recency	FI15	FI30	Reproduction	Empty	Filled	Total Error
Korsakoff Group	+.60	+.09	+.07	-.04	+.47	-.14
Alcoholic Controls	+.12	+.36	-.01	+.71 $p=.05$	+.37	+.45
Normal Control Group	-.07	-.35	-.05	-.18	+.07	-.24

All probabilities two tailed

4.1.4. Discussion

Both amnesic groups were impaired on the object recency task compared to their control groups, the two amnesic groups exhibiting similar levels of performance. The comparable level of performance by the two amnesic groups on this memory task serves to highlight the different levels of performance in the duration estimation tasks of experiment 1 and 2. Although the two groups are matched on the standard memory tests and also in this test of temporal order memory the post-encephalitic group performed relatively well on tests of temporal estimation. This dissociation in performance on the two types of temporal processing suggests that they are not dependent upon the same cognitive process. Further evidence for this comes from the finding that performance on the object recency task did not correlate systematically with performance on any of the time estimation tasks carried out in the previous experiments (table 4.5).

Although memory for sequential order and behaviour has been attributed to frontal lobe function, there was no evidence that the impairment in temporal order memory in this experiment was related to impairments on tests of frontal lobe function. None of the correlations with frontal lobe tests reached statistical significance. The cognitive estimation task which had shown strong correlations with the time estimations did not show any correlation with recency memory. This further highlights the different nature of the two aspects of temporal processing and also fails to support the hypothesis that deficits in temporal order memory are a result of frontal lobe damage in amnesic subjects.

The proposal that deficits in the utilisation of the temporal order of events in the environment is a cause of amnesia was not supported. No relationship was found between tests of memory function and the object recency task in the Korsakoff group. Neither does it support the proposal that temporal order memory is merely a result of poor memory. The lack of a consistent relationship between memory function and recency memory impairment suggests an impaired cognitive function independent of their retention deficits.

The prediction that performance would improve with increasing lag was borne out by the results. As two events become closer in time they become less discriminable temporally. It is more difficult, therefore, to distinguish which of two items occur more recently when they are presented consecutively in the study list than if they are presented at the beginning and end of the list. It was also predicted that if the amnesic subjects suffer from a temporal order deficit they would be impaired across all lags, that more distant events would be as indiscriminable as consecutive events. Both amnesic groups failed to show this effect of lag to the same extent as their control groups which was con-

firmed by the group X lag interactions.

It was expected that all subjects would perform less well on the small set size because of the increase in task difficulty but that the amnesic groups would be more impaired compared to the controls on this condition as it taxes the ability to make temporal position judgements to a much greater extent. Neither of these predictions were borne out. There was no overall difference in performance on the two conditions and neither the Korsakoff nor post-encephalitic subjects were differentially affected by set size although this may have been masked by floor effects as both the Korsakoff and post-encephalitic groups were performing at or close to chance in both conditions. The control groups may not have shown a set size effect because the objects in this set were somehow more distinctive and thus easier to remember. The next experiment addresses this possibility. It is also possible that the subjects became more familiar with the objects presented repeatedly and thus had greater opportunity to ascribe verbal labels to the objects and consequently develop a mnemonic strategy. It may be that the general impairment exhibited by the amnesic subjects in the recency task is a result of the control subjects utilising mnemonic strategies whilst the amnesic subjects failed to do so. The following experiment addresses this issue.

In conclusion, both amnesic groups were equally impaired on the object recency task, but no relationship was found between the impairment on this task and tests of frontal lobe damage or memory function. The impairment, therefore, may be attributed to a cognitive impairment unrelated to their retention deficits. Temporal order memory was also found to be independent of duration estimation as no relationship was found between performance on the time estimations carried out in experiments 1 and 2 and the recency task in the present experiment. This was further emphasised by the findings that the post-encephalitic subjects exhibited comparable performance to the Korsakoff group in the present experiment but showed unimpaired performance on the time estimations. The results did not support the proposal that amnesia results from the inability to place events in their temporal context. It is possible that the superior performance of the control subjects was due to the utilisation of mnemonic strategies which will be discussed further in the following experiment.

4.2. Experiment 4: One trial object recency with control subjects.

4.2.1. Introduction

In the previous experiment (experiment 3) the amnesic groups showed an impairment in the object recency task that was apparently unrelated to impairments in tests of frontal lobe function and tests of memory function. It was suggested that the poorer performance of the amnesic subjects may have been a result of the control subjects adopting a mnemonic strategy, whilst the amnesic subjects failed to do so. Although Korsakoff subjects can use strategies appropriately they often do not use them spontaneously (Mayes, Meudell & Neary, 1980).

In this experiment a group of normal subjects were tested on the object recency task without being allowed the opportunity to develop a strategy. To achieve this aim the subjects were not given instructions as to the nature of the task prior to testing and only one set of eight objects were presented for study and recall to each subject i.e. each subject received only one 'run'. It was expected that if the control subjects performance in the previous experiment was dependent upon the use of a mnemonic strategy their performance would be significantly higher than that of the subjects in the present experiment.

The experiment also examined whether the sets of objects used in experiment 3 varied in qualities that would render the task easier, such as distinctiveness or the ease with which they could be verbally labelled. This was to acsertain whether the choice of objects for the small set size had inadvertantly affected task difficulty which might explain the lack of a 'set size' effect in the previous experiment.

4.2.2. Methods
4.2.2.1. Subjects

The subjects were 90 undergraduate students recruited from first and second year practical groups. There were 42 male and 48 female subjects, their ages ranging from 18 to 59 years (mean 21.6 years).

4.2.2.2. Apparatus

The apparatus was as described in experiment 3.

4.2.2.3. Procedure

The procedure was as described in experiment 3 except that only one run was given to each subject. Also, the subjects were not informed as to the nature of the task but were merely asked to look at the objects and told that they would be required to answer

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questions about them after their presentation.

All nine sets of objects were used, each set being randomly allocated to ten subjects. The objects were presented for study and recency judgement in the same order for each subject.

4.2.3. Results

Analysis of variance was carried out on the students' data comparing each group presented with each of the nine sets of objects at each lag. No significant difference was found between the performance on each set of objects as there was no main effect of group and neither was there a difference between the groups at each lag length as there was no group X lag interaction. Subjects did perform differently at the different lags as shown by this main effect [$F(3, 243) = 25.79, p<.001$].

The data was converted to percent correct in order to compare the performance of the students with that of the two control groups of the previous experiment. Figure 4.3 shows the mean percent correct for the students, alcoholic control and normal control groups at each lag in the large set size condition and figure 4.4 the small set size condition. The normal control group perform at similar levels to the students in both conditions whereas the alcoholic control group achieve lower scores at all lags in both conditions except the longest lag of 5 and the lag of 1 in the small set condition.

Analysis of variance comparing the students and the normal and alcoholic control groups revealed no significant difference between the groups in either condition although the difference in the large set size condition just failed to reach significance [$F(2,107) = 2.95, p=.056$]. That percent correct increased with increase in lag was confirmed by a main effects of lag [*large set* $F(3,321) = 16.53, p<.001$; *small set* $F(3,321) = 10.01, p<.001$] There was no difference between the groups in performance across the lags as shown by non-significant group X lag interactions.

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Figure 4.3: Mean % correct at each lag in the large set size condition of the object recency test for the students, alcoholic control group and normal control group.
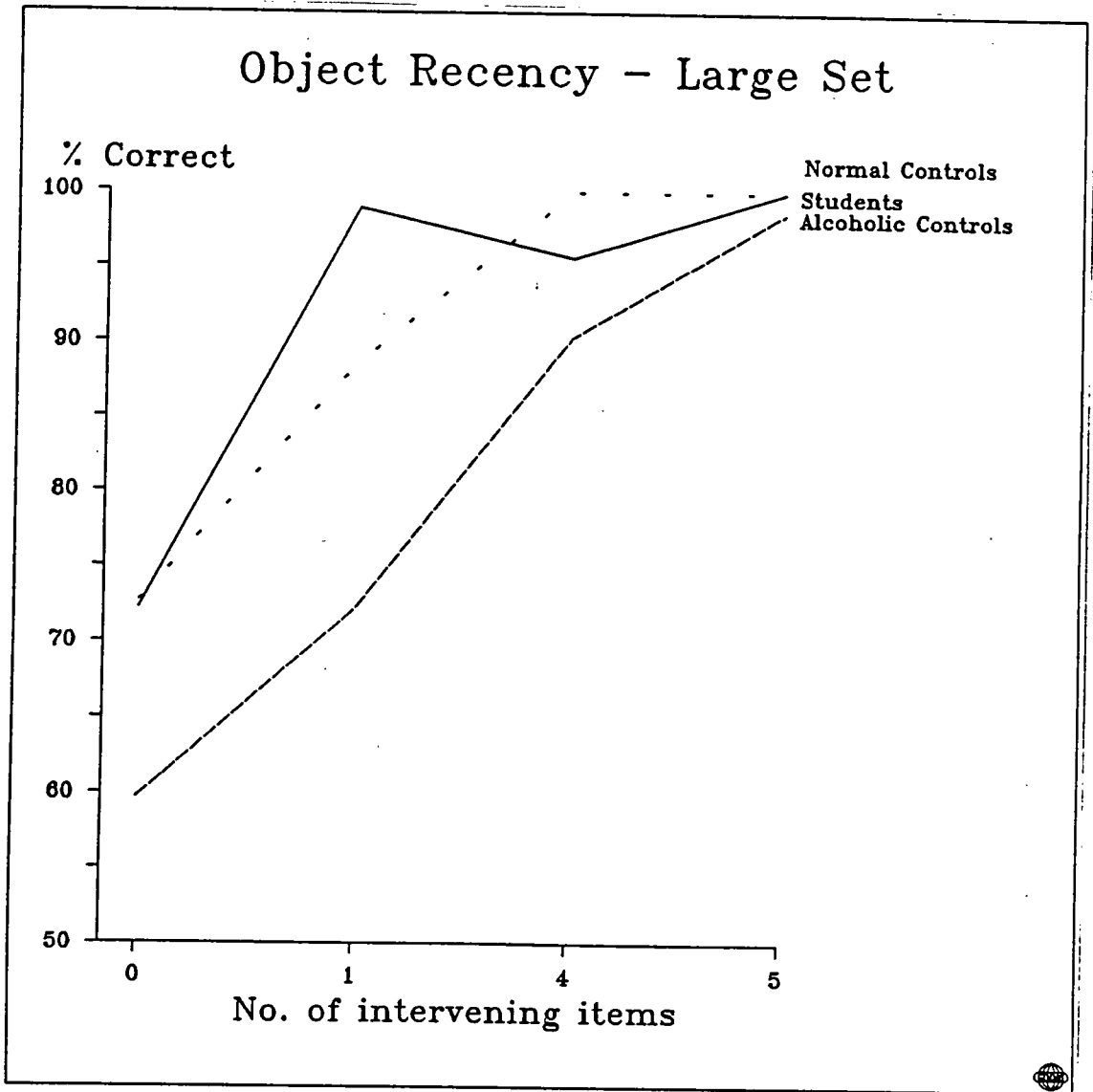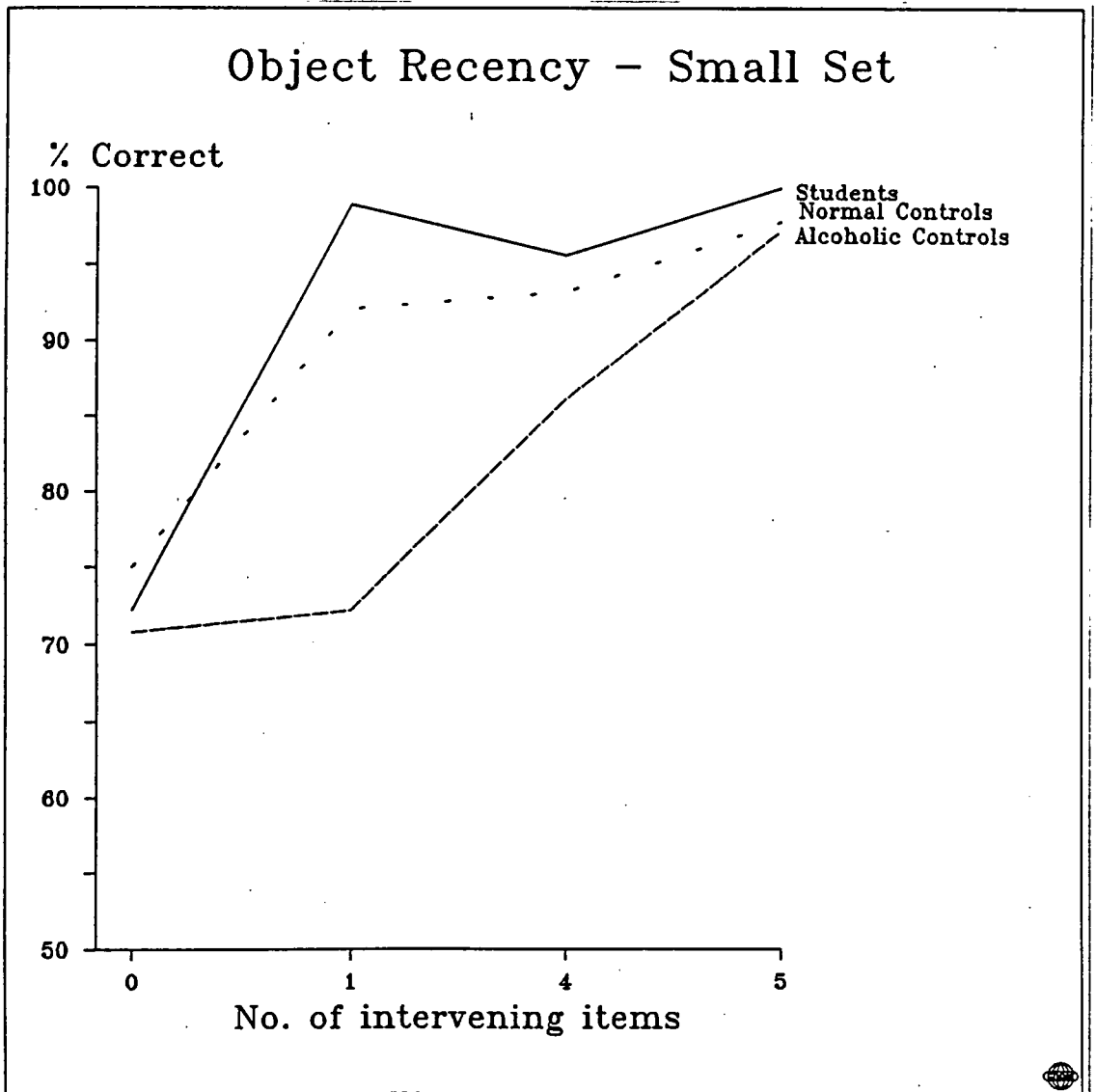

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Figure 4.4: Mean % correct at each lag in the small set size condition of the object recency test for the students, alcoholic control group and normal control group.

4.2.4. Discussion

There was no difference in the performance of the students on each of the different sets of objects. The choice of objects in each set size condition does not, therefore, account for the lack of a set size effect in the control groups in the previous experiment. It is possible that familiarity with the objects, brought about by repeated presentations, aided either the formation and utilisation of verbal labels and strategies or the distinctiveness and temporal discriminability of the objects even though the control subjects performance in the small set size condition was similar to that of the students who had no opportunity to develop a mnemonic strategy. The control subjects could be expected to show depressed performance compared to the students because of the high levels of interference and difficulty of the temporal judgment in this condition. There is a problem of interpretation, however, as the student scores are very close to ceiling on several of the lags and this could mask a greater difference between the students and the control groups than is apparent from this data.

Although the amnesic subjects also failed to show an effect of set size in the previous experiment it does not mean that they were also aided by familiarity of the objects in the same way as the control subjects. Their performance was close to chance in both conditions which would mask any differences in the two conditions brought about by level of difficulty of the temporal order judgement.

It is unlikely that the control subjects accuracy was a result of the use of mnemonic strategies in the large set size condition as their performance was comparable to or, in the case of the alcoholic control group, lower than the student groups performance. Again, though, there is the problem of ceiling effects at the longer lags in both the student and the normal control data.

In conclusion, no difference was found in the recency memory performance of student subjects on the nine different sets of objects used in the previous experiment. It was concluded that the the lack of an effect of set size i.e. presenting objects repeatedly within a session and thus increasing the difficulty of discriminating the temporal occurrence of an object, was not due to an artifact of the design of the experiment. The objects used in the small set size condition were no more distinctive or more amenable to recency judgements than the other objects used in the experiment. It was suggested that repeating the objects increased their familiarity and aided recency judgements by allowing greater opportunity to note distinctive features or assign verbal labels to them. The proposal that the amnesic subjects impairment was due primarily to a failure to utilise mnemonic strategies seems unlikely, as the control groups did not perform any better in

the large set condition than the students, who were performing the task under incidental instructions and thus had no opportunity to develop a strategy.

4.3. Experiment 5: Object recency and recognition in amnesic subjects

4.3.1. Introduction

This experiment examined further the relationship between temporal order judgments and memory. As mentioned in experiment 3 some researchers believe that a loss of the temporal relationships between events is a primary cause of amnesia (Hirst & Volpe, 1982; Winocur & Kinsbourne, 1978). Others, however, believe that temporal order deficits are a result of poor memory (Squire, Nadel & Slater, 1981). Both points of view suggest that temporal order judgments and recognition memory are interdependent. There is a growing body of evidence to suggest, however, that temporal order and recognition memory are dissociable, and that recency memory is an aspect of temporal processing that is not dependent upon those brain structures whose damage results in an amnesic syndrome. H.M. is severely impaired in recognition memory but has normal temporal order memory (Sagar, Gabrieli, Sullivan, & Corkin, 1990). Hirst and Volpe (1982) found that amnesics of mixed aetiology had impaired order memory but normal event recognition. Patients with frontal lobe lesions typically exhibit deficits in sequencing events but show no impairment in recall and recognition (Shimamura, Janowsky, & Squire, 1990). Also subjects having Parkinsons disease have been shown to be impaired on recency for verbal material but not recognition (Sullivan & Sagar, 1989) and no correlation was found between temporal order judgments and recognition memory in such subjects (Vriezen & Moscovitch, 1990). And finally the finding in experiment 3 in the present research that there was no correlation between performance on the object recency task and tests of memory function also suggests that temporal order and memory function are dissociable.

The present experiment, therefore, repeated the object recency test in the amnesic groups but incorporated a recognition test of the same objects being tested for recency memory. To avoid the floor effect found in experiment 3 the number of objects in a set were reduced from eight to six. A manipulation was then carried out that was designed to enhance recognition. This took the form of an orienting task, requiring the subjects to make a judgment as to the material from which the object was made. As this manipulation not only requires further examination of the stimulus but also allows a longer length of time to study the object, a long presentation condition was also given. In this condition the stimuli were presented for a longer period than in the standard condition of the previous experiment.

If recency memory is, indeed, independent of the recognition memory impairment in amnesic subjects the orienting task would be expected to produce a differential effect upon recency and recognition judgments. The experiment also allows examination of recognition and recency judgment of the same items. If order and content recognition are independent it would be expected that there would be no correlation in performance between the two types of test on individual items. And finally, as in the previous experiment, it was expected that there would be no lag effect in the recency judgment if there is a deficit of temporal ordering.

4.3.2. Methods
4.3.2.1. Subjects
Subjects in the Korsakoff and post-encephalitic groups took part in the experiment. The Korsakoff group was the same as that in experiment 3 except for one subject (J.B.) who was unavailable for testing. This left a group of 6 subjects, four men and two women, whose mean age was 57.3 years. The post-encephalitic group remained unchanged.

4.3.2.2. Apparatus
The presentation screen was the same as that used in experiments 3 and 4. 189 junk objects consisting of electronic, hardware and laboratory equipment were used as stimuli. Seven sets of nine objects were used in each of the three experimental conditions. Three of the objects in each set were used as distractor items for the recognition memory part of the test and these objects were chosen for their similarity to the target items.

4.3.2.3. Procedure
Each subject carried out all three conditions; short presentation (S), long presentation (L), and long presentation + orienting task (LO). The experiment was carried out over two sessions at weekly intervals. All subjects received the LO condition last, the remaining two conditions being presented in a counterbalanced order. One session comprised one condition and the other, two conditions. The order of the one or two condition sessions were also counterbalanced across subjects.

The subject sat in front of the screen as in experiment 3 and 4 and it was explained that he would be shown a number of objects one at a time followed by two objects, one of which he had just seen and one new item, and that he would be required to indicate the object that he had seen before. He was also told to pay particular attention to the order of presentation of the items as he would then be shown two objects, both of which

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he had seen before and that he would be asked to point to the one that had appeared latest in the presentation sequence.

Short presentation condition.

On each run six stimuli were presented for study in the same manner as in experiment 3, each object being shown for 1.5s at a rate of one every 5s. after an interval of 12s the subject was shown two objects, one of which had been presented in the study phase, and a novel distractor item. The subject was asked to indicate the object that he had seen before, and was allowed as long as required to make a choice. The subject was told whether he had made a correct choice and the distractor item was removed from view, replaced with another object from the study set, and the subject asked to indicate which of the pair had appeared latest in the study sequence. After a choice had been made the two objects were removed and a further two objects presented for recognition judgment and so on, until three recognition and three temporal order judgments had been made. The complete set was then removed from behind the backboard and replaced with the next set, giving an interval of 30s between each run. All seven sets of objects were presented in the same way.

Long presentation condition.

The procedure was exactly the same as for the S condition but the stimuli were presented for study for an extended period of 5s, and the test phase commenced immediately after presentation of the sixth object in the set, and not after a 12s interval.

Long presentation + orienting task condition.

This was carried out as for the L condition but when each object was presented for study the subject was asked to make a judgment of what material the object was made. This took approximately 5s per object.

The presentation orders for recognition and temporal order judgments were the same in each condition. Each presentation position of the study phase appeared as the recognition target item an equal number of times as far as possible (i.e. 3 or 4 times). The spatial position (right or left) of the correct item in both the recognition and temporal order tests were presented in a pseudorandom order so that there were, as far as possible, an equal number of right and left correct positions. On each run the number of intervening items during the study phase of the two items presented for recency judgment (lag) was 4, 2 and 1 item; their order of presentation being counterbalanced across runs.

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When two conditions were carried out in a session a break of approximately 15 minutes was given between each condition during which the subject carried out psychometric tests.

4.3.3. Results

Figure 4.5: Mean number correct in the test of temporal recency at each lag in each of the three presentation conditions for the Korsakoff subjects.
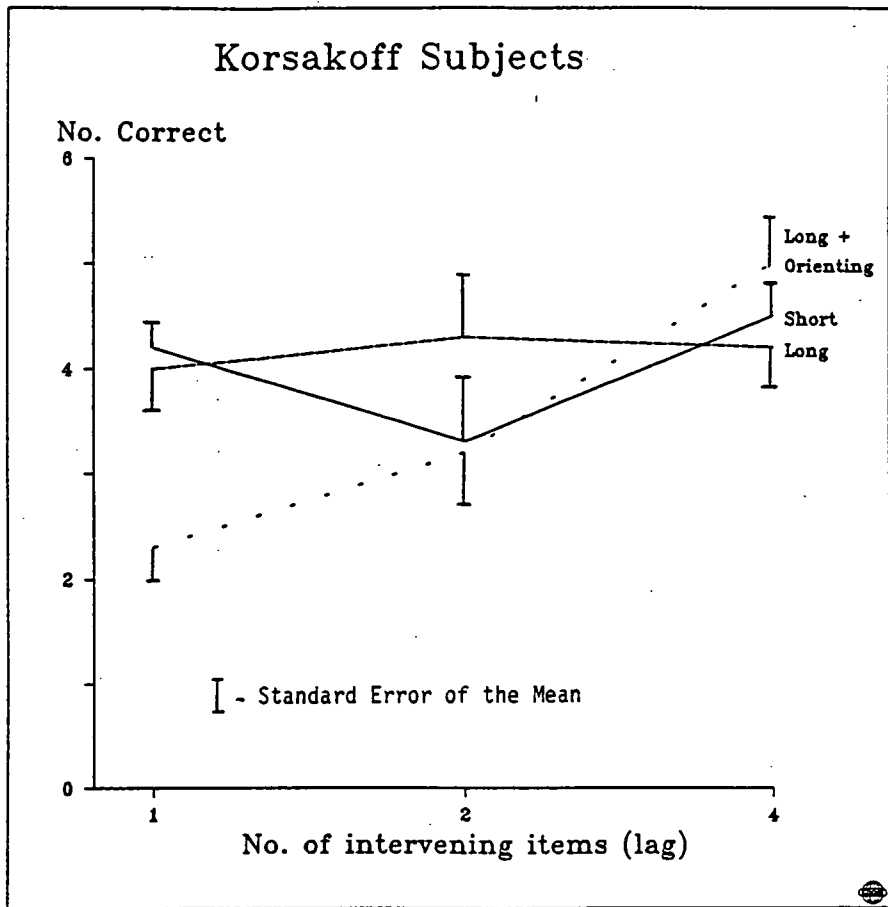

Figure 4.5 shows the results of the temporal order judgments for the Korsakoff group. This figure depicts the number correct at each lag for each of the three conditions; short presentation, long presentation and long presentation + orienting task. Performance is very similar across the lags in both the S and L conditions whereas there is an increase in number correct with increasing lag in the LO condition. Analysis of variance was carried out on the data with the factors condition and lag. This showed there to be no difference in performance between the three conditions as the main effect of condition was not significant. The main effect of lag just failed to reach significance [$F(2,10) = 3.52, p=.070$]. That the lag effect was more pronounced in the LO condition was confirmed by a condition X lag interaction [$F(4,20) = 4.27, p=.012$].

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Figure 4.6 shows the results of the temporal order judgments of the post-encephalitic subjects. Again, there appears to be more of a lag effect in the LO condition but this was not statistically significant. There was no main effect of lag or a condition X lag interaction, and there was no significant difference between the three conditions.

Figure 4.6: Mean number correct in the temporal recency test at each lag in each of the three presentation conditions for the post-encephalitic subjects.
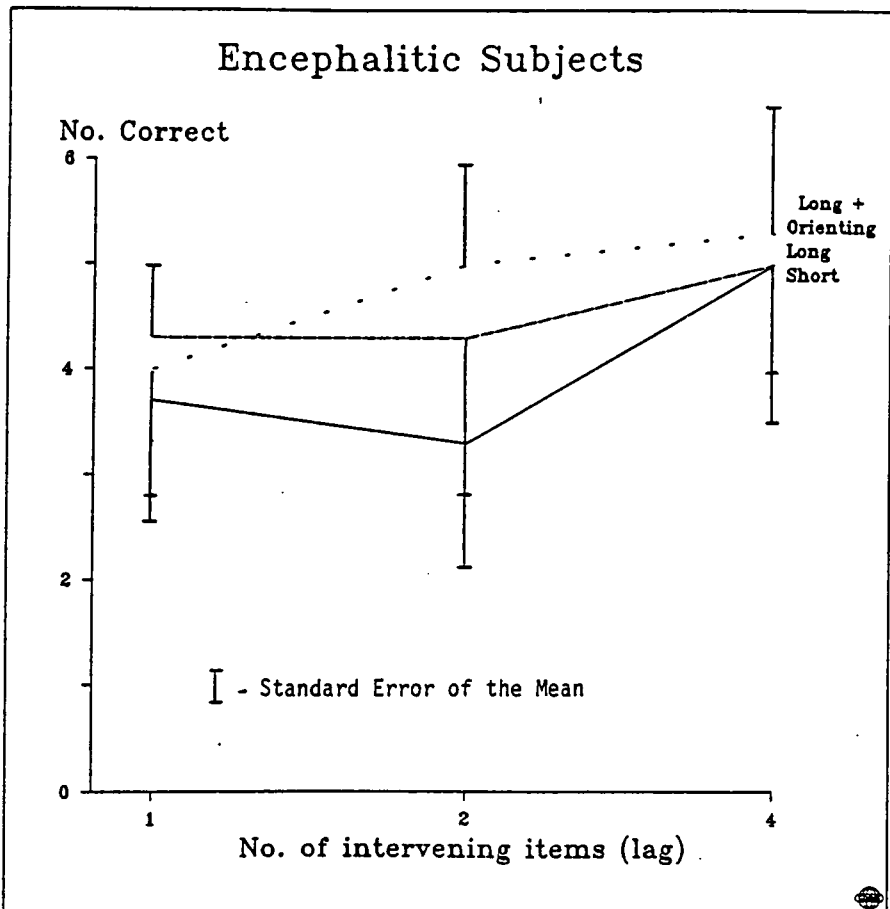

Figure 4.7 shows a comparison of the recency and recognition judgments for the Korsakoff subjects and figure 4.8 shows this same comparison for the post-encephalitic subjects. These figures show the number correct for the recency and recognition tests for each condition. Performance is higher in both groups on the recognition task compared to the recency. In the Korsakoff group performance is marginally higher on the L condition than the S condition for both recency and recognition but performance improves in the recognition task on the LO condition but declines in the recency task. This pattern of results is not seen in the encephalitic group's data. Performance on the recency and recognition show a similar level of performance on all three conditions apart from a slightly higher level of performance on the recognition task in the short presentation condition.

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Analysis of variance was carried out on each groups results with the factors test i.e. recognition or recency judgment and presentation condition. For the Korsakoff group there was no significant difference in the performance on the two types of test [$F(1,5)=2.71$]. There was also no significant difference between performance in the three conditions but the difference in performance in the LO condition in the two types of test was confirmed by a test X condition interaction [$F(2,10) = 15.96, p=.001$].

For the post-encephalitic group the higher performance in the recognition test just produced a significant main effect of test [$F(1,2) = 19.00, p=.049$] whilst there was no significant difference in performance on the different conditions. There was also no differential effect of type of test on presentation condition.

Figure 4.7: Mean number correct on the recency and recognition tests in each presentation condition for the Korsakoff subjects.
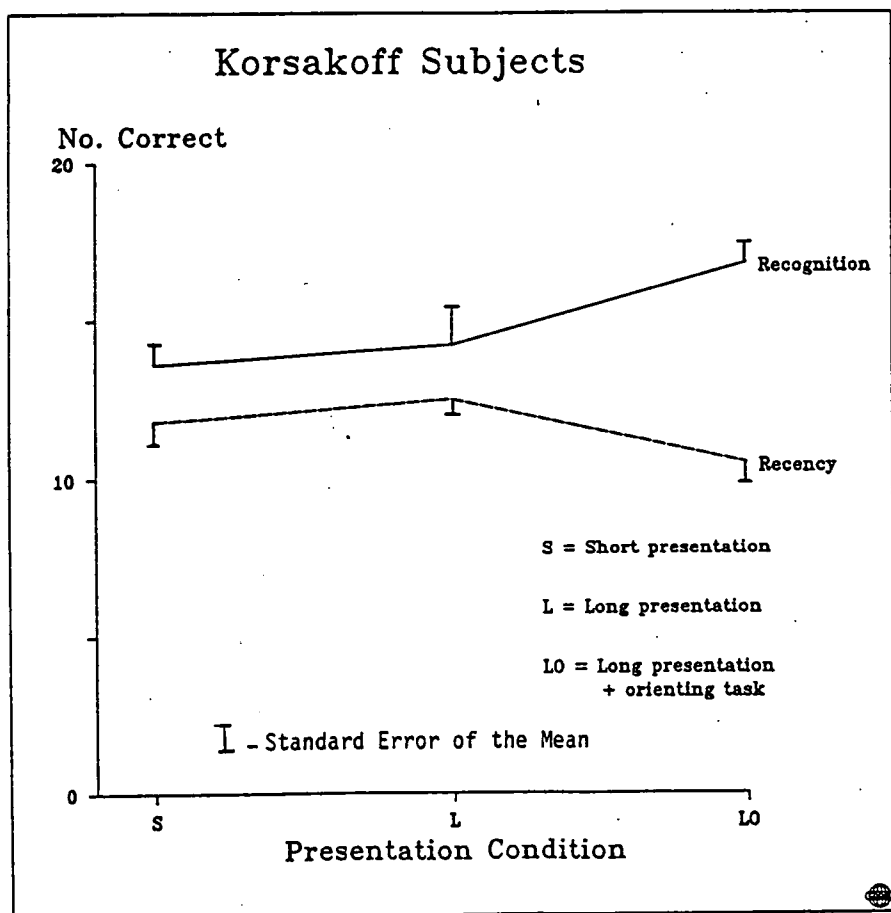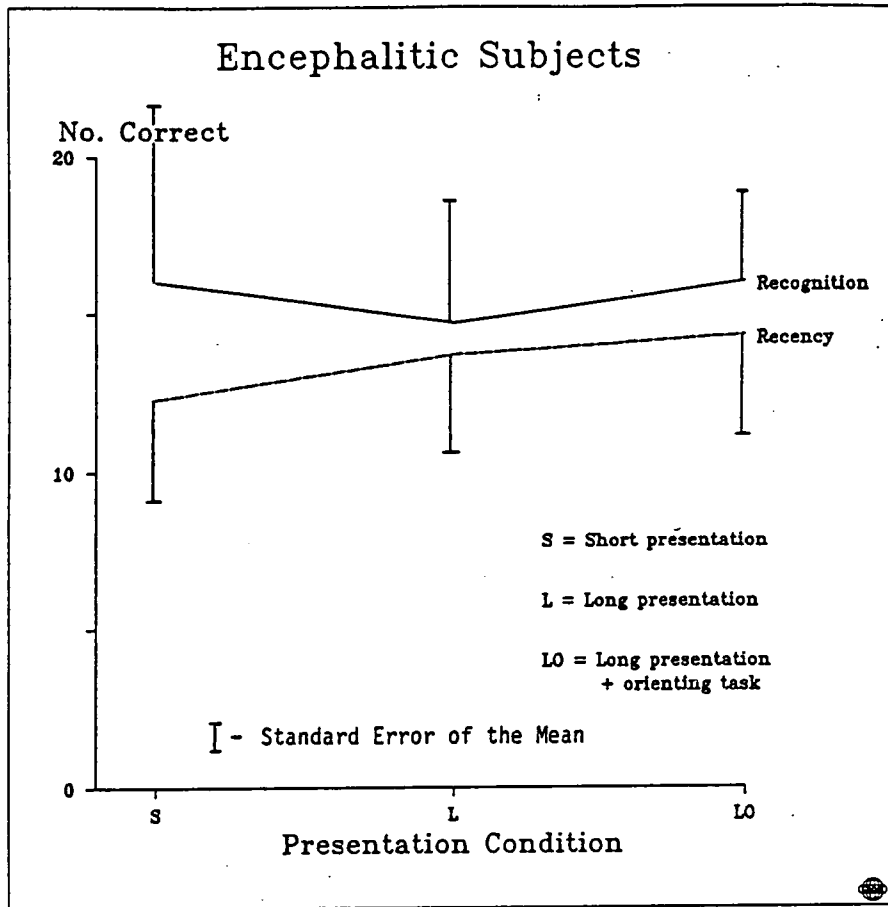

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Figure 4.8: Mean number correct on the recency and recognition tests in each presentation condition for the post-encephalitic subjects.

To further assess the relationship between recency and recognition judgments it was calculated whether a subject was more likely to make a recency error if that object had not been recognised. Figure 4.9 depicts this analysis for the Korsakoff group. R+ represents a correct recognition judgment and R- an incorrect one. The data is plotted for each presentation condition and shows the number of incorrect recency judgments when recognition was either correct or incorrect for that object as a percentage of the total number of correct or incorrect recognition judgments. As can be seen there are more recency errors in all three conditions when recognition was incorrect than when it was correct. This, however, just failed to reach significance [$F(1,5) = 6.16, p=.056$]. There was no significant difference between the three conditions and there was no effect of condition on the correct or incorrect recognition judgments.

The post-encephalitic subjects were less likely to make a recency error when the recognition judgment was incorrect in the long presentation condition but more likely

to make a recency error with incorrect recognition judgment in the short and long+orienting condition (figure 4.10). Analysis of variance revealed that the difference between the conditions failed to reach significance [$F(2,4)$ = 4.85, $p=.085$]. The number of recency errors after a correct or incorrect recognition judgment was not significant and neither was the interaction of condition on correct/incorrect recognition judgment.

Figure 4.9: Mean % recency errors when recognition is correct (R+) and incorrect (R-) at each presentation condition for the Korsakoff subjects.
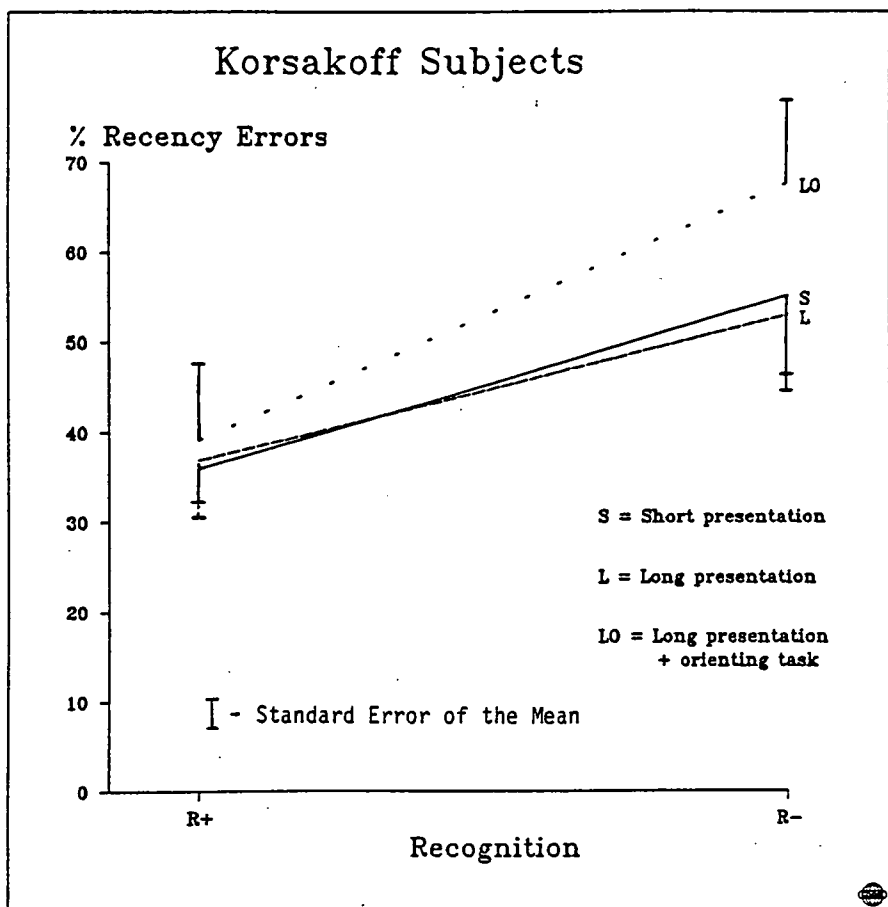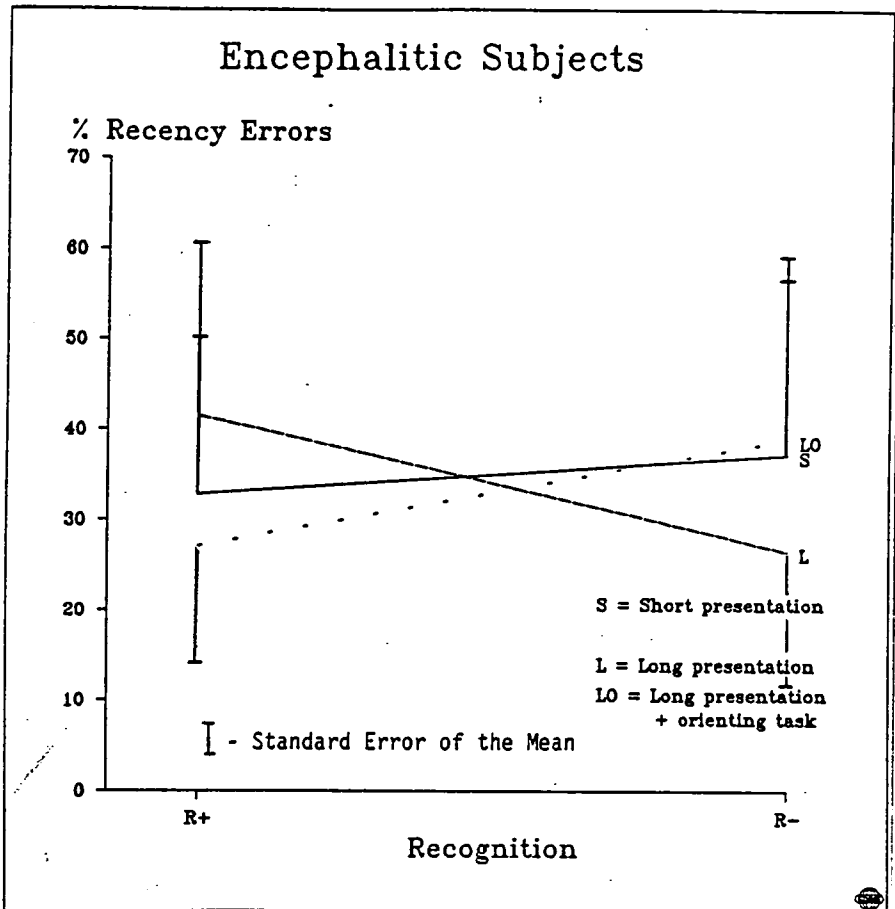

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Figure 4.10: Mean % recency errors when recognition is correct (R+) and incorrect (R-) at each presentation condition for the post-encephalitic subjects.

4.3.4. Discussion

This experiment showed a dissociation between recognition and recency memory in the Korsakoff group but the results of the post-encephalitic subjects were somewhat inconsistent. The orienting task proved to have a differential effect on the recognition and recency judgments of the Korsakoff group. Recognition performance improved with the orienting task whereas recency declined. This is consistent with the suggestion that recognition and recency memory are independent processes and presumably based upon different neurological substrates. Further support for this comes from the comparison of recognition and recency judgments for individual items. Although it appeared that a recency error was more likely to occur when recognition was incorrect this proved not to be statistically significant showing errors on the two tests for the same items to be independent.

The Korsakoff subjects also failed to show any effect of lag in their recency judgments except in the orienting task condition. It is possible that the orienting task helped the subjects to utilise temporal ordering strategies in some way but as the lag effect was produced mainly by

particularly poor performance on the most difficult lag of one it is more likely to be the result of an attentional problem. The orienting task could have interfered with temporal order judgment by directing attention away from temporal processing. The failure to show a lag effect supports the findings of the previous experiment and suggests the Korsakoff subjects are suffering a specific deficit in temporal ordering.

The post-encephalitic data also showed a pattern of a deficit in temporal ordering with a dissociation between recency and recognition apart from the lack of a differential effect of the orienting task on the tests of recency and recognition. They, like the Korsakoff group, did not display a lag effect in their recency judgments, suggesting a deficit in temporal ordering. The comparison of recency errors for items that were correctly or incorrectly recognised produced a more definate pattern of independence of recognition and recency than that of the Korsakoff group. It is, therefore, surprising that the orienting task did not differentially affect the two types of judgment. Because of the small group size it is difficult to come to any firm conclusions as to whether there is a real lack of a dissociation in this particular instance or whether for some reason these subjects were not responding to the orienting task.

In conclusion, this experiment demonstrated a dissociation between recognition memory and recency memory in Korsakoff subjects. This supports the hypothesis that temporal ordering impairments are independent of retention deficits in amnesic subjects. The results of the post-encephalitic subjects were inconclusive as some results were consistent with the suggestion that recency memory impairment in these subjects is independent of recognition memory whereas the orienting task did not show the expected differential effect on these two types of memory task. These inconsistencies are probably a result of the small group size and could only be resolved by testing further subjects.

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Chapter 5
Temporal order judgments in rats with specific brain lesions

5.1. Experiment 6: Delayed non-matching to sample in rats with fornix and medial prefrontal cortex lesions.

5.1.1. Introduction

Although the most influential theories of hippocampal function have proposed an involvement in spatial or working memory there is much evidence to suggest that the hippocampus is also involved in processing temporal information. Rats with hippocampal system damage typically show deficits in operant schedules (Boitano, Dokla, Mulinski, Misikonio, & Kaluzynski, 1980; Rawlins, Winocur & Gray, 1983; Sinden, Rawlins, Gray & Jarrard, 1986) which provides direct evidence for an impairment in temporal duration judgments. Indirect evidence comes from studies of classical conditioning of the rabbit's nictitating membrane response. It is unlikely that spatial factors play any part in the rabbit NMR preparation and the results of such experiments have suggested that the hippocampus plays a role in modulation of the timing of the CR in classical conditioning paradigms (Port, Romano, Steinmetz, Mikhail & Patterson, 1986).

There is also evidence for the involvement of the hippocampus in sequential behaviours. Both fornix and hippocampal lesions have been found to disrupt sequencing behaviours in rats (Olton, Shapiro & Hulse, 1984; Kesner & Novak, 1982) and, like human amnesics, rats with hippocampal lesions appear to behave differentially towards temporal and environmental context (Kesner, 1980; Rudy & Sutherland, 1989; Winocur, Rawlins & Gray, 1987). The working memory hypothesis can account for these findings as working memory is defined as *'a process responsible for coding the information about the temporal context in which an event happens'* (Olton et al., 1979).

Many tasks have been devised to test the working memory theory, one of which is the delayed matching or non-matching to sample task (DMS/DNMS). In this task a sample object is presented at the beginning of a trial followed by a choice between the sample object and a novel object and the rat is rewarded for choosing the sample object in the DMS procedure and the novel object in the DNMS. Working memory is required for information pertaining to a single trial as opposed to information concerning the general nature of the task. There have been many inconsistencies in the results of experiments using DMS and DNMS (discussed in Chapter 2) and it would appear that the working memory hypothesis is not specific enough to account for the data.

Although the working memory theory accounts for temporal factors, tasks such as DMS and DNMS vary from study to study in the degree to which they depend upon the temporal tagging of events, although all can be designated as working memory tasks. Rawlins, Lyford and Seferiades (1991) examined these procedural difference systematically and concluded that there were two important variables which accounted for the discrepancies in the results of DMS/DNMS tasks, the nature of the stimuli and the extent to which they were reused within a session. Both of these variables could result in temporal interference effects. It is possible, then, that temporal factors may explain the inconsistencies in the results of some working memory tasks.

To test the importance of temporal factors in the DNMS procedure and their relationship to hippocampal function the present experiment examined the performance of rats with hippocampal lesions on a DNMS task using a small set of stimuli, the number of which were decreased progressively over the experiment. The animals learned the task with 13 pairs of stimuli, each occurring once per session. The number of stimuli were then gradually reduced over the experiment until just 3 pairs remained. As the number of stimuli are reduced they are reused more times within a session so that the choice the rat has to make becomes one of relative recency rather than to choose the unfamiliar object. It was expected that an impairment in the temporal tagging of events would result in greater decrease in performance as the number of stimuli decrease than exhibited by control animals.

The present task was designed to be comparable to those experiments discussed in Chapter 2 that used a restricted set of stimuli in the DNMS/DMS procedure and also the object recency experiment carried out with the human amnesic subjects in the present research. As in the object recency task there were different set size conditions, within which the lag was varied systematically. In this experiment the 'lag' represented the number of intervening boxes between the first and second presentation of a stimulus as correct less familiar item. It was expected that the longer the lag the better would be performance on the recency test. It was also expected that a disorder of temporal tagging would eliminate the lag effect as items occurring in close proximity would be as temporally indiscriminable as those occurring more remotely.

Because of the debate concerning the area of the brain responsible for temporal order judgments in human amnesic subjects a group of rats having medial prefrontal cortex lesions were also tested on the DNMS task. It has been proposed that animals with prefrontal cortex lesions, like humans with anterior cortical damage, are impaired at

recalling the serial order of events (Kolb, 1984) but the evidence is mainly indirect and inconclusive. This experiment, then, tested rats having medial prefrontal cortex lesions (cingulate areas 1, 2 and 3 of Paxinos and Watson, 1986) on the task of recency judgment in an attempt to establish if animals display the same impairment in sequencing behaviour as human subjects having frontal lobe damage and whether their pattern of performance can be compared to human amnesic subjects.

5.1.2. Methods
5.1.2.1. Subjects
The subjects were 33 male pigmented rats of the DA strain (15 of which were bred by Bantin and Kingman, Hull, UK and 15 at Durham University). All rats were housed individually having a 14/10-h light/dark photoperiod and maintained on 15g of laboratory diet (Beekay Rat and Mouse, Bantin and Kingman, Hull) per day so that their body weights remained at no less than 85% of normal. Water was freely available in the home cage. At the start of the experiment they were aged about 3 months and weighed between 225 and 260g. They were randomly allocated to one of three surgical groups.

5.1.2.2. Apparatus
The animals were tested in an aluminium Y-Maze, each arm of which was 13 cm. wide and 20 cm. high and covered with a wire grid. Thirteen pairs of hardboard boxes (16.5cm. x 11.5cm. x 17cm.) acted as the start and goal boxes. Each member of a pair was made as similar as possible but each pair as distinctive as possible from all other pairs. To do this the walls and floors were painted in different colours and patterns and the boxes contained various junk objects such as perspex cylinders, metal brackets, nuts and bolts and wooden blocks. Each member of a pair contained identical objects but no two pairs contained similar objects. The boxes could be fitted into the ends of the arms of the maze forming a total arm length if 26cm. The floor of the box began 9 cm. from a Y-shaped guillotine door located at the centre of the maze. Reward pellets (45mg, Campden Intruments Ltd.) could be dispensed via a plastic tube and funnel situated above the box. The Y-Maze was illuminated by a fluorescent ceiling light 215 cm. above the apparatus giving a luminant light level of 290 lux.

5.1.2.3. Surgical Procedure
Each rat was anaesthetized by intraperitoneal injection (4 ml/kg) of a solution containing 42 mg/kg of chloral hydrate and 9.7 mg/kg of pentobarbitone sodium (Equithesin). The animal was then placed in a stereotaxic head-holder (David Kopf Instruments). The

scalp was shaved and betadine solution applied before being cut and retracted to expose the skull, part of which was removed with a dental drill exposing the dura over the sagittal sinus.

For the fornix lesions an electrode (stainless steel insect pin), insulated except for the tip (1.2 mm.) was lowered vertically into the fornix at two locations per hemisphere. The stereotaxic coordinates relative to ear bar zero with the incisor bar set at + 5.0 relative to the horizontal zero plane, were AP=+4.4, LAT=+/-0.9 and AP=+4.2, LAT=+/-1.9. In all cases the dorsal/ventral coordinate was 4.0mm below the height of the dura. A radiofrequency current of 20 V/8 mA was passed for 30 secs. at each location in each hemisphere (Grass LM4 Lesion Maker)

An identical procedure was used for the sham operated controls except that the probe was lowered to just above the fornix and then immediately withdrawn with no current being passed.

Medial prefrontal cortex lesions were made by aspiration using a 23 gauge needle attached to a SAM 12 aspirator (Aerosol Products Ltd.). The lesions were carried out under visual control and extended from bregma for 5mm. anteriorly towards the frontal pole and included an area 1.5mm. on each side of the midline. The wounds were packed with sterispon (Allen and Hanbury) soaked in physiological saline.

Sulphanilamide powder was applied in all the rats before suturing the skin. Post operative mangement included heat and oxygen supplement, and injections of etamphylline (35 mg/kg) and buprenorphine (0.15mg/kg). 9 rats received fornix lesions, 15 medial prefrontal cortex and 9 sham operations.

5.1.2.4. Histological Procedure

At the end of the study each rat was perfused intracardially with 5% formol saline. The brains were subsequently blocked, embedded in wax (paraplast), and cut in 10 u coronal sections. Every tenth section was mounted and stained with a Nissl stain (cresyl violet). Every adjacent section was also stained with a fibre stain (luxol fast blue). Each lesion was examined under light microscopy and extent of fibre and cell loss plotted on four coronal sections for the fornix lesions (+6.0, +5.6, +5.2, +4.8) from a stereotaxic atlas (Pelligrino & Cushman, 1967) and five coronal sections for medial prefrontal cortex lesions (+5.2, +3.7, +2.2, +0.7, -1.3) from the Paxinos and Watson, (1986) stereotaxic atlas.

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5.1.2.5. Behavioural Procedure

The rats were handled daily for a week before pretraining began. At the beginning of pretraining the rats were allowed to explore the maze freely for about 10 minutes per day and to eat reward pellets which were scattered around the maze. Blank boxes were placed at the end of each arm. After several days the rat was then trained to move from one arm to another via the guillotine door, which was raised and lowered, and to eat the reward pellets dispensed through the funnels.

Once all the rats were moving readily around the maze and eating the reward pellets the experiment proper began (approximately one week). Each rat received twelve trials a day, five days per week. At the beginning of each session the rat was placed in one of the arms and a blank start box was inserted in the arm. A pair of identical boxes was placed in the other two arms. The guillotine door was raised and the rat allowed to enter one of these arms. The guillotine door was then lowered and three reward pellets were dispensed through the funnel. Trial one then followed in which the rat was given a choice of a box identical to the one that it was already in and a novel box. A choice was deemed to have been made when both hind feet had been placed in the choice arm. If the rat chose the novel box this was designated as correct, the rat was rewarded (after the choice had been made) and, after a period of approximately 20 seconds, the next trial was commenced in which the rat again had to choose between an identical and a novel box.

If an incorrect choice was made a correction procedure was carried out in which the rat was given the same choice of goal boxes until the correct one was selected. If a correct choice had not been made after three correction trials the guillotine door was raised and the rat allowed to wander freely around the maze until it entered the correct box. The guillotine door was lowered and the next trial commenced. During these correction trials the goal boxes were rearranged so that entering the correct box required the same body turn as in the test trial.

The position of the correct box on the test trials was balanced so that there was an equal number of right and left positions per session. Each pair of boxes was encountered once per session and the same set of boxes was used for each session.

When a rat achieved a criterion score of 46 or more correct responses over five consecutive sessions the second phase of the experiment commenced. This consisted of ten sessions in which the goal box was replaced by a blank start box during the 20 second confinement prior to the rat making a choice between familiar and novel box on each

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trial. This prevented the rat from making a simultaneous discrimination thus ensuring reliance on working memory to solve the task. This procedure was used throughout the rest of the experiment.

During the following ten sessions a set of six pairs of boxes was used repeatedly so that each pair was presented twice per session. The same six pairs were presented on trials one to six, and on trials seven to twelve. Order of the boxes was such that the number of intervening trials between the first and second presentation of a particular box as correct least familiar item (lag) was 2, 5 or 8. An equal number of trials were given at each lag. As a consequence, on trials seven to twelve the rat was required to make a judgment of relative recency rather than recognition.

Following the six pair condition a similar procedure was carried out for ten sessions with just four pairs of boxes. The four boxes were presented for recognition on trials one to four and for recency recall on trials five to twelve with an equal number of inter-vening trials ranging from 1 to 5. Five 'normal' sessions were interspersed between the ten days of the four pair condition in which the full set of thirteen boxes was used. A further ten sessions were given using three pairs of boxes with intervening trials of 1, 3 and 2 and five 'normal' days at regular intervals throughout this condition.

Finally, two sessions were run in which a completely novel set of thirteen pairs of boxes was used. Table 5.1 shows a summary of the experimental procedure.

Table 5.1: Summary of the training and experimental conditions of the DNMS task.

	No. of stimuli	No. of sessions
Phase 1: Acquisition		
	13 pairs	To a criterion of 46/60 correct trials in 5 consecutive sessions
Phase 2: Training with blank box inserted between sample and choice trials		
	13 pairs	10 sessions (120 trials)
Phase 3: 6 pair repeated box condition		
	6 pairs	10 sessions (120 trials)
Phase 4: 4 pair repeated box condition		
	4 pairs	10 sessions (120 trials)
	13 pairs	5 sessions (60 trials)
Phase 5: 3 pair repeated box condition		
	3 pairs	10 sessions (120 trials)
	13 pairs	5 sessions (60 trials)
Phase 6: Completely novel set of stimuli		
	13 pairs	2 sessions (24 trials)

5.1.3. Results

5.1.3.1. Histological Results

The fornix lesions produced major damage to the fornix between the posterior portion of the septum and the anterior portion of the hippocampus. In one animal, however, more than half of the fimbria fornix was spared in one hemisphere and the thalamus was quite extensively damaged. As a consequence this rat was excluded from the study. Histological sections for the rats with the most and least damage are shown in figures 5.1 and 5.2 and the median lesion, representative of the remaining rats, is shown in figure 5.3. One animal had a complete transection of the fornix bilaterally and one a complete transection in one hemisphere with sparing of the lateral tip in the other. The remaining animals had sparing of the lateral tips of the fimbria bilaterally. The rat having complete transection of the fornix also exhibited slight medial septal damage. In all cases there was some callosal damage and four had additional cortical damage in the cingulate areas. Only two animals had thalamic damage, which was slight in both cases,

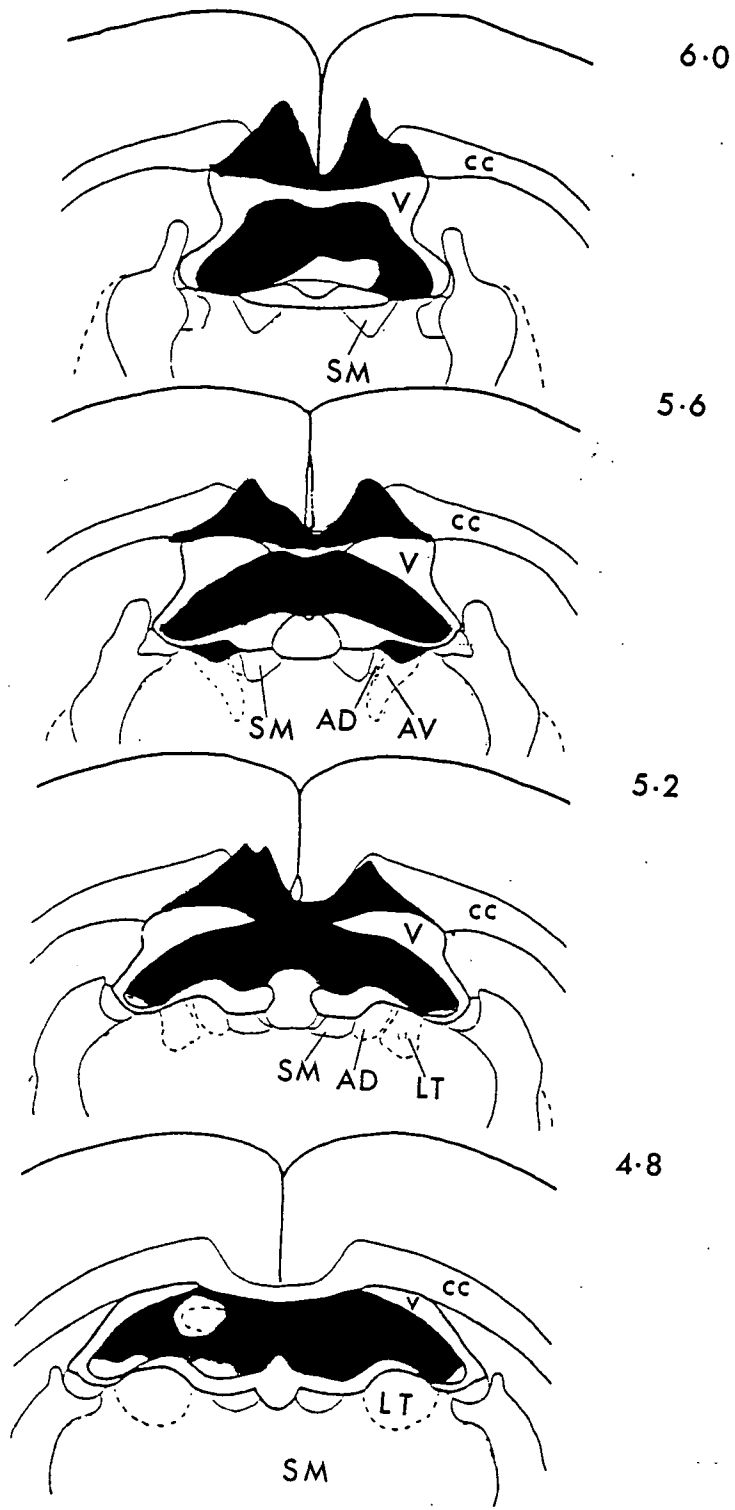**Figure 5.1: Largest lesion in the fornix group.**

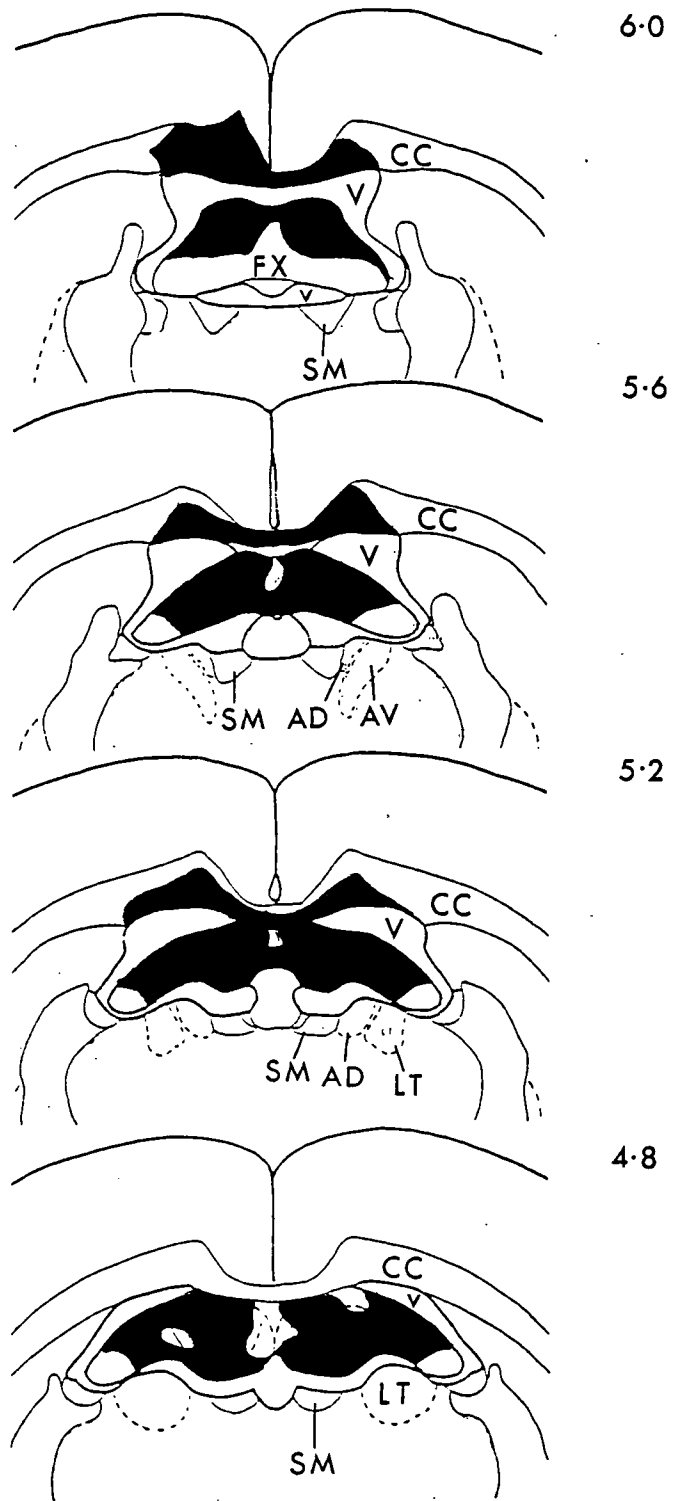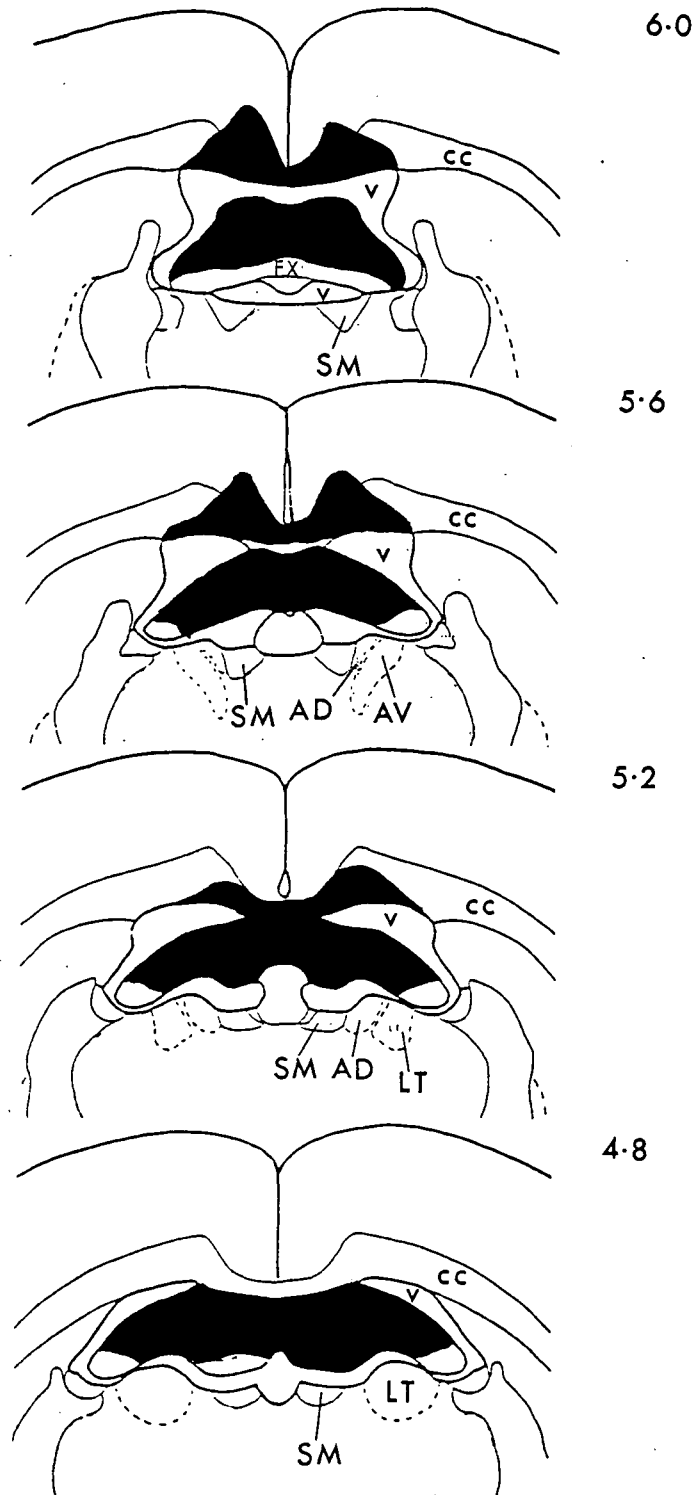**Figure 5.2: Smallest lesion in the fornix group.**

Figure 5.3: Median lesion in the fornix group.

one having damage to the anterodorsal and lateral nuclei in one hemisphere and the other to the anterodorsal and anteroventral nuclei bilaterally. Thalamic damage appeared unrelated to behavioural performance. All rats showed some damage to the most anterior portion of the hippocampus.

Of the animals having prefrontal cortex lesions one had only slight damage and in two the damage was too lateral, leaving the target area intact. These three animals were, therefore, excluded from the study. On the basis of the histology results the remaining twelve rats were divided into two groups, a large and a small frontal group, each containing six animals. The largest and smallest lesions of the rats in the large frontal group are shown in figure 5.4. None of the lesions encroached upon the retrosplenial cortex. Cingulate area 1 (Paxinos & Watson, 1986) was completely removed in one rat, the remaining rats having some sparing in the most posterior portions with slight sparing of the anterior portion in two animals. All rats had some sparing of cingulate area 3 in the most ventral area which was quite large in one rat only. Cingulate area 2 was completely removed in two rats with the remaining four rats having sparing of the most posterior part. All had damage to frontal areas 1 and 2. This was quite extensive in area 2 in all animals except that with the smallest lesion. In general the damage to area 1 was small and most rats had some damage to the medial orbital area. The corpus callosum was transected in all animals and three rats had some septal damage. This was slight in two rats, the lateral septal nucleus being clipped dorsally whilst one rat had more extensive lateral septal damage. Septal damage was not found to relate to performance on the experimental tasks.

The largest and smallest lesions of the small frontal group are shown in figure 5.5. Again the lesions did not encroach on the retrosplenial cortex. There was some sparing of cingulate area 1 in all rats. In three animals this was slight, although in two the lesion was asymmetrical with greater sparing in one hemisphere. In the remaining three rats approximately 33 to 66 % was removed. There was also some sparing of cingulate area 2 in all rats, this being the most posterior segment. Four rats had only a small amount of damage to cingulate area 3, two had more extensive damage with the most ventral portion spared. None of the animals had damage to frontal area 1 but all had some damage to area 2. The corpus callosum was encroached in only one rat but this was not a complete transection.

There was no evidence of retrograde degeneration in the dorsomedial thalamic nucleus in any of the rats with medial prefrontal cortex lesions.

Figure 5.4: Largest (cross hatched shading) and smallest (dark shading) lesions in the large frontal group.
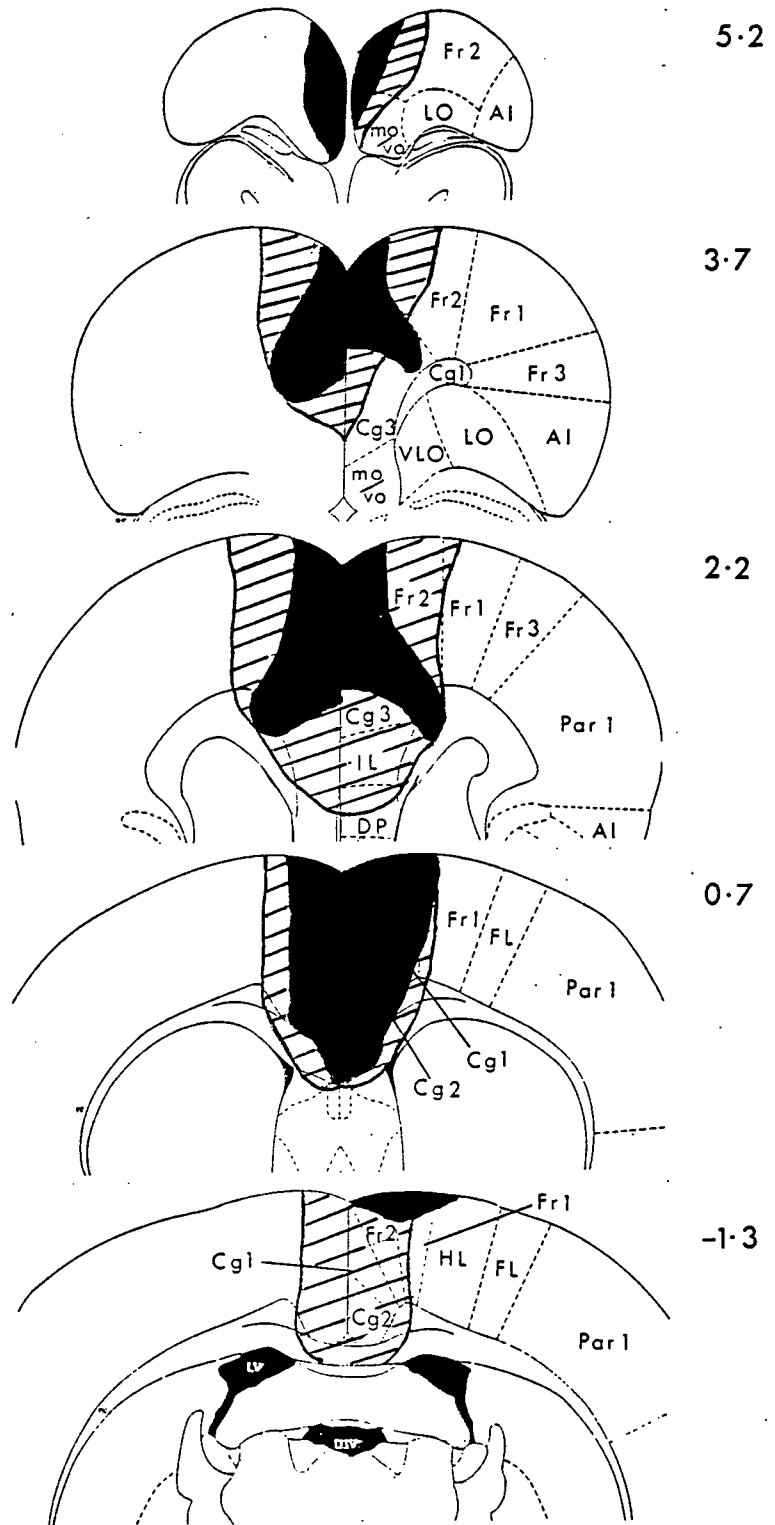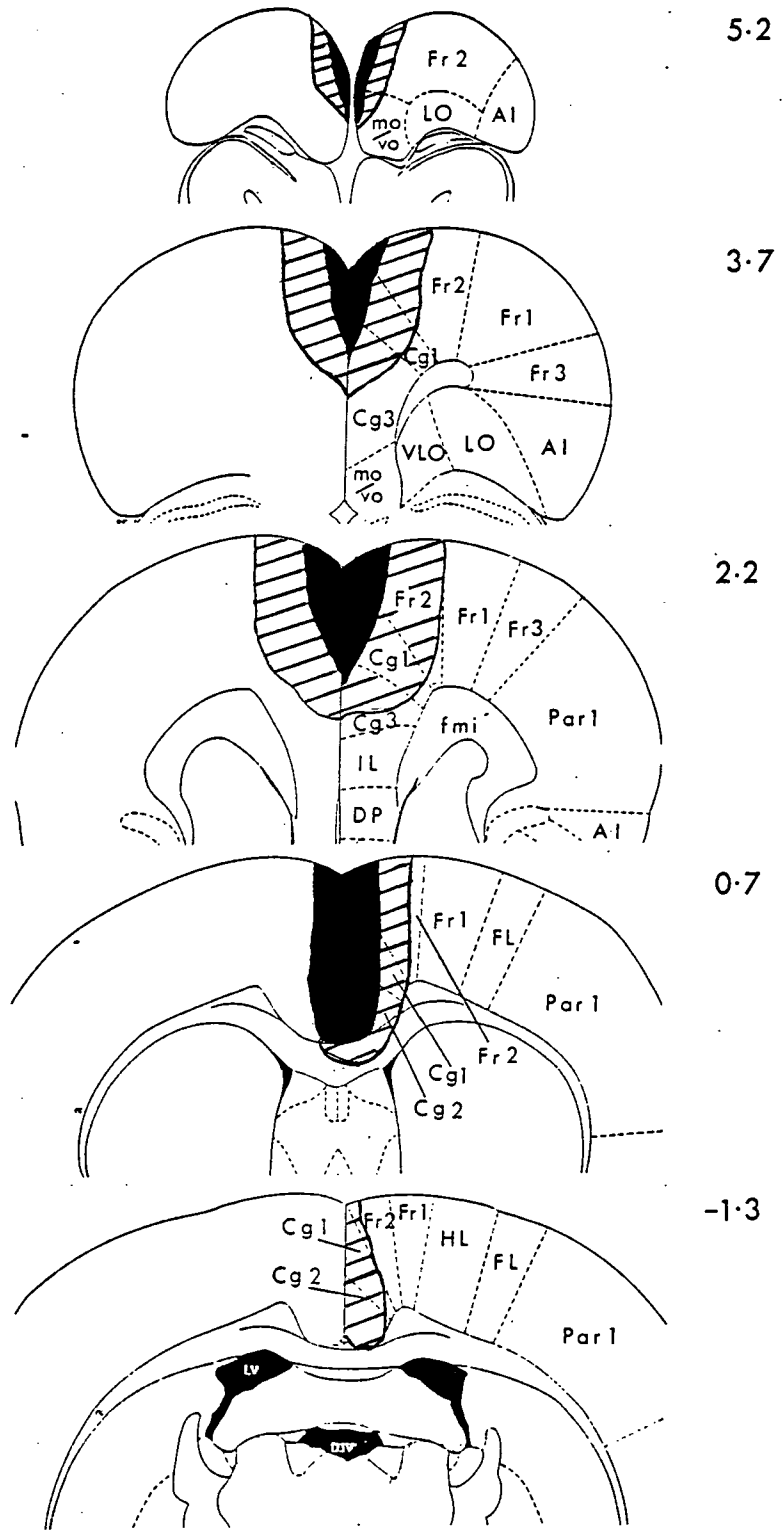
Figure 5.5: Largest (cross hatched shading) and smallest (dark shading) lesions in the small frontal group.

5.1.3.2. Behavioural Results

Following histological analysis the groups contained 9 controls, 8 fornix, 6 large frontal and 6 small frontal.

Acquisition

Figure 5.6a shows the mean number of days for each group to reach criterion. The animals in the large frontal group took most days to reach criterion with a mean of 22.3, followed by the control animals with 20.9, then the rats in the small frontal group with 19.8 and the rats with fornix lesions the least with 12.4. This difference between the groups failed to reach significance as shown by a one way analysis of variance [$F(3,25) = 2.14$] and no two groups differed significantly from each other.

Although the fornix group's performance in terms of days to reach criterion was not significantly better than that of the other groups they did exhibit superior performance during acquisition which was confirmed by analysis of variance main effect of group in a comparison of the number of correct trials during the first ten sessions [$F(3,25) = 22.81, p<.0001$]. Subsequent comparisons revealed that the fornix group was better than each of the other three groups (Neuman-Keuls, all p<.05) Patterns of performance were, therefore, examined in greater detail to assess if spatial factors were responsible for their speed of acquisition of the task. Although an equal number of right/left body turns occurred within a session the number of returns required to the arm that the animal had just left exceeded the number of entries to a different arm in order to make a correct choice (See figure 5.7). Entries required to the previously visited arm ('*same*' arm) were 7 and to a '*different*' arm 4 in each session. The % correct on entering the '*same*' or '*different*' arm were analysed for the first 10 days of acquisition and for the 5 intervening normal sessions in the 3 pair condition.

Although all groups tend to make less errors when a correct choice requires entry into a '*different*' arm during the first ten days of acquisition, this appears to be more marked in the control group (figure 5.8a). By the end of the experiment this effect has disappeared with the control group making only slightly less errors when required to enter a '*different*' arm whilst in all the other groups the pattern is reversed (figure 5.8b). An analysis of variance was carried out with the factors group, beginning/end i.e. the first 10 days acquisition vs the 5 normal days of the three pair condition and same/different arm.

Figure 5.6a: Number of days to criterion for all groups in the DNMS.

Figure 5.6b: Mean % correct on trials using repeated boxes in the DNMS for each group in the 6 pair, 4 pair and 3 pair conditions.

5.6a DAYS TO CRITERION

FX = FORNIX LESIONS

C = SHAM OPERATED CONTROL

SF = SMALL FRONTAL
        LESIONS

LF = LARGE FRONTAL
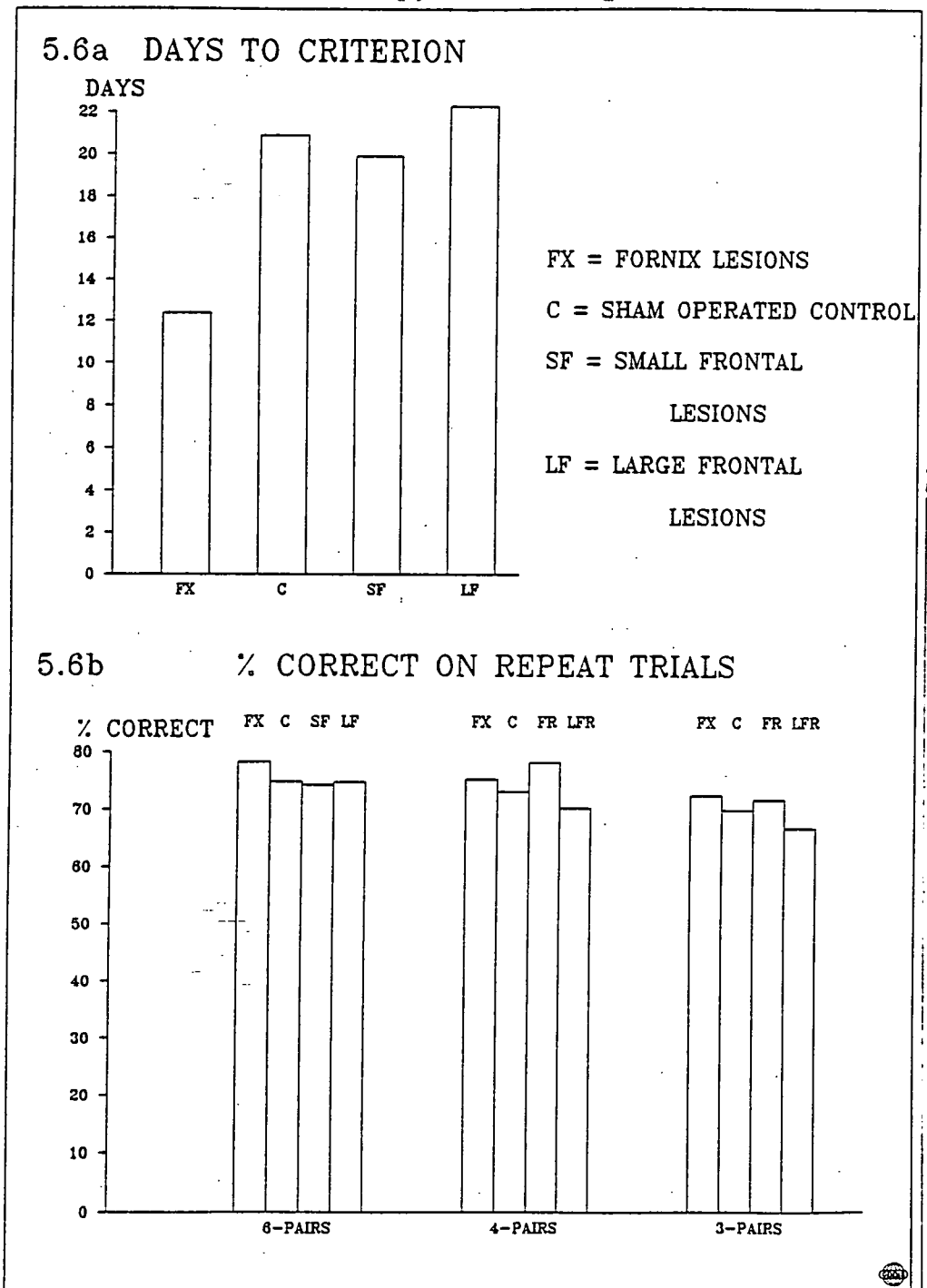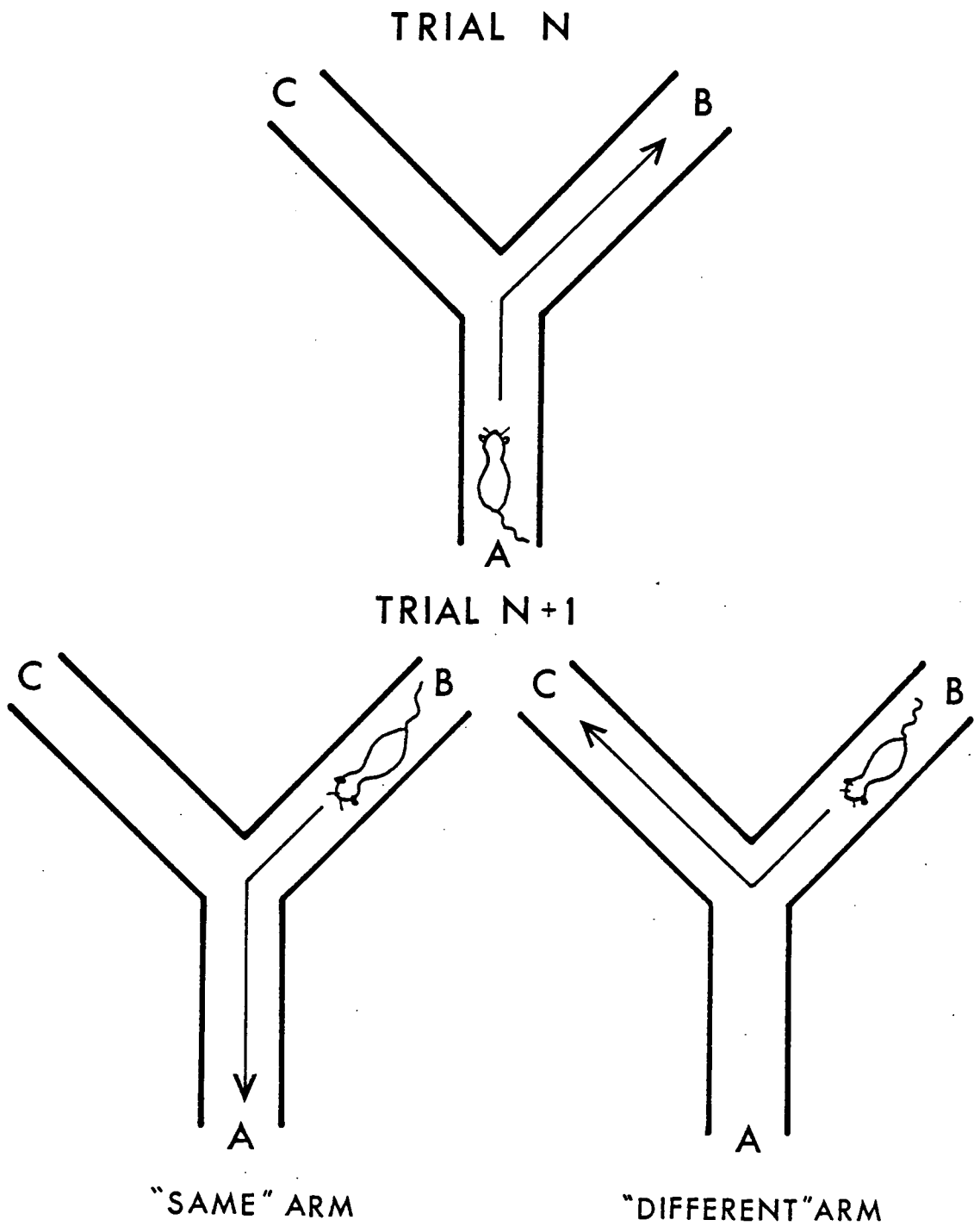   LESIONS

5.6b % CORRECT ON REPEAT TRIALS

Figure 5.7: 'Same' arm and 'different' arm responding in the DNMS task. If the rat leaves arm A and enters arm B on trial N a 'same' arm correct response requires the rat to re-enter arm A on trial N+1 whereas a 'different' arm response requires the rat to enter arm C on trial N+1.

TRIAL N

TRIAL N+1

"SAME" ARM   "DIFFERENT" ARM

There was a significant difference between groups in overall % correct [*F(3,25) = 5.77, p=.004*]. Pairwise comparisons revealed that this was due to the fornix group achieving higher scores than both frontal groups [*fornix vs large frontal F(1,12) = 15.7, p=.002; fornix vs small frontal F(1,12) = 6.34, p=.027*]. and the control group higher scores than the large frontal group [*F(1,13) = 7.34, p=.018*]. All groups improved performance over the experiment with the % correct being significantly higher at the end of the experiment compared to the beginning [*F(1,25) = 318.55, p<.001*]. The groups differed in their improvement across the experiment as shown by a significant group X beginning/end interaction [*F(3,25) = 4.11, p=.017*]. This significant effect was a result of the control and the small frontal animals improving to a greater extent than the fornix group across the experiment [*control vs fornix F(1,15) = 10.09, p=.006; small frontal vs fornix F(1,12) = 6.36, p=.027*]. The main effect of same/different failed to reach significance [*F(1,25) = 3.22, p=.085*] with the mean overall % correct on entering a '*same*' arm being 73.1 as opposed to 76.3 for entering a '*different*' arm. This pattern of performance varied between groups as the group X same/different interaction was statistically significant [F(3,25) = 3.02, p=.048]. This interaction was brought about by the control group's greater increase on '*different*' arm responding compared to '*same*' arm than all the other three groups [*control vs fornix F(1,15) = 6.07, p=.026; control vs small frontal F(1,13) = 5.83, p=.031; control vs large frontal F(1,13) = 14.15, p=.002*]. All groups showed a different pattern of performance at the end of the experiment as compared to the beginning as shown by a significant beginning/end X same/different interaction [*F(1,25) = 57.48, p<.001*] This pattern only differed between the two frontal and the fornix groups as both large and small frontal groups show a greater decrease in '*different*' arm correct responding at the end of the experiment [*large frontal vs fornix F(1,12) = 10.13, p=.008; small frontal vs fornix F(1,12) = 5.56, p=.036*].

In view of the relative insensitivity of the fornix animals to spatial predispositions the data from the Aggleton, Hunt and Rawlins (1986) experiment, which tested rats with hippocampal lesions on the DNMS Y-Maze task was analysed in the same way. Figure 5.9 shows the correct entries to the '*same*' and '*different*' arm on the first 120 trials of acquisition and the last 150 trials of the experiment for the hippocampal group and the sham operated animals and cortical controls combined. Analysis of variance revealed significant interactions of beginning/end X same/different [*F(1,17) = 4.71, p=.045*] and group X same/different [*F(1,17) = 8.99, p=.008*]. The experimental and control groups show a very similar pattern of results to the animals in the present study apart from a lower level of performance of the animals with hippocampal lesions compared to the animals with fornix lesions. This data from the last 150 trials cannot be directly

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Figure 5.8: Mean % correct when choice requires entry to the 'same' or 'different' arm from that of trial N-1 for the first 10 days (120 trials) of acquisition (5.8a) and for the 5 intervening normal days in the 3 pair condition (5.8b) in the DNMS task.

% CORRECT

5.8a: 10 DAYS ACQUISITION

FORNIX
CONTROL
LARGE FRONTAL
SMALL FRONTAL

SAME   DIFFERENT
SAME OR DIFFERENT ARM

5.8b: 5 NORMAL DAYS − 3 PAIR CONDITION

% CORRECT

CONTROL
FORNIX
SMALL FRONTAL
LARGE FRONTAL
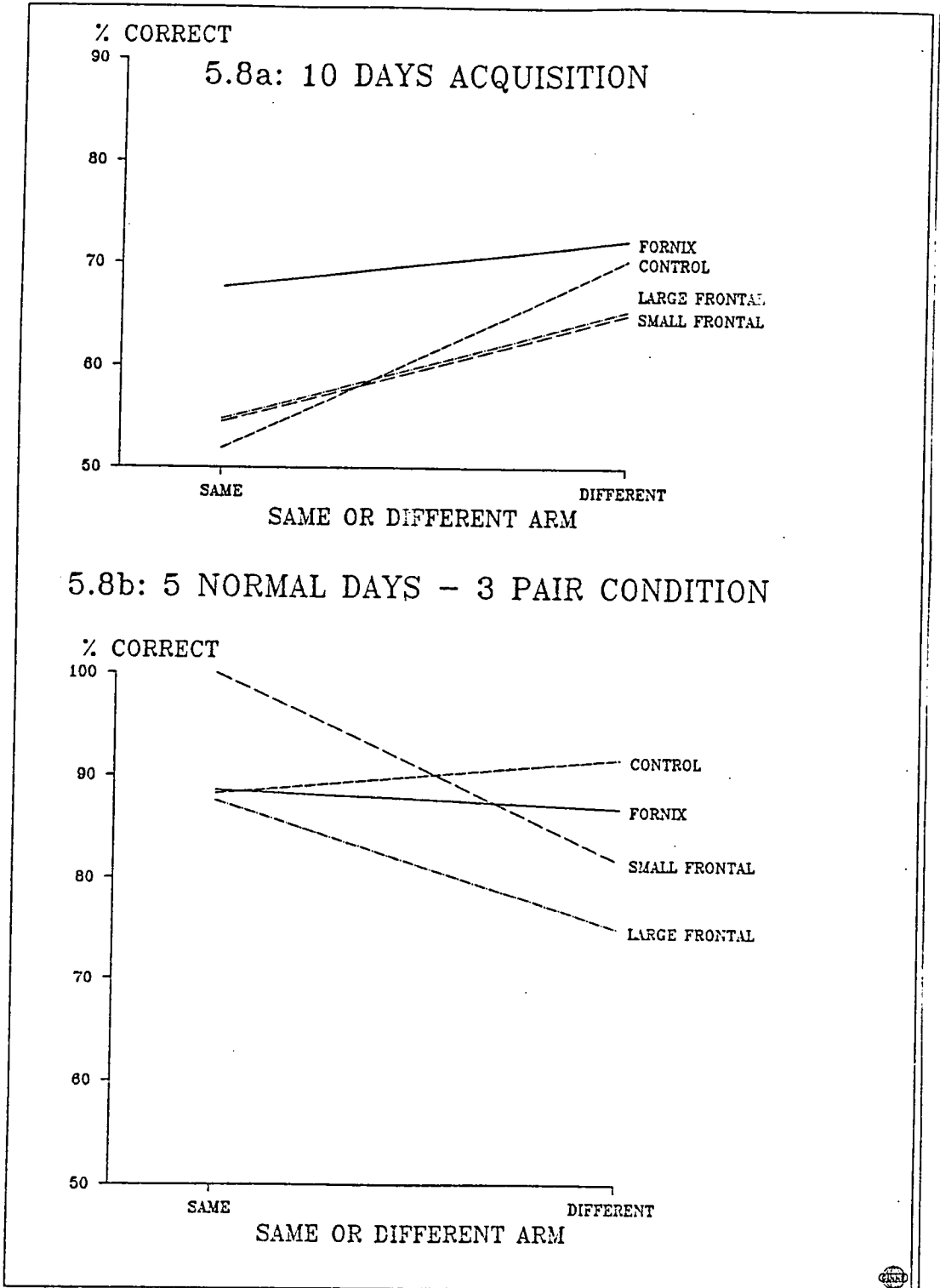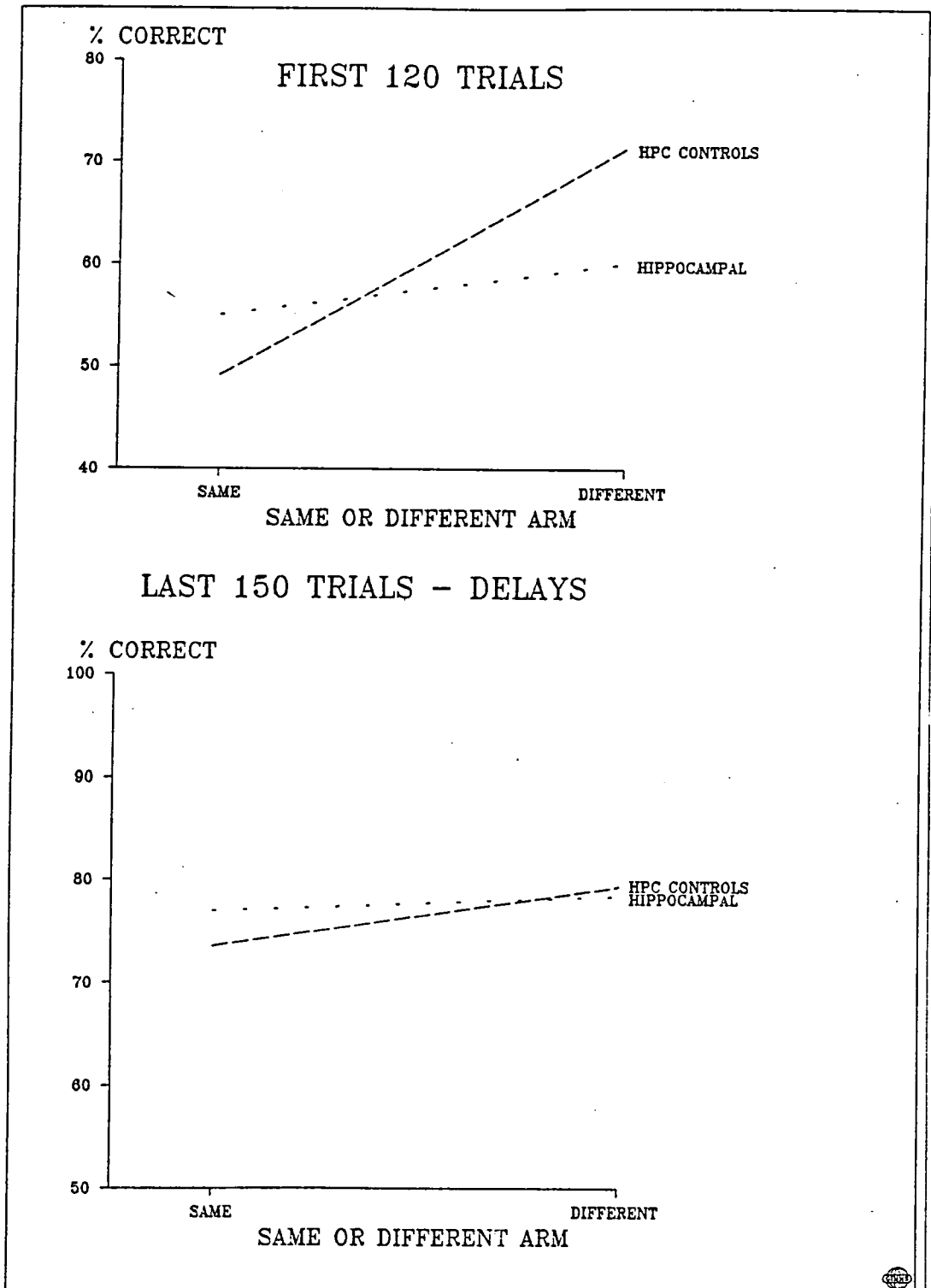
SAME   DIFFERENT
SAME OR DIFFERENT ARM

Figure 5.9: Mean % correct on entering the 'same' or 'different' arm in the DNMS task to that entered on trial N-1 for the control and hippocampal groups of the Aggleton, Hunt & Rawlins (1986) study.

compared to the performance of the rats in the present study as in the Aggleton et al. (1986) experiment the animals were carrying out the task with delays of up to 60 seconds between information and choice trials. As in the present study the control animals make less errors when the correct choice requires entering a '*different*' box at the start of the experiment whereas at the end of the experiment this effect has almost disappeared. The rats with hippocampal lesions, on the other hand, show no difference in their pattern of performance at the beginning and end of the experiment with only slightly better scores on entering a different box.

Performance with repeated stimuli.
The mean per cent correct on the repeat trials for the 6, 4 and 3 pair conditions are shown in figure 5.6b. There was little difference between the groups on any of the conditions as revealed by a non-significant main effect of group in an analysis of variance. Performance declined with decreasing number of stimuli which was confirmed by a significant main effect of condition [$F(2,50) = 6.71$, p=.003]. There was no difference between the groups, however, in this decline in performance across the conditions as the group X condition interaction was not significant [$F(6,50) = .69$].

The mean % correct at each lag in each condition is shown for all the groups in figure 5.10. All groups improve performance as the lag increases in all conditions. Analyses of variance were carried out comparing all the groups in each condition across lags. There was no group effect in any of the experimental conditions but there were significant effects of lag confirming the increase in % correct with increase in lag [**6 pairs** $F(2,50) = 11.94$, p<.001; **4 pairs** $F(4,100) = 9.80$, p<.001; **3 pairs** $F(2,50) = 13.35$, p<.001]. There was no difference between the groups in their lag effect as none of the group X lag interactions proved significant.

The initial trials of each session in which the stimuli were presented for the first time did not require a recency judgment in the same way as those trials in which the stimuli were repeated. These trials were thus considered control trials, that is, trials 1 - 6 in the 6 pair condition; 1 - 4 in the 4 pair condition and 1 - 3 in the 3 pair condition. Analysis of variance was carried out comparing performance on the control trials with that on the repeat trials in each condition. All groups achieved higher scores on the control trials as confirmed by main effects of type of trial [*6 pairs $F(1,25) = 55.21$, p<.001; 4 pairs $F(1,25) = 100.46$, p<.001; 3 pairs $F(1,25) = 78.30$, p<.001*]. There was no significant difference between the groups in overall performance. There was no interaction between group and trial type (repeat or control) except in the four pair condition which

did reveal a significant interaction [$F(3,25) = 3.91$, $p=.02$]. Pairwise comparisons

Figure 5.10: Mean % correct in the DNMS at each lag for all groups in each experimental condition, and mean % correct on control trials and intervening normal days for each condition.
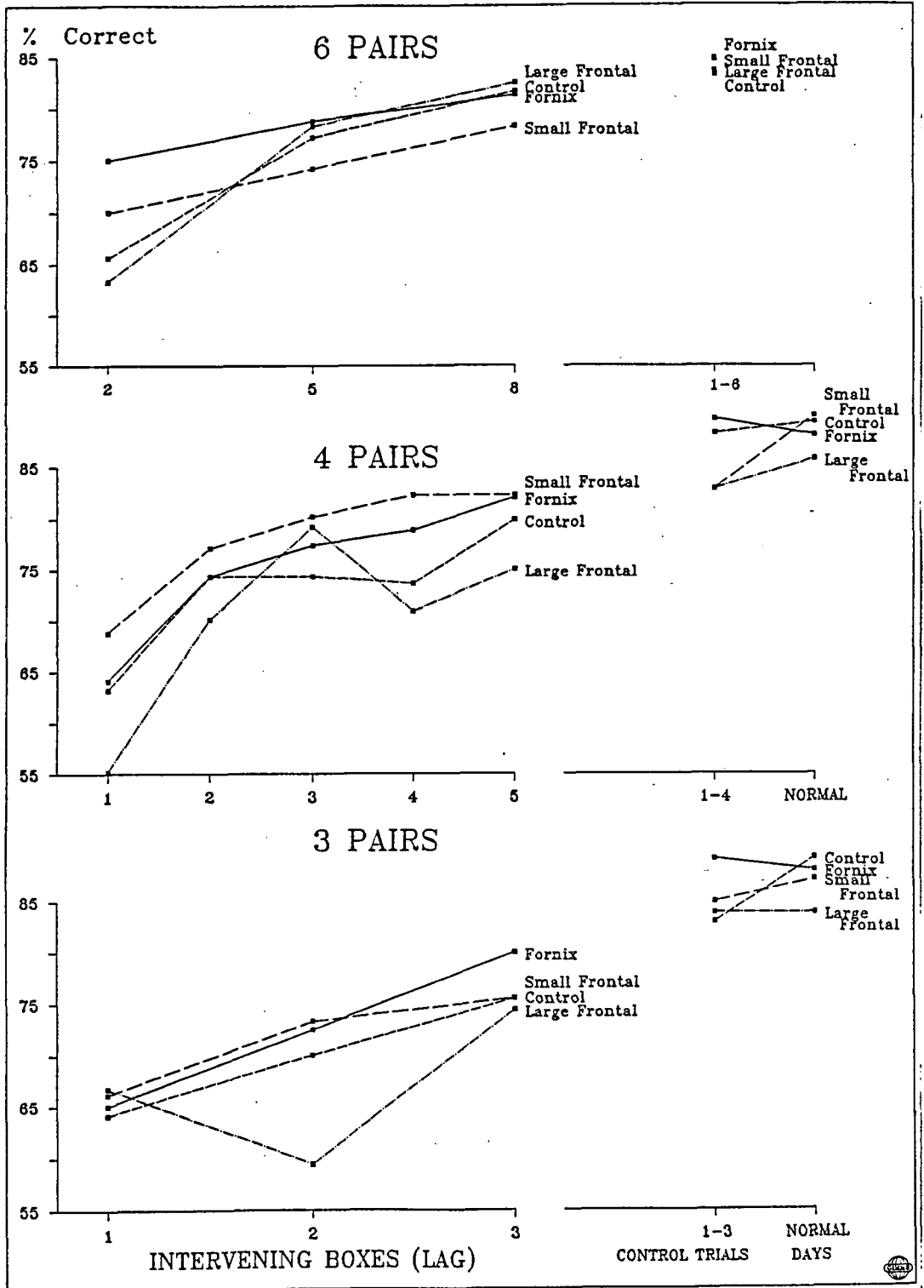
revealed that this interaction was due to the small frontal group having a smaller differential between performance on the repeat trials and control trials than any of the other groups [*small frontal vs controls $F(1,13) = 9.84, p=.008$; small frontal vs large frontal $F(1,10) = 9.28, p=.012$; small frontal vs fornix $F(1,12) = 11.82, p=.005$*]. The small frontal group performed similarly to the other groups on the control trials but this interaction was brought about by their performing slightly better than the other groups on the repeat trials.

The inclusion of five intervening normal sessions in the 4 and 3 pair conditions also makes it possible to check baseline performance. Performance was higher on the intervening normal sessions compared to repeat sessions in all groups as shown by analyses of variance main effects of type of trial [*4 pairs $F(1,25) = 116.31, p<.001$; 3 pairs $F(1,25) = 239.41, p<.001$*] but there was no difference between the groups in % correct overall or in the difference in performance on repeat and normal sessions.

The fornix group achieved a mean number correct on the two final sessions with completely novel stimuli of 21.6 whereas the control group achieved 20.3, the large frontal group 19 and the small frontal group 18.7. This difference between the groups just failed to reach significance in a one way analysis of variance [*$F(3,25) = 2.843. p=.058$*]. The Neuman-Keuls test showed no two groups to differ significantly from each other at the .05 level.

5.1.4. Discussion

All three experimental groups, the animals with fornix lesions, and small and large frontal lesions were unimpaired on all measures of the DNMS task. As expected all groups showed a decline in performance as the number of stimuli decreased but none of the lesion groups were differentially affected by the number of stimuli. Therefore, all three groups were unimpaired at making recency judgments even with high levels of temporal interference. There was also no evidence of an impairment in temporal tagging in the performance of these animals across lags. The three experimental groups showed a similar increase in performance to the control group as the number of intervening boxes increased.

All three experimental groups appeared to show some lack of sensitivity to spatial factors. The rats natural predisposition is to alternate their spatial responses and this resulted in the control animals being more likely to make an incorrect response when required to enter the arm that they had just left in the early stages of training. The animals with fornix lesions and both large and small frontal cortex lesions appeared to

be insensitive to these spatial factors. As the schedule of right and left turns contained more same arm correct choices, this could have inadvertantly inflated the experimental groups' scores compared to the control group's. But it is clear that by the end of the experiment this spatial predisposition has disappeared from the control group. It seems unlikely, therefore, that this spatial bias could explain the good performance of the experimental groups. The frontal groups did, in fact, show a reverse pattern at the end of the experiment having higher scores when required to enter the same arm. This could possibly be due to perseverative tendencies in the frontal animals rather than spatial factors alone. Perseverative responding is more common with orbitoventral lesions but most animals did sustain some damage to medial orbital and ventral orbital areas at the most rostral aspect of the lesion.

The Aggleton, Hunt and Rawlins (1986) experiment tested animals with aspiration lesions of the hippocampus on the DNMS task using the same apparatus and acquisition procedure including the same spatial schedule of responses. A similar lack of sensitivity to spatial factors was found in those animals with hippocampal lesions as the rats with fornix lesions in the present experiment. As the effect was eliminated by the end of the experiment it is, again, unlikely that the spatial impairment in the animals with hippo-campal lesions can account for the negative results found in that study. It is possible that this artifact aids acquisition of the task but probably has little effect once the task is learned.

Rawlins, Lyford and Seferiades (1991) suggested that temporal interference factors could explain the inconsistencies in the results of DNMS experiments. In particular they pointed to two factors, the type of stimuli used and the degree to which they were reused within a session. All the studies showing an impairment in DNMS in rats with hippocampal system damage used stimuli that varied only in surface texture and shade except for their own experiment that used 'Aggleton goal boxes' containing three dimensional objects. This experiment used just two stimuli and produced an initial impairment that was alleviated with practice. This experiment is the closest in proce-dure to the present experiment which also used 'Aggleton goal boxes' and in the last condition utilised three pairs of stimuli. The main difference between this and the Rawlins et al (1991) study is that the present experiment trained the rats using a rela-tively large set of stimuli (thirteen pairs of goal boxes) the set size being gradually reduced over the experiment. Rawlins et al (1991) also found no impairment when using trial unique 'Aggleton goal boxes'. It would appear that these temporal interfer-ence factors are important in acquisition of the DNMS task but once the task has been learned they do not affect performance. An obvious comparison to make would be the

acquisition of the task using the procedure employed in the present experiment but with just three pairs of stimuli from the outset. Pilot studies have shown, however, that normal rats could not learn this task, still performing at chance levels after 400 trials.

Acquisition of the DNMS using few or many stimuli could affect the nature of the task as suggested by Jagielo, Nonneman, Isaac and Jackson-Smith (1990). They proposed that using a small number of stimuli to train the animals requires a conditional discrimination whereas using a larger set of stimuli requires the rat to learn a single response, that is, to always approach the novel object. The results of the present experiment give some support to this hypothesis as the task was not learned as a conditional discrimination as performance was not affected by the introduction of a completely novel set of stimuli in the last two sessions of the experiment. An impairment in conditional operations would render the animal sensitive to temporal interference as conditional discriminations require the allocation of events to their correct temporal context. It is surprising, then, that increasing temporal interference in the manner of the present experiment had no effect on performance of the fornix group at all. It is possible that temporal factors were not required to make the recency judgment in the small set conditions. The animals could have used trace strength as an indicator of the recency of the presented items. In always having to approach the least recently seen item the rat could solve the problem by always entering the goal box having the least trace strength. Experiment 8 will examine this issue in more detail.

From this experiment there was no evidence that prefrontal cortex lesions in rats produce a similar impairment in recency judgment as that shown by human subjects having frontal lobe damage. Neither the small nor the large frontal group showed any impairments in any of the DNMS measures. However, there was some sparing of cingulate areas 1, 2 and 3 even in the large frontal group and in most animals the infralimbic area was intact. It is possible that more complete lesions would have produced an impairment but there is also the possibility, as has already been mentioned, that rats were using attributes other than temporal tagging to make the recency judgment.

The following experiment addresses the question of whether the lack of impairment in both rats with fornix and prefrontal cortex lesions was a result of the inadequacy of the lesions behaviourally by testing the animals on a spatial delayed alternation task. Both fornix and frontal lesions have produced impairments in this task, although this is generally more marked in animals with fornix lesions.

5.2. Experiment 7: Delayed alternation in a T-Maze by rats with fornix and medial prefrontal cortex lesions.

5.2.1. Introduction

In view of the high level of performance of the experimental animals in the previous experiment the lesions were assessed behaviourally using a spatial delayed alternation procedure. Damage to the hippocampal system including lesions to the fornix typically produce impairments in spatial working memory tasks such as delayed alternation (Johnson, Olton, Gage & Jenko, 1977; Stevens & Cowey, 1973). In this task the animal is first of all given an information run in which it is forced to enter one arm of a T-Maze where it receives a reward. This is followed, after some delay, by a choice run in which the rat is allowed to choose which arm to enter. The rat is then rewarded for entering the opposite arm to that of the information run.

Tonkiss, Feldon and Rawlins (1990) found that fornix lesions produced an initial impairment in acquisition of a T-maze task at 0 secs. delay but the animals improved to control levels over eight days of testing. Introducing a delay of 20 secs., however, produced greater impairment in the lesioned animals. Accordingly the present experiment tested the rats that took part in experiment 6 on a T-maze alternation procedure using a 20 sec. delay between information and choice run.

As discussed in Chapter 2, animals with prefrontal cortex lesions generally show impairments in delayed alternation and delayed response tasks. This impairment appears to be dependent upon the size of the lesion (Silva, Boyle, Finger, Numan, Bouzrara & Almli, 1986; Thomas & Spafford, 1984). Animals having small lesions tend to show initial impairment which is attenuated with practice (Thomas & Spafford, 1984; Van Haaren, De Bruin, Heinsbroek & Van De Poll, 1985) although rats with large lesions have also been shown to relearn the alternation task post-operatively but at a slower rate than controls (Thomas & Brito, 1980).

It is expected, then, that the rats having fornix lesions will show a significant impairment in the alternation task relative to the control animals and that the rats having medial prefrontal cortex lesions will show an initial impairment that improves across sessions and that this impairment will be dependent upon the size of the lesion.

5.2.2. Methods
5.2.2.1. Subjects
The subjects were those animals that took part in experiment 6. The rats that were excluded from the previous experiment because of the inadequate lesions were also excluded from this experiment. This resulted in a group of 8 rats having fornix lesions, 9 sham operated control, 6 small frontal and 6 large frontal.

5.2.2.2. Apparatus
The T-maze had an aluminium floor and clear acrylic sides 17 cm. high. The stem of the maze was 80 cm. long with an aluminium guillotine door 33 cm. from the beginning. The cross piece was 136 cm. long with a food well 4 cm. wide and 0.75 cm. deep at each end. The maze was supported on stands 93 cm. high and was illuminated by fluorescent room lights suspended 92 cm. above the apparatus. At the choice point and the food wells the luminant levels were 320 and 280 lux respectively. Testing was carried out in a different room from that used in experiment 6, and provided a number of salient spatial cues.

5.2.2.3. Behavioural Procedure
Testing on the T-maze commenced between one and three weeks after completion of experiment 6. Each rat was given two days pretraining before starting the experiment proper. On the first day the animal was allowed to wander freely around the maze and eat reward pellets (45 mg., Campden Instruments ltd.) from the food wells for a period of approximately 20 minutes. On the second day the rat was trained to run from the start box to either of the food wells where it was allowed to eat three pellets.

The rats were tested in groups of three or four for six trials a day so that there was an inter-trial interval of approximately three to five minutes. Each trial consisted of an information and a choice run. Prior to each information run three food pellets (45 mg. Noyes) were placed in each food well and a wooden block was placed at the choice point to force the rat to enter either the right or left arm. There was an equal number of right and left information runs each day presented in a predetermined random order. The rat was placed in the start box, the guillotine door raised, and the rat allowed to run down the maze and into the open arm to the food well. After eating all the food pellets the rat was lifted out of the maze and returned to the start box where it was confined for a period of 20 secs. before making the choice run. The wooden block was removed from the choice point, the guillotine door again raised, and the rat allowed to run down the maze to the choice point. The rat was free to enter either arm and once both hind feet had been placed in a goal arm a choice was deemed to have been made. If a correct

choice had been made, that is if the rat entered the arm not entered in the information run, it was allowed to eat the reward before being removed to its home cage. If an incorrect choice was made the rat was confined in the arm for a few seconds before being removed.

Testing was carried out for twelve days giving a total of seventy two trials.

5.2.3. Results

Figure 5.11 shows the mean number correct in each block of 12 trials (2 sessions) for all groups. The control animals perform at a higher level than both the large frontal and fornix groups. The small frontal group's performance was lower than that of the control group over the first four sessions but rapidly improved thereafter. The fornix group performed at chance for the first three sessions and improved slightly in the last three sessions.

Analysis of variance was carried out comparing all four groups with the factors group and block. The groups differed significantly in the overall number correct [$F(3,25) = 53.94, p<.001$]. Pairwise comparisons revealed this effect to be due to the fornix group performing significantly worse than each of the other three groups [*fornix vs controls* $F(1,15) = 266.01, p<.001$; *fornix vs small frontal* $F(1,13) = 18.55, p=.001$; *fornix vs large frontal* $F(1,12) = 35.91, p<.001$] and both the small frontal and large frontal groups performing significantly worse than the control group [*small frontal vs control* $F(1,13) = 11.17, p=.005$; *large frontal vs control* $F(1,13) = 8.02, p=.014$].

All groups improved their performance across sessions as shown by the main effect of block [$F(5,125) = 10.29, p<.001$] but not all the groups improved to the same extent as the group X block interaction was significant [$F(15,125) = 2.12, p=.013$]. The small frontal group exhibited greater improvement across the experiment than all other groups [*small frontal vs control* $F(5,65) = 3.00, p=.017$; *small frontal vs large frontal* $F(5,50) = 4.83, p=.001$; *small frontal vs fornix* $F(5,60) = 2.71, p=.028$].

Figure 5.11: Mean Number correct on each block of 12 trials (2 sessions) in the T-Maze alternation for all groups.
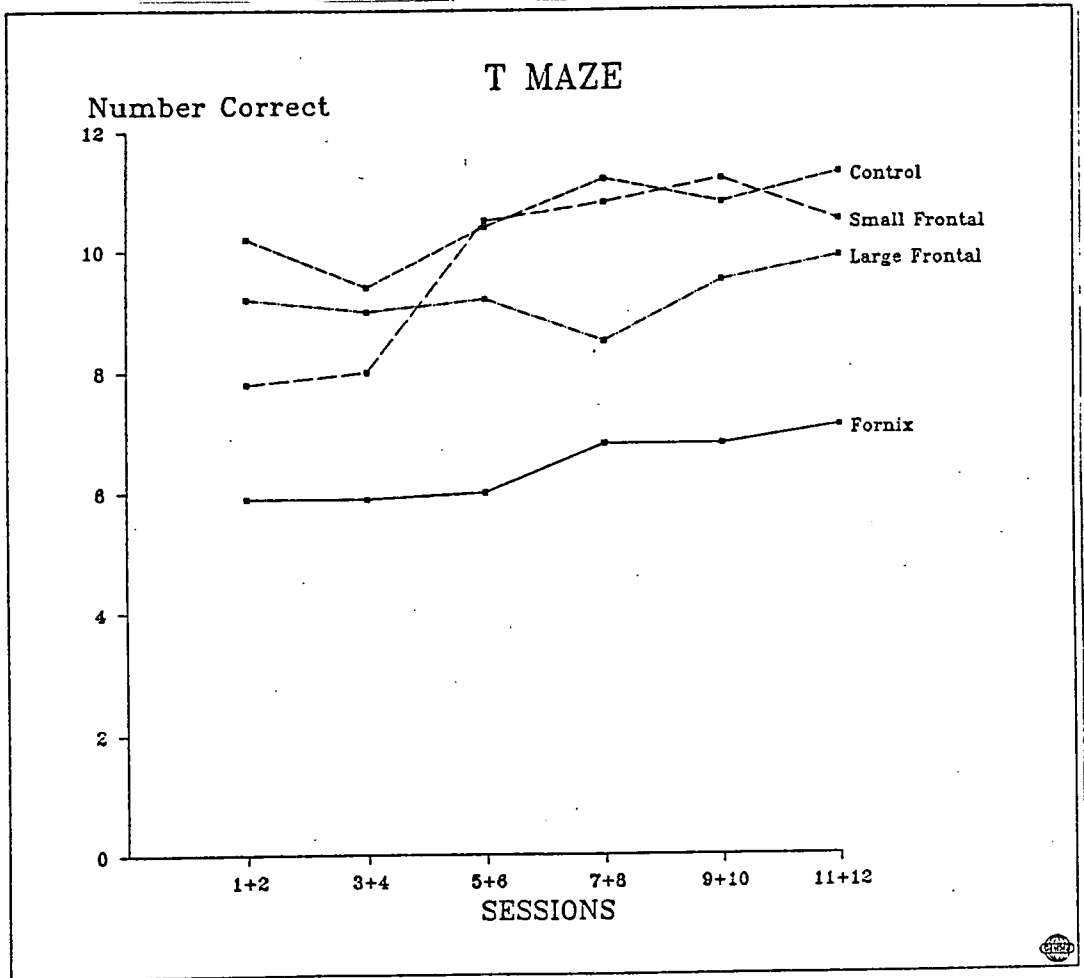
5.2.4. Discussion

All three experimental groups performed significantly worse than the control group on this spatial delayed alternation test. In striking contrast to their performance on the DNMS task the fornix group were performing at levels not much better than chance in the T maze alternation. The animals with smaller lesions in the prefrontal cortex groups achieved somewhat higher scores than those with larger lesions although not significantly so. They did, however, improve across sessions to a greater extent than the larger frontal group. This confirms the prediction that the rats with prefrontal cortex lesions would be impaired, but that this would be attenuated with practice and also that performance would be dependent upon lesion size.

These findings suggest that the results of the previous experiment cannot be attributed to inadequate lesions as the present test, known to be sensitive to such lesions, produced significant impairments.

5.3. Experiment 8: Delayed non-matching to sample in normal rats.

5.3.1. Introduction

The DNMS procedure carried out in experiment 6 was designed to test the animals' ability to make recency judgments and it was assumed that this would require the use of specific temporal information. That is, that the rat would assign a temporal tag to each occurrence of a stimulus and then base their recency judgments upon this information. It is possible, however, that the recency judgment did not depend upon temporal information but upon the strength of the trace of the stimulus. The DNMS procedure requires the animal to choose the novel or least recently encountered object which in all cases is the object with the least trace strength.

Trace strength depends upon a number of attributes including the frequency of presentation of the stimulus, the recency of presentation and the length of time that it is presented. This experiment attempted to resolve the issue of how the rat makes the recency judgment in the DNMS procedure by increasing the frequency of presentation of the target stimulus, thus increasing its trace strength. This manipulation should prevent the rat from making a correct choice by entering the goal box having the least trace strength. The rat was forced to enter a goal box on two occasions in succession. This goal box was then re-presented at a later point in the session as the correct least familiar stimulus. The rat had then to choose between a goal box entered once but more recently and one entered twice but less recently. Therefore, an increase in trace strength of the target stimulus would have a detrimental effect on the rats performance if it relies upon trace strength to make the recency judgment but if it relies upon temporal tagging it is likely that the manipulation would improve performance. By entering the goal box twice the rat has two temporal tags assigned to that stimulus both of which occurred in the more distant past than that of the alternative stimulus and presumably the rat is more likely to be able to discriminate the item which occured least recently, the more temporal tags it has assigned to it.

5.3.2. Methods
5.3.2.1. Subjects
The subjects were 8 naive rats of the DA strain (Bantin and Kingmam, Hull). All rats were housed individually having a 14/10-h light/dark photoperiod and maintained on 15g of laboratory diet (Beekay Rat and Mouse, Bantin and Kingman, Hull) per day so that their body weights remained at no less than 85% of normal. Water was freely available in the home cage. At the start of the experiment they were aged about 3 months

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and weighed between 225 and 260g.

5.3.2.2. Apparatus

The apparatus was the same as that used in experiment 6.

5.3.2.3. Procedure

The initial procedure was the same as that carried out in phase 1 (acquisition) of experiment 6. All rats were trained to a criterion of 46 correct responses in five consecutive sessions. The same 13 pairs of goal boxes were used as in experiment 6. The second phase of the experiment was carried out for two sessions instead of the ten given in experiment 6. In this phase the goal box was replaced by a blank start box during the 20 second interval before making a choice between familiar and novel box on each trial. This procedure, designed to prevent the rat making a simultaneous discrimination was used throughout the rest of the experiment.

In the third phase of the experiment each rat received 16 trials a day in the same manner as before except that four of the boxes were repeated in each session with a lag of two intervening boxes between their first and second presentation as correct novel box. In each session the rat was forced to enter two of these repeat boxes twice in succession on their first presentation. After having made a correct choice and entered the box and received reward in the usual way the rat was then given a choice between this same box and a blank start box. If the rat entered the blank start box the guillotine door was kept raised until it entered the goal box. A further three reward pellets were then dispensed. For the remaining two repeated boxes the procedure was as normal and the rat entered it just once on the first presentation as correct novel box. The first presentation of repeat boxes occurred on trials 1, 5, 9 and 13, with double presentations occurring either on trials 1 and 9 or 5 and 13. Testing continued in this manner for 20 sessions.

5.3.3. Results

Two of the rats did not reach criterion within 400 trials and were therefore excluded from the experiment. The remaining 6 rats reached criterion in a mean of 250 trials.

Table 5.1 shows the number correct for each rat on the repeated trials when the box was entered either once or twice during the first presentation.

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Table 5.1: Number correct on repeat trials when box initially presented once or twice.

Rat	Box entered once (40 trials)	Box entered twice (40 trials)	Difference scores
1	21	24	3
2	27	20	-7
3	27	22	-5
4	25	29	4
5	21	22	1
6	26	21	-5
Mean	24.5	23.0	
SD	2.8	3.2	

The means of the two conditions were very similar and a t-test revealed no significant difference between the scores when the box had been presented once or twice. Some of the scores were, however, close to chance which may have masked more marked differences between the conditions. Two of the rats performed at chance in the box entered once condition and slightly higher on the box entered twice condition and three above chance on the box entered once but at chance on the box entered twice. This analysis also does not take account of correction trials. The number of times the box is entered on the first presentation also depends upon the number of correction trials that occur on the trial following the first presentation, when the target box becomes the incorrect box. However, analysis of the data taking correction trials into account produces a mean of 60.4% (*SD 7.4*) correct when the box is entered once and 59.1% (*SD 9.6*) when the box is entered twice. A t-test revealed no significant difference between these scores.

This analysis was also carried out for the rats in experiment 6 in the 6 pair condition. Correction trials on the trial following the first presentation of a repeated box results in greater exposure to the target stimulus. Table 5.2 shows the mean % correct on repeated trials for each group when the box was initially entered once or twice because of correction trials.

Table 5.2: Mean % correct when target stimulus was entered once or twice on first presentation.

Group	Box entered once	Box entered twice
	% correct (Standard deviation)	
Fornix	79.1 (8.3)	80.0 (13.8)
Control	76.1 (7.0)	71.9 (9.0)
Small Frontal	74.3 (4.2)	68.0 (18.0)
Large Frontal	76.0 (5.0)	68.9 (21.2)

Analysis of variance was carried out on this data with the factors group and condition i.e. whether the target stimulus was entered once or twice on the first presentation. There was no significant difference between the groups in % correct or between the two conditions as shown by non-significant main effects of group and condition (*Group*, $F(3,25) = 1.25$; *Condition*, $F(1,25) = 2.02$). There was also no difference between the groups in performance across the two conditions as the group X condition interaction was not significant ($F(3,25) = .32$). On examining the difference scores between the two conditions for individual rats it appeared possible that they represented two groups of rats using two different strategies i.e. temporal ordering and trace strength rather than a single group whose difference scores represented a normal distribution around a mean of 0.

As there was no difference between the groups the scores were combined and a frequency polygon generated of the difference scores for all subjects (figure 5.12). This analysis also includes data from the three animals that were excluded from the frontal group because of incomplete lesions. The performance of these animals did not differ from the rest of the groups on the DNMS task and were thus included in this analysis. The expected frequencies were calculated for a group of n=32 having the same mean and standard deviation (*mean = 2.93, SD = 15.68*). and a chi-square test carried out which showed that the observed frequencies differed significantly from those expected of a normal distribution. ($X =17.17$, $df=9$, $p<.05$).

Figure 5.12: Frequency polygon of the difference scores of the box entered once or twice conditions in the DNMS task for all subjects
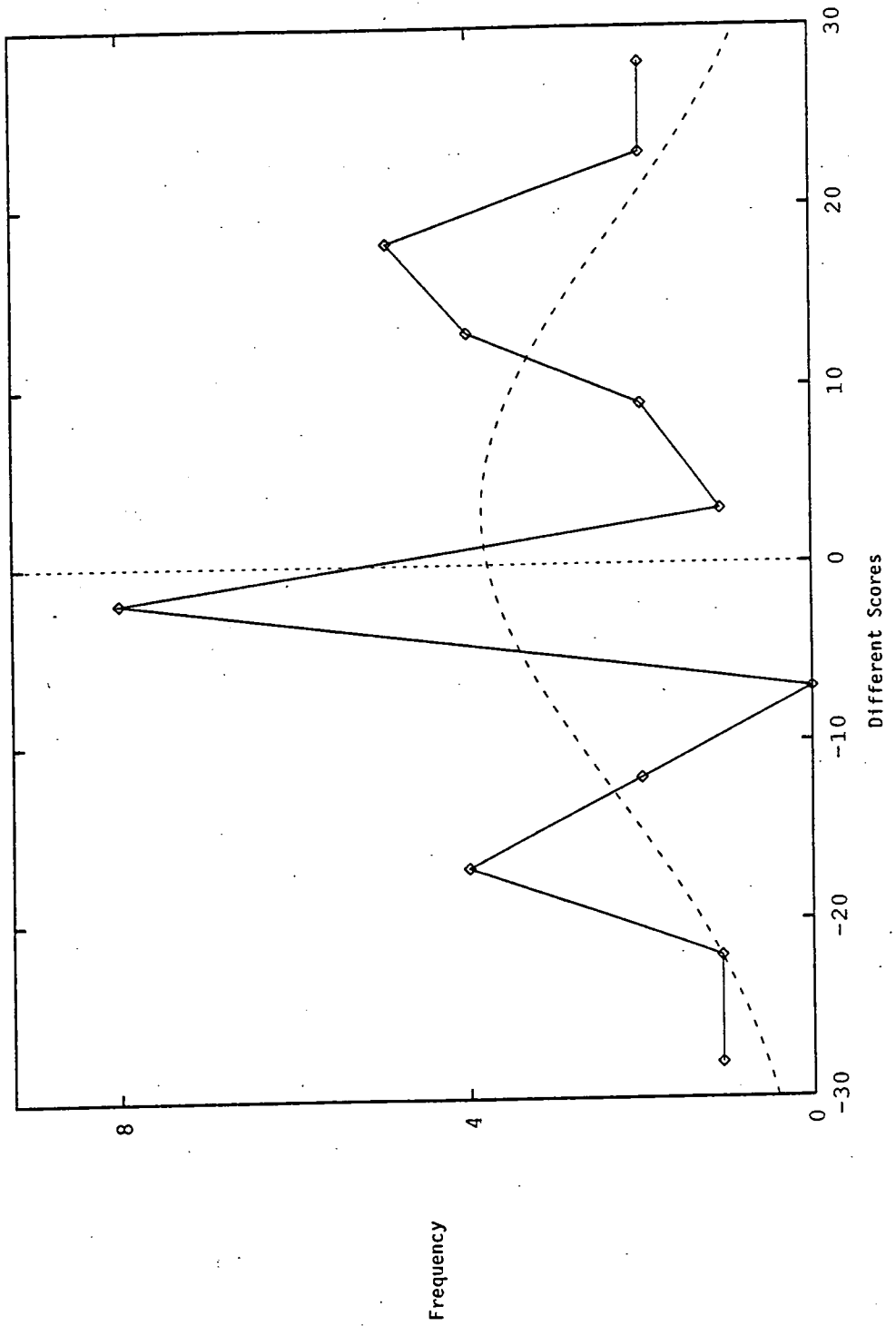
5.3.4. Discussion

This experiment did not support either the trace strength or the temporal ordering explanation of the DNMS task. It was expected that entering a box twice on its first presentation as correct novel box would increase trace strength and affect performance detrimentally on its second presentation as correct novel box, if the rat was solving the DNMS task by always entering the box with the least trace strength. On the other hand, if the rat was solving the task by using temporal tagging, performance may be expected to be enhanced by such a double presentation as the stimulus will have become more distinctive temporally. Neither of these two outcomes occurred as there was no difference in performance in the two conditions.

Nearly all the rats, however, were performing close to chance on at least one condition, which prevents accurate interpretation of the difference scores between the two conditions. Also half of the rats showed an improvement in performance in the 'box entered twice' condition whilst the performance of the remaining three rats declined. It is possible that some of the rats were using a trace strength strategy and the rest a temporal strategy. It is not possible to assess if this is the case from such a small group of subjects. The difference scores could represent a normal distribution around a mean of 0 that could be expected to occur by chance alone. The data from the previous experiment, however, suggests that the number of exposures to the stimulus could have more than a single outcome as the difference scores for these rats do not represent a single normal distribution. This data was based on the number of correction trials that produced repeated entry to the target stimulus and thus may reflect a more conservative measure of increase in trace strength. Correction trials are not rewarded and so the rat is less likely to spend time examining the box in search of reward pellets, but generally waits facing the guillotine door for the next correction trial to commence. There appeared to be no difference, however, between the responding of the control group and the experimental groups. All groups had equal numbers of subjects showing improvement and decline in performance with the double presentation. If two strategies are being used the rats having lesions to both the fornix and frontal lobes are as likely to use either strategy as the control animals.

Trace strength was manipulated in this experiment by increasing the frequency of presentation of the stimulus. The rat had then to choose between a stimulus presented twice but less recently than one presented once. Both frequency and recency are factors affecting trace strength but it is not known the relative contributions of these two at-

tributes to the strength of the trace. If recency contributes more to trace strength than frequency the manipulation may not have had the desired effect. To overcome this problem the experiment could have been extended to include a greater range of frequencies of presentation. The data from experiment 6 did give some information concerning more entries to the target stimulus than two, but on too few trials to make any useful analyses.

This experiment, then, did not provide unequivocal evidence as to the nature of the temporal order judgment made by the rat in the DNMS task. Data from the previous experiment did suggest that the strategy used may not be consistent across individuals. A rat may use either a temporal or a trace strength strategy depending upon the individual and the nature of the task. It is also quite likely, however, that an individual may use a combination of these attributes of the stimulus to make the temporal order judgment. It was clear, though, that the experimental animals in the previous experiment were not behaving differently from the control animals in their response to trace strength manipulations and are, therefore, making temporal order judgments in a qualitatively similar way.

Chapter 6
General Discussion

6.1. Duration Judgments

This research examined the performance of temporal lobe and diencephalic amnesic subjects on a number of tests of temporal estimation. The finding that Korsakoff amnesics were impaired in temporal estimation is consistent with related research that has shown amnesic subjects of varying aetiology to be impaired in the temporal domain. It was surprising that the temporal lobe amnesic group showed comparable levels of performance in all time estimation tasks to that of the controls, particularly in the light of the findings by Richards (1973) of temporal disturbance in the amnesic patient H.M. who also suffers temporal lobe damage.

In both the time estimations and the fixed interval task the Korsakoff amnesic subjects underestimated the intervals, and this became more pronounced as the length of the intervals increased. Presenting the data in the same way as that of H.M. (Richards, 1973) and B.W. (Williams et al. 1989) it did appear that the post-encephalitic subjects produced accurate time estimations up to 20 seconds thereafter underestimating the intervals but on closer examination of the error from target this was found not to be the case. The post-encephalitic subjects were statistically unimpaired in both experiments. Their performance was, however, slightly depressed compared to the control group in the time estimation tasks of experiment 1, particularly in the longer intervals. It is possible that an impairment would have become apparent if even longer intervals had been assessed.

Absolute error scores are a more sensitive measure in detecting decrements in timing performance (Brown, 1985; Goldstone, 1975) and it is possible that the data from H.M. and B.W., analysed in terms of error from target, would yield a different pattern of results and so calls into question the conclusions drawn by Richards (1973) and Williams et al. (1989) concerning the deficits in timing behaviour of temporal lobe amnesics. It is also difficult, however, to draw firm conclusions as to the exact nature of the time estimation performance of temporal lobe amnesic subjects from such a small group. The post-encephalitic subjects in this research appeared well motivated whereas the Korsakoff subjects displayed the apathy typical of subjects suffering this syndrome. Motivational factors may have been partly responsible for the impairment in the Korsakoff group although this is unlikely to account for all the findings.

6.1.1. Relationship to findings from animal experiments

The performance of the Korsakoff subjects bore some striking similarities to the pat-

terns of responding of rats and monkeys having damage to the hippocampus or its major fibre connection, the fornix. Both rats and monkeys with such lesions have been found to overrespond on operant schedules (Jackson & Gergen, 1970; Schmaltz & Isaacson, 1966; Sinden et al. 1986). The Korsakoff subjects in this research also showed evidence of overresponding in the FI schedules with significantly greater rates of responding over the sessions as well as higher rates of responding in the early segments of the intervals. Observation of their responding suggested that this was not entirely due to an inability to time the interval, as they often indicated that they knew that a reward would not be available. There has been some debate as to whether the overresponding in rats with hippocampal lesions is the primary cause of the impairment but it appears that there is a combination of factors responsible, that is, lack of inhibition of responding coupled with a deficit in the temporal component of the task (Braggio & Ellen, 1976; Rawlins, Winocur, & Gray, 1983).

In timing tasks the impairment of animals with hippocampal lesions increases with longer intervals (Boitano et al. 1980; Sinden et al., 1986). This was also true of the Korsakoff group. The impairment was greater in the longer intervals of the time estimation tasks and there was evidence to suggest that they failed to use temporal strategies to the same extent in the FI30 as in the FI15. The error was found to be in the direction of underestimation of the intervals in both types of time estimation. This has also been shown to be the case in rats with fornix lesions (Olton, Meck, & Church, 1987; Olton, Wenk, Church, & Meck, 1988). These animals show a left shift in peak time in the peak interval procedure producing, in effect, an underestimation of the expected time of reinforcement. This left shift in peak time has been attributed to a decrease in the remembered time of reinforcement stored in reference memory according to the internal clock model of temporal estimation (Olton et al., 1987; Olton et al., 1988). The shift in the peak rate function is fairly consistent and appears to be about 20% of the target duration.

If the shift is due to a memory problem one would expect the error to be more random. The authors propose that the memory problem is one of an increase in memory storage speed, thus decreasing the remembered time of the duration. It does not necessarily follow that an increase in speed of memory storage effects 'what' is stored, and it also seems unlikely if one applies the model to human amnesic subjects. A decrease in memory storage speed would be more likely in the cognitive processing of human amnesic subjects with a resulting overestimation of temporal duration.

A consistent underestimation of a proportion of the actual duration suggests a deficit in

the actual timing mechanism, that is, the internal clock as proposed by the model. However, the proponents of the model claim that the permanence of the left shift is evidence for a deficit in memory storage because the animal would eventually learn to rescale time if the clock was faulty. According to the model there is, however, more than one clock that can time several durations simultaneously (Meck & Church, 1984). One could assume, therefore, a role for the hippocampus in the control and integration of these timing mechanisms in relation to the timing of responses. This would be consistent with the findings from the literature on classical conditioning of the rabbit NMR that hippocampectomy affects the onset latency of the CR and a role has been proposed for the hippocampus in modulation of the timing of the CR (Port et al., 1986).

Further evidence that the hippocampus plays some part in regulation and control of the timed response is seen in an analysis of the sequence of over- and under-estimations on successive peak intervals (Meck, 1988). Over- and under-estimates of the remembered time tend to alternate in an orderly sequence and the number of crossings of the median peak time (runs) for successive peak intervals is an indicator of whether the sampling of the temporal criterion used on each trial is controlled in some way by the rat or is random. Rats with fornix lesions show significantly fewer runs than control animals although the temporal criteria used by the rats with lesions is not random.

The prefrontal cortex appears to play a complementary role in the modulation of the timing of responses. In contrast to the left shift in peak time of the rats having fornix damage, rats with prefrontal cortex lesions exhibit a right shift in peak time (Olton, Wenk, Church, & Meck, 1988). These authors proposed a role for the prefrontal cortex in attentional mechanisms, as rats with anterior cortical lesions are impaired at timing simulataneous intervals. The model does not explicitly account for such factors as attention, motivational and behavioural state, and cognitive processes that may affect perceived duration and so does not account for mechanisms that integrate these factors into

the decision making process. It is possible that the prefrontal cortex serves such a function. Indeed, it has been proposed that the prefrontal cortex in humans carry out the functions of executive control such as planning, organization and use of feedback (Stuss & Benson, 1986).

Evidence from the performance of animals on operant schedules suggests that the prefrontal cortex plays a lesser role in timing than the hippocampus. The deficit in DRL and FI tasks is inconsistent and often mild and transient (Glickstein, Quigley, & Stebbins, 1964; Stamm 1963b; Pribram, 1961; Manning 1973). Human subjects having

frontal lobe lesions are impaired at temporal duration estimation but their pattern of responding appears somewhat different from that of amnesic subjects (Bruyer & Bontemps-Devogel, 1979). Their deficits do not appear to be markedly more pronounced with increasing length of the interval although, contrary to the findings in animals, their errors tend to be of underestimation.

The present research found some evidence for a contribution of frontal cortex systems in time estimation in terms of planning and utilisation of strategies and use of contradictory feedback. The time estimations but not the FI performance correlated with performance on the cognitive estimation and picture arrangement tests. It was proposed that the time estimations were dependent upon internal monitoring and feedback, whereas the FI procedure was more dependent upon the use of external monitoring. It is most probable that the relationship of the cognitive estimation to time estimations reflects a more general cognitive deficit rather than a primary deficit in timing. This could be a very general executive function such as the control and use of feedback and strategies, as has already been proposed. If this were the case it would be expected that other tests of frontal lobe function such as the WCST would also show some correlation with the experimental tasks but no other correlations were found with tests of frontal lobe function. Alternatively, time estimations could represent a further example of a general impairment in the ability to make cognitive estimations. This does not appear to be due to an impairment of numerical ability as no significant correlations could be found between performance on the cognitive estimation task or the time estimation task and the arithmetic subtest of the WAIS. A combination of these explanations is possible in that this relationship between performance on the cognitive estimation tests and the time estimation tasks is a result of a deficit in the utilisation of more abstract concepts of deductive reasoning. It was noted that the block design test correlated negatively with performance on the time estimation and the fixed interval tasks. This test involves more concrete constructional abilities. That is, the formation of plans and strategies and the use of feedback gained from explicit external stimuli and not from internal abstract properties as must be utilised in the cognitive estimation and time estimation tasks. This can be compared to Kesner's (1984) proposal that the hippocampus codes 'real' time or the processing of information based on data input, while the prefrontal cortex codes 'abstract' time or information based on expectancies.

To assess frontal lobe contribution to temporal estimation one subject (F.L.) having frontal lobe damage was tested on all the time estimation tasks used in the present research. This 25 year old female subject suffered frontal lobe damage as a result of a road traffic accident when she was 18 years old. Her full scale WAISR IQ is 102 and

she shows no sign of any memory impairment having a WMS memory quotient of 121 and Warrington word and face recognition memory scores of 50 and 45 respectively. She showed a high level of perseverative responding on the Wisconsin Card Sorting test of 47 perseverative responses whilst achieving 4 categories suggesting the presence of frontal lobe damage, although in all other tests of frontal lobe function she scored within normal limits. Figure 6.1 shows F.L.'s performance on the time reproduction and estimation tasks in terms of the relationship of estimated time to real time. Her temporal estimations were quite accurate and whilst she underestimated the longer intervals in the reproduction task there was a tendency to overestimate the longer intervals in both estimation tasks. These responses were, however, well within the range of estimates made by control subjects and cannot be considered to be impaired. This subject did not display any evidence of impairment in executive control functions in any of the psychometric tests other than the WCST which suggests that frontal lobe damage was not extensive. In addition she showed no impairment on the object recency task. There may, therefore, have been some sparing of frontal lobe function which could explain the accuracy of her temporal estimations.

To return to the comparison of human amnesics and the performance of animals on operant schedules, it is of course problematic that the primary locus of the impairment in animals appears to be the hippocampal system and the diencephalic amnesics display a comparable pattern of responding on such tasks, whereas the temporal lobe amnesics are unimpaired. Diencephalic lesions in rats do not produce the same impairments as hippocampal lesions on operant schedules. Rats with lesions to the mediodorsal thalamus have been found to be unimpaired on fixed interval schedules (Delacour 1971; Lejeune, 1977) and although their response rate and number of rewards obtained on a DRL20 schedule has been shown to be lower than that of control animals (Lejeune, 1977), a dissociation has been found between septal and mediodorsal thalamic lesions on the same schedule (Ellen & Butter, 1969). Impairments in operant schedules by rats

Figure 6.1: Mean estimated length of the interval in relation to actual length of the interval for subject F.L. in the time reproduction and estimations with filled and empty intervals.
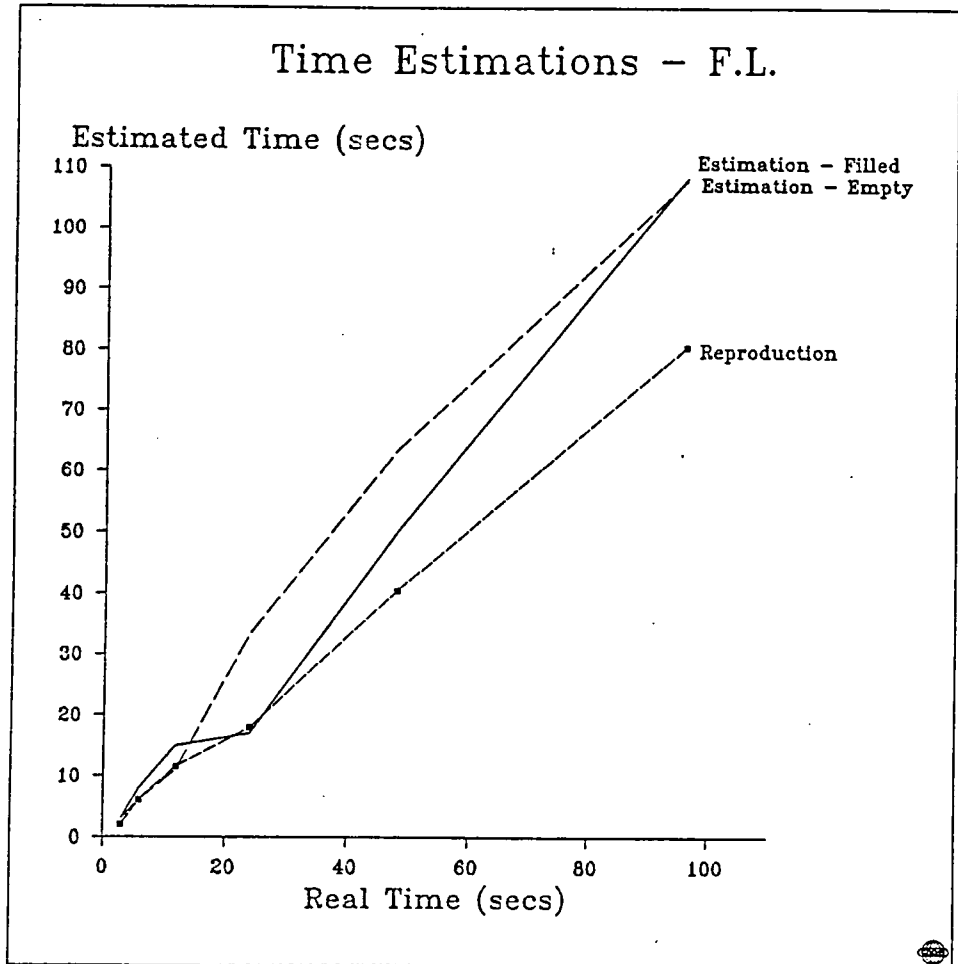
with mediodorsal thalamic lesions appear to be milder than those of rats with hippocampal lesions and overresponding is relatively transitory, disappearing with training (Braggio & Ellen, 1976). Mammillary body lesions do not appear to affect performance on DRL20 schedules apart from a deterioration in performance after a number of sessions (Smith & Schmaltz, 1979).Therefore, in animals diencephalic lesions alone do not produce as marked an impairment as that exhibited by the human diencephalic amnesics such as the Korsakoff subjects in the present research, although it has been observed that thalamotomy in human subjects produces temporal disorientation (Spiegel, Wycis, Orchnik & Freed, 1955). Such patients show confusion regarding dates, season and time of day and make errors in estimations of longer intervals such as time since operation or their stay in hospital. The region implicated in this 'chronotaraxis' was the medial dorsal nucleus of the thalamus (MD). These disturbances, however, did not occur in all cases and, when present, were transitory. The authors concluded that multiple circuits were probably involved in the mechanism, as one patient suffered further transient temporal disorientation when a lesion was made in the anterior thalamic nuclei several months after the original lesion to MD (Spiegel et al. 1955). Unfortunately, temporal estimation judgments were not tested experimentally in these patients. The temporal deficits observed were fairly gross representations of temporal disorientation but there may have been more subtle residual impairments of temporal estimation. However, a study by Williams, Medwedeff & Haban (1989) showed a patient, B.W., who had an anterograde amnesia after removal of a large dermoid cyst located near the third ventricle, to be impaired at time reproduction and estimation tasks of intervals of 5 - 120 seconds. This patient's amnesia would, therefore, result from damage to midline structures, most probably involving the thalamus. Like the diencephalic subjects in the present research her errors were of underestimation of the intervals. The mass extended bilaterally but was more pronounced on the right side but there was no detailed neuropathological information concerning the extent of the damage brought about by the cyst or its surgical removal. This case does, however, provide further evidence that diencephalic structures may be involved in the perception of temporal events.

It would appear that control of temporal estimation is not a function of a single structure. If the hippocampus alone was responsible for timing then the post-encephalitic subjects would have been impaired, assuming that these subjects have hippocampal damage. The similarity between the impairments exhibited by Korsakoff subjects and those of animals with hippocampal system lesions suggests related temporal processing in hippocampal and diencephalic structures, the thalamus being the most likely candidate. The research also suggests that the prefrontal cortex plays a contributory role in executive control of these functions. Although the Korsakoff group were impaired in

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making time estimations there was obviously some residual capacity as their response curves were not flat; this residual capacity probably being carried out by the hippocampus. That the Korsakoff subjects were impaired in temporal estimations whereas the post-encephalitic subjects were not, may be due to greater damage in those areas of the prefrontal cortex that contribute to regulation and control of temporal estimations in this group. Four of the subjects in this group had scores outside of normal limits on the picture arrangement test whereas all post-encephalitic subjects achieved normal scores.

6.1.2. Implications for other models of time estimation

Models derived from the performance of human subjects on time estimation tasks tend to emphasise the cognitive factors involved in the judgment of duration. Block (1986) distinguishes between stimulus based and context based theories. Stimulus based theories concentrate on the nature of the information processed during the time interval. Ornstein (1969) and Vroon (1970) explain remembered duration in terms of the amount of information stored. Storage size, however, is difficult to define and measure and as a consequence no straightforward relationship has been found between the amount of information processed and the duration judgment. The present research varied the content of the target intervals by requiring the production of filled and empty intervals but there was no difference found in the performance of these two types of estimation. Hogan (1978) proposed that the complexity of the material is the important factor, producing a U-shaped function. That is, apparent duration diminishes from very simple to optimum complexity whereas it increases from optimum to excessive complexity. The filled interval task in the present experiment was a straightforward reading task of simple material and so it is difficult to determine whether this involved more complex processing than the subject might have been covertly engaged in during the empty interval condition.

Block (1986) and Fraisse (1963) both suggest that perceived duration is dependent upon the number of contextual changes that occur in and around the interval to be measured. The role of contextual factors has implications for hippocampal theories of temporal processing in that rats with hippocampal lesions, like human amnesic subjects, are differentially sensitive to contextual manipulations. According to Block's model this would explain their impairments in temporal judgment. But, although changes in environmental context aid maze learning in rats with hippocampal lesions, there is no direct evidence as to the effects of contextual manipulations on timing tasks. This proposal cannot be directly assessed in the present research but as with the information processing models it points merely to cognitive factors that can influence duration estimation but does not provide a sufficient explanation as to the actual timing mechanism.

Michon and Jackson (1984) suggest that temporal order constitutes the effective temporal attribute. If this were the case it would be expected that temporal duration and temporal order would show some relationship. The present research found no correlation between the recency task and the time estimation tasks. Furthermore, a striking dissociation was found in the performance of the post-encephalitic subjects on these two tasks. They showed no impairment on the time estimations but were severely impaired on the recency task. If the perception of temporal order is the perception of duration it is difficult to account for such a dissociation. It appears more likely that the two types of temporal judgment are dependent upon different mechanisms and different brain structures and thus provide little support for this model.

Richards (1964), in an analysis of human temporal estimations, proposed that internal rhythms influence the values of reproduced intervals. He suggested that the subjects in his experiment were using intervals that were periodic multiples of 1.5 seconds as cues for the time estimates. It is commonly found that estimates of intervals greater than 500 msecs and less than 2 mins are linearly proportional to physical duration. This close mapping of estimated and actual duration does suggest a dependence upon some sort of timing mechanism rather than being purely the result of a variety of extrapolations from cognitive influences. Michon (1975) relates this directly to processes of immediate, short term and long term memory. Whereas estimates of intervals over 500 msecs are linearly proportional to actual duration, interval estimates below 500 msecs increase with the square root of the physical duration. This transition, he proposes, is attributable to the transition from immediate to short term memory. In normal subjects no such transition can be found at around 20 to 30 seconds when a transition from short term memory to long term memory could be expected. But Michon (1975) cites the findings from HM as evidence for a transition in the psychophysical law at around 20 seconds. HM's temporal estimations appeared to be proportional to the square root of physical time at intervals over 20 seconds although linearly proportional below this interval. But, as has been pointed out previously, the accuracy of H.M.'s temporal estimations are in doubt for all time intervals without an analysis of his absolute error scores. This proposal also requires an explanation of temporal estimation in terms of a direct relationship to memory processes. This research found no such transition in the time estimates of amnesic subjects at a period around 20 seconds. As Michon (1975) proposes that this transition is only evident in subjects suffering impairments in long term memory it would be expected that deficits in time estimation would show a correlation with memory function. The tendency was for the Korsakoff subjects to exhibit a negative relationship between performance on memory tests and performance on the time esti-

mations and the post-encephalitic subjects who were equally impaired on the memory tests were able to carry out the time estimation tests at a comparable level to control subjects.

6.2. Temporal Order Processing

Several different aspects of temporal memory have been examined in amnesic subjects. Studies reporting 'temporal order' deficits have used a procedure in which the subject was required to identify in which of two lists the target stimuli were presented (Kopelman, 1989; Meudell, Mayes, Ostergaard, & Pickering, 1985; Squire, 1982; Squire, Nadel, & Slater, 1981). Yet others have examined 'source' memory, requiring subjects to identify the context in which the target stimuli had been presented (Schacter, Harbluk, & McClachan, 1984; Pickering, Mayes, & Fairbairn, 1989). All found amnesics of varying aetiology to be impaired in 'temporal order' and 'source' memory.

The experiments in the present research testing temporal memory extended previous findings of an impairment in 'recency' memory in amnesic subjects. Previous studies directly assessing 'recency' judgments have all used verbal stimuli (Hirst & Volpe, 1982; Kovner, Dopkins & Goldmeier, 1988; Parkin, Leng, & Hunkin, 1990) whereas the present study used obscure objects that would be difficult to label verbally. Studies utilising non-verbal stimuli such as abstract paintings found no impairment of subjects having temporal lobe excisions but the subjects in these experiments had unilateral damage which varied in extent, particularly in the degree of hippocampal involvement (Corsi, cited in Milner 1971; Milner, Corsi, & Leonard, 1991). Their memory deficits were not comprehensively assessed apart from their showing mild deficits in the recognition part of the experiment. Of those studies reporting verbal recency memory deficits both Korsakoff and temporal lobe subjects were shown to be impaired although there was some suggestion that Korsakoff subjects were more markedly impaired than the subjects having temporal lobe damage (Kovner et al., 1988; Parkin et al., 1990).

The debate continues, however, as to the fundamental deficit responsible for these disorders of temporal processing. The contextual deficit hypothesis proposes an impairment in encoding and retrieving contextual information as the primary deficit in amnesia. This is based on the findings that amnesics' temporal and contextual memory is disproportionately impaired in comparison to their recognition memory. The procedures used to assess this involve equating amnesic and control subjects' recognition memory and then testing temporal order memory. Both 'source' memory and 'temporal order' memory response patterns cannot be accounted for in terms of generally degraded memory (Hirst & Volpe, 1982; Kopelman, 1989; Meudell, Mayes, Ostergaard, &

Pickering, 1985; Pickering, Mayes, & Fairbairn, 1989; Schacter, Harbluk, & McCla-chan, 1984; Shimamura & Squire, 1991) but this disproportionate deficit in temporal order memory has sometimes been found to be worse in Korsakoff amnesics than in amnesics of other aetiology such as ECT patients and NA (Shimamura et al., 1990; Squire, 1982). If this impairment in contextual memory is the fundamental cause of amnesia it would be expected that some relationship would be found between measures of contextual memory and the severity of the amnesia. Positive correlations have been found between 'recency' memory and the WMS (Parkin, Leng, & Hunkin, 1990), and tests of modality memory and the Warrington Recognition Test (Pickering, Mayes, & Fairbairn, 1989). Others have found no correlation between 'temporal order' memory and the WMS (Shimamura, Janowsky, & Squire, 1990) and 'source' memory and the WMS (Shimamura & Squire, 1991).

The present research found the temporal lobe amnesics to be equally impaired on the 'recency' memory task to the diencephalic amnesic group. There was no evidence of a disproportionate deficit in temporal order memory in the Korsakoff group compared to the post-encephalitic subjects, although experiment 3 was confounded by floor effects in both amnesic groups. However, by reducing the number of stimuli in experiment 5 the floor effects were eliminated and both groups showed comparative levels of per-formance. This confirms the general findings that temporal order judgments are im-paired across amnesic groups of varying aetiologies and fails to support those studies that propose a disproportionate deficit in Korsakoff subjects alone. Also, no relationship could be found between performance on the object recency task and tests of memory function, and in experiment 5 there was a dissociation between recognition memory and recency memory. This dissociation was not as consistent in the post-encephalitic group as in the Korsakoff group but because of the small group size it is unclear whether this represents a real qualitative difference in the pattern of responding of the two amnesic groups. This fails to support the contextual deficit hypothesis but also fails to support the notion that temporal order judgments are merely a result of a degraded memory. Recency memory would appear to be a specific class of memory that is independent of retention deficits. That this is not merely a failure in the utilisation of mnemonic strate-gies was suggested by experiment 4.

Many experimenters have attempted to localise this specific memory impairment to frontal lobe function. Subjects with frontal lobe lesions are impaired on self ordered tasks requiring the organization of pointing responses and recency memory (Petrides and Milner, 1982), organizing words into the order in which they had been presented (Shimamura, Janowsky, & Squire, 1990) and source memory (Janowsky, Shimamura,

& Squire, 1989). As Korsakoff subjects have additional cortical pathology particularly in the frontal lobes, as do some temporal lobe amnesics such as post-encephalitic patients, it is quite possible that disorders of temporal ordering may be attributable to this damage which is unrelated to the amnesic syndrome. Failures to find a relationship with memory function and temporal order memory would support this. Indeed, amnesic subjects often show great variability in their performance on tests of temporal order memory. Shimamura and Squire (1991), in a study assessing the relationship between fact memory, source recall and event recognition showed that amnesics fact and source memory was similar to that of controls tested at 6 - 8 weeks delay. Superficially this would support a view that source recall in amnesic subjects is a consequence of degraded memory but on closer examination of individual performance the distribution of source recall scores was bimodal. Some amnesic subjects showed disproportionate deficits in source memory whereas others did not and this was unrelated to their fact recall.

This situation may be the case in other experiments which report the group means for amnesic subjects. The heterogeneity of amnesic groups could be the result of variability in the degree of frontal involvement. The present research found a large variability in the performance of both Korsakoff and alcoholic control subjects on tests of frontal lobe function. The use of correlational techniques could, therefore, provide useful information concerning the possible relationships between temporal memory and frontal lobe function. Unfortunately, this approach has yielded inconsistent results and interpretations. Performance on frontal tests have been found to correlate with modality memory (Pickering, Mayes, & Fairbairn, 1989); source recall (Schacter, Harbluk, & McClachan, 1984); and temporal order memory (Squire, 1982). Others, on the contrary, have found no correlation between frontal tests and temporal order memory (Kopelman, 1989); recency memory (Parkin, Leng, & Hunkin, 1990); and source recall (Shimamura & Squire, 1991). Parkin et al. (1990) proposed that all the temporal discrimination tasks that have shown a correlation with frontal tests have required the subject to identify which of two temporal contexts the target stimulus occurred in. The present research was in line with this contention in that the tests of object recency showed no relationship with tests of frontal lobe function. It may be that a distinction should be drawn between tests of *contextual* memory and *recency* memory, with contextual memory being dependent upon frontal lobe function. However, this does not resolve the inconsistencies because, as has been pointed out, in some studies no correlations have been found between tests of contextual memory and frontal lobe function. Parkin et al. (1990) suggested that in recency judgments the primary emphasis is on attempting to retrieve the original learning event rather than allocating a familiar stimulus to one of

two plausible contexts and should thus be more related to the subjects' memory disorder. In that particular experiment this was the case but in the present research there was not only no relationship between frontal lobe tests and recency memory but also no relationship between severity of amnesia and recency memory.

Correlations of this nature should, however, be viewed with caution. Reliable indices of frontal lobe damage have been difficult to demonstrate (Stuss and Benson, 1986). The two most widely used tests of frontal lobe function, the Wisconsin card sorting test and the Verbal Fluency test, are as sensitive to diffuse cortical damage as focal frontal lesions, although quite reliable in determining the site of focal lesions (Heaton, 1981; Robinson, Heaton, Lehman, & Stilson, 1980). The most successful measure of the WCST for predicting frontal lobe damage is the number of perseverative responses, but significant perseverative tendencies have been demonstrated in a substantial minority of young normal subjects (University students) and to be quite common in older normal subjects (Berg, 1948). In the normative study (Heaton, 1981) 79.8 % of subjects having focal frontal damage achieved a score greater than the recommended cut-off of 18 or more perseverative responses but 77.7% of subjects having diffuse cerebral injury and 51.4% of focal non-frontal subjects also scored higher than 18. Using this cut-off point the test can only be used as an indication of brain damage per se. In the present research a perseverative response score of greater than 46 was used as a more conservative indicator of frontal lobe damage, as only 2% of normal subjects scored above this cut-off in the normative study. These findings suggest that perseverative tendencies can originate in a variety of cortical areas but in cases of non-focal pathology the prefrontal cortex would be implicated most frequently because of the richness of the afferent and efferent connections with other brain regions. For this reason Goldberg and Bilder (1985) proposed that the prefrontal cortex is "*more likely than any other region to be a functional 'mirror' of disturbances affecting different loci anywhere in the brain than is any other structure*".

The inconsistencies in correlations between performance of temporal order tasks and tests of frontal lobe function may, therefore, reflect the inadequacies of the frontal tests in determining frontal lobe damage. A reliable index of frontal lobe damage may not be possible if, as proposed by Goldberg and Bilder (1985), the presence of prefrontal focal pathology is sufficient but not necessary to produce the 'executive syndrome'. It is apparent that a single test would not suffice as measures of frontal lobe function often do not correlate with each other (Pickering, Mayes, & Fairbairn, 1989), as was the case in the present research, which reflects the functional heterogeneity of the frontal lobes. Different tests may be sensitive to different parts of the cortex and it would be errone-

ous to pool the results as, for example, in the study of Squire (1982).

A further problem arises if we consider the contribution of subcortical structures to the performance of such tests. Normative studies assessed the performance of subjects having lesions in different areas of the cortex and no direct assessment has been made of subcortical contributions to, for example, perseverative tendencies. Rats with hippocampal lesions tend to show perseveration of responses when required to shift set as in reversal of discrimination learning (Silveira & Kimble, 1968; Winocur & Olds, 1978). Severe perseverations can be elicited in a number of diseases such as schizophrenia, Alzheimers disease and viral encephalitis all of which can have possible damage in the frontal lobes but are also quite likely to have hippocampal lesions.

Bearing these reservations in mind, it is parsimonious to conclude that tests such as the WCST are, at the least, indicative of diffuse cerebral dysfunction and if the groups under consideration exhibit cortical impairment it is most likely to involve the frontal lobes. The lack of neuropathological data makes it necessary to infer the contribution of frontal lobe function to the experimental tasks from correlational techniques. Other tests such as the cognitive estimations, picture arrangement etc. have been less rigorously tested in connection with brain damage in general but have been implicated in frontal lobe functioning. Correlations with these tests are, therefore, not direct evidence for a contribution of frontal lobe function but do point to the processes that may be involved in carrying out the experimental tasks.

6.2.1. Temporal order judgments in animals

Rats with both fornix and prefrontal cortex lesions were found to be unimpaired in the DNMS task that required judgment of relative recency rather than recognition of the novel object. The decreasing set size in this experiment was designed to allow comparison with the large and small set size conditions in the test of recency memory in amnesic subjects. Whereas both the diencephalic and temporal lobe amnesics were severely impaired in both conditions of high and low temporal interference this factor had no effect on the lesioned animals. This would imply that the hippocampal system on its own is not responsible for recency memory and also that the amnesic deficit in temporal order judgment is not due to frontal lobe damage. This is assuming that these neural systems are functionally equivalent across species and that the DNMS task is being solved using temporal cues.

In view of the obvious limitations of experiments with humans in assessing brain/behaviour relations it is necessary to develop animal models of amnesia. Compar-

ative neuropsychology using non-human primates would be most informative but not always practical. It is, therefore, necessary to develop rodent models of human behaviour despite rodent brain structure being farther removed from that of humans. Although there are inconsistencies in behavioural results across species, when equivalent testing procedures are used in rodents and primates similar lesions are increasingly producing similar results (Markowska, Olton, Murray, & Gaffan, 1989). The important point is that experimental tasks actually test the processes that one is interested in. This is probably more difficult to assess in animal than in human experiments.

In the present research it was assumed that the DNMS task requires the temporal tagging of events in order to make a judgment of relative recency. Temporal tagging is just one of a number of attributes of the stimulus that may be utilised in making the recency judgment. Huppert and Piercy (1978) found that judgments of recency and frequency in Korsakoff amnesics and normal subjects are not wholly independent of one another. It would appear, then, that human subjects use a combination of attributes of the stimulus to make temporal order judgments. The Korsakoff subjects did show some residual capacity for making recency judgments. This was due, according to Huppert and Piercy (1978), to their using information concerning the strength of the trace rather than the temporal tag. Presumably this temporal information was not available to the amnesic subjects who, as a consequence, utilised alternative strategies. In their study trace strength alone was not as efficient a cue as trace strength plus temporal tagging as the Korsakoff subjects were still impaired compared to the control subjects. In the present research the Korsakoff subjects did not appear to use trace strength to make the recency judgment as the manipulation that improved recognition and presumably increased the strength of the trace did not improve the recency judgment.

It is quite likely that the rats in the present research were also using a combination of attributes of the stimulus to make the temporal order judgement and it is also probable that when certain types of information are unavailable to the animals they will develop alternative strategies. The data analysed in experiment 8 suggested that the rats may have had a predisposition to use either temporal tagging or trace strength but that the lesioned animals were not more likely to be relying on the strength of the trace than the control animals. This suggests that they were not differentially impaired in using temporal information. It does not preclude, however, the use of other attributes of the stimulus not accounted for in the analysis.

This notion of multi-faceted information is encompassed by Kesner's (1986) attribute theory of hippocampal function. He proposed that the hippocampus is required for both

long term temporal and absolute spatial information processing. This theory predicts that when both temporal and spatial aspects are important for a task hippocampal lesions will produce a severe deficit. When only one of these attributes is important there will be a moderate deficit but when neither are required there will be no deficit. The present task would, therefore, be expected to produce a moderate impairment in the rats with fornix lesions as temporal processing was required but not spatial. But, as has been discussed, it is not clear to what extent temporal tagging is a necessary requirement of the task and also spatial factors were inadvertently affecting performance during acquisition. These spatial factors i.e. whether the rat was required to enter the same or different arm in order to make a correct choice, aided the experimental animals during acquisition but not later in the experiment when the temporal aspects of the task were being tested. This finding did support theories that propose a spatial function for the hippocampus and prefrontal cortex. It also shows that it is necessary to examine test procedures closely in order to establish what factors are influencing task solutions as many tasks purporting to be spatial or non-spatial and working memory or reference memory tests may be incorporating unintentional factors.

The spatial impairment exhibited by rodents with fornix and hippocampal lesions is a fairly consistent finding, although there is debate as to the exact nature of this impairment. Spatial memory has not been examined as systematically in human subjects as the primary mode of representation in humans is verbal. The relative salience of spatial stimuli may represent a real species difference particularly when comparing rodents to humans. The relative importance of spatial and visual stimuli may differ, also, for monkeys and rats as normal rats learn to alternate in a T maze faster than monkeys, whereas normal monkeys but not rats learn visual tasks more rapidly than spatial ones (Mahut, 1972). Spatial impairment in rats may be evidence of a general mnemonic deficit that could be similar to verbal impairments exhibited by humans. Temporal processing, however, is more likely to show equivalence across species as it is intuitively a more basic fundamental process that is of similar importance for a wide range of organisms and is to some extent beyond verbal control.

The results of the DNMS experiment did not support the suggestion made by Rawlins et al. (1991) that the inconsistencies in the results of such tasks are a result of two factors; the nature of the stimuli and the number of times they are reused within a session. Increasing the number of presentations within a session did not differentially affect rats with fornix lesions. It is possible that the type of stimuli is a more important factor in these discrepant results as all the experiments showing an impairment in DNMS with small set sizes have used non-distinctive stimuli varying only in texture and pattern,

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except for the Rawlins et al. (1991) experiment in which an impairment was found using two 'Aggleton' type goal boxes. This was a moderate impairment, though, that was alleviated with practice. There were two differences between that and the present experiment; the number of stimuli and the acquisition procedure. The present research used three stimuli as the smallest set. It is possible, but appeared unlikely from the results, that the lesioned animals would have been impaired if the number of stimuli had been reduced still further. In the Rawlins et al. (1991) experiment the animals acquired the task using just two pairs of stimuli whereas the present procedure used thirteen pairs at acquisition. An attempt was made to replicate this procedure in the present research by training rats using three pairs of stimuli from the outset but normal rats could not learn the task. This was also found in the Aggleton, Hunt and Rawlins (1986) experiment when an attempt was made to train the rats on a two pair DNMS. This failure of the animals to learn the task is probably a result of the continuous trial procedure used in both of these experiments. The correct choice box of a preceding trial becomes the sample box of the present trial with no clear delineation between trials. This lack of temporal structuring coupled with high levels of between-trial interference creates a task that is too difficult for normal rats to accomplish. In all the studies that utilised a small set size from the outset the trials were discrete. Rawlins et al. (1991) also pointed out that rats could not learn the task using a continuous trial procedure and few stimuli.

Whether the task is learned with few or many stimuli could change the nature of the problem to be solved. Jagielo, Nonneman, Isaac and Jackson-Smith (1990) proposed that when the animal is trained with just two stimuli, as in their experiment, the task becomes a conditional discrimination. The animal must learn a particular relationship between the stimuli; a black arm response is appropriate when the animal has just left a white arm and vice versa. Of the studies using small sets, all except Olton and Feustle (1981) used a choice of just two stimuli which are in effect conditional discriminations. The Olton and Feustle study (1981) used a four arm maze each arm being visually and tactually different from each other arm. The rat was required to enter each arm of the maze on a trial in a non-matching procedure. The most consistent findings, therefore, is that experiments using two stimuli have all produced impairments whereas only one study using more than two (Olton and Feustle, 1981) has shown any deficit with hippocampal system lesions. Rawlins et al. (1991) conclusion was correct to some extent in that accuracy after hippocampal system lesions depends upon the number of times the stimuli are reused within a session, but this applies to the condition where only two pairs of stimuli are used, but not more than two. Whether this applies only to acquisition of the task, thus supporting the notion of an impairment in conditional discrimination learning, must be resolved by further experimentation. It is also necessary to

determine the circumstances under which hippocampal lesions could affect conditional learning. As discussed in Chapter 2 hippocampectomy does not affect simple conditional discriminations but does affect more complex conditional learning (cf Gaffan, 1989).

A deficit in complex conditional responding would be encompassed by theories that propose a role for the hippocampus in discriminating cue relationships. The configural association hypothesis (Rudy & Sutherland, 1989) states that the hippocampus is necessary for the acquisition of compound stimuli as functional units as distinct from the individual elements in the compound. This is supported by experiments showing an impairment in compound conditional discriminations (Leaton & Borszcz, 1990; Ross, Orr, Holland & Berger, 1984; Rudy & Sutherland, 1989; Sutherland, McDonald & Hill, 1989). This is similar in some respects to the explanation put forward by Gaffan (1989) of the visual-spatial conditional deficits exhibited by fornix transected monkeys. These monkeys can respond correctly to stimuli which are correct dependent upon the animals' spatial location in the room, but not when the correct response is dependent upon changes in the spatial array of a common set of objects. This has also been demonstrated in rats with fornix lesions (Markowska, Olton, Murray & Gaffan, 1989). This, Gaffan (1989) suggests, is a form of snapshot memory which stores not only the items present in a scene but also their spatial relationship to each other. An extension of this to event memory proposes, in effect, an impairment in the memory for the contextual elements that cue a specific event which has similarities with the contextual deficit hypothesis of human amnesia.

Although human data would suggest that frontal cortex damage alone can produce impaired recency memory, there has been no clear demonstration of such an impairment in animals. The present research also failed to provide an animal model of frontal cortex temporal ordering deficits. Obviously further research is required to establish if there is such a correspondence between animals and humans. The research also failed to provide an animal model of the recency impairment of amnesic subjects. Damage to the hippocampal system alone did not produce a recency memory deficit. The next step would be to assess the performance of animals with combined lesions on such tasks. The fornix and the prefrontal cortex represent stations in the two memory circuits proposed by Mishkin (1978), that is, the hippocampal, fornix, mammillary body, anterior thalamus, posterior cingulate cortex circuit and the amygdala, MD, anterior cingulate cortex circuit. If the assumption that damage to both circuits is necessary to produce a full-blown amnesic syndrome is correct then it is possible that combined lesions of fornix and medial prefrontal cortex will show an impairment in the DNMS task. Indeed, combined amygdala and fornix lesions in rats produce no impairment in acquisition of

the same DNMS task with pseudo trial-unique stimuli but a clear impairment with four repeated boxes (Aggleton, Hunt & Shaw, 1990). Also, diencephalic structures implicated in Korsakoff's syndrome do not, on their own, produce the severe deficits exhibited by human amnesics. Whilst damage to MD in rats results in deficits in the early stages of learning, that is acquisition of the DNMS task, there is no effect once the task is learned (Hunt & Aggleton, 1991) and mammillary body lesions show no impairments (Aggleton, Hunt & Shaw, 1990).

6.3. Conclusions

In conclusion I shall return to the questions posed in the introduction.

1. *Is memory for temporal order and the perception of time dependent upon the same neural substrate?*

This research found no evidence for a relationship between recency judgments and temporal estimation. Performance on the time estimation and the fixed interval tasks did not correlate with performance on the recency task in any of the groups. Also, a dissociation was found in the post-encephalitic group on these two tasks as they performed normally on the time estimations but were severely impaired on the object recency. The post-encephalitic time estimations, however, were at odds with previous reported findings from temporal lobe subjects. Further research is needed to clarify the exact nature of temporal lobe amnesics timing behaviour as these results are based on only three subjects in the present research and two subjects in previous research.

There have been a number of methods used to assess amnesic subjects temporal order judgments, some testing recency memory whilst others test source or contextual memory. It is possible that not all such temporal order tasks are equivalent in terms of their neural substrates. The relationship between such tasks and the relationship of temporal order tasks, other than recency memory, to temporal estimation should be examined in more detail.

The research is obviously constrained by the lack of detailed information concerning the neuropathology of subjects. The contribution of specific brain regions must be inferred from very indirect evidence as, for example, correlations with tests of frontal lobe function. The problems arising from this approach have been discussed, but until more valid tests of frontal lobe function are developed the existing tests must be used, but bearing in mind the reservations that have been mentioned.

It was felt that the hippocampus plays a role in time estimation but that there are other structures that process temporal information in parallel. The locus of this parallel processing is most likely to involve thalamic nuclei. The correlation between both the cognitive estimation and picture arrangement tests and the temporal estimation tasks suggested that frontal lobe function contributed to temporal estimation by the formation of plans and strategies and the monitoring of internal expectancies and feedback. No relationship could be found between tests of frontal lobe function and the recency memory task, although subjects with frontal lobe damage typically show deficits in temporal ordering tasks. From this it would appear that amnesic deficits in recency memory

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should be attributed to subcortical structures affected in both diencephalic and temporal lobe amnesia. The results of the animal experiment suggest that damage to the hippo-campal-mammillary body pathway alone is not sufficient to produce recency memory impairments and future research should assess the effects of combined lesions.

2. *Are deficits in temporal processing a result of poor memory?*

Neither temporal estimation nor recency showed any relationship to memory function. Performance of the temporal estimations could not be predicted by degree of amnesia and although both amnesic groups performed poorly on the object recency task no correlation could be found between measures of memory function and performance on the recency test. Standard tests such as the WMS cover several aspects of memory ability in a fairly superficial manner. It would be appropriate in future research to devise a more extensive and specific battery of memory tests to assess memory function and its relationship to temporal order tests. However, in the light of the present findings, recency memory was considered to be a specific class of memory independent of retention deficits, and there was also no evidence to place the locus of this impairment in the frontal lobe.

This lack of a relationship between temporal order and memory function failed to support a contextual deficit hypothesis of amnesia. But, as mentioned above, a closer examination should be made of the relationship of tests of recency memory to tests of contextual memory in order to establish if these two tasks are testing the same function.

3. *Is there a correspondence between tests used with animal and human subjects?*

The fixed interval procedure was successful in producing patterns of responses similar to that found in animals. Many of the subjects exhibited scalloping, although some of the controls had low response rate patterns with only one or two responses in each interval. This occurred more frequently in the shorter intervals but shows that with longer intervals measures of temporal estimation can be compared across species. This comparison produced strikingly similar patterns of performance between rats with hippocampal system lesions and the Korsakoff amnesic subjects. It is, therefore, useful to compare the performance of rodents and humans when appropriate tasks are used.

Hippocampal lesions in rats do not appear to provide an appropriate model of human amnesic temporal estimation when one considers the normal timing ability of the temporal lobe amnesics (who presumably have hippocampal damage) in this research. But, as mentioned previously, the status of temporal lobe amnesics' timing ability is in need of verification, and also it is unlikely that there is a single structure/function rela-

tionship. The need to postulate multiple circuits is again shown in the tests of temporal ordering. Damage to neither the prefrontal cortex nor the fornix in rats had any effect on recency memory. Further tests of non spatial-recency memory must be carried out as it is not clear to what extent temporal information is required in the DNMS task, and thus how far these findings can be applied to human recency memory.

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Appendix 1.

Cognitive Estimation Test.

1. What is the height of Nelson's column?

2. How fast do race horses gallop?

3. What is the age of the oldest person in Britain today?

4. What is the length of the average man's spine?

5. How tall is the average English woman?

6. How heavy is a full pint bottle of milk?

7. How long, on average, is a man's tie?

8. What is the width of a double decker bus?

9. What is the length of a new five pound note?

10. On average how many TV programmes are there on any one channel between 6.00pm. and 11.00pm.?