Neurotoxicology and Teratology, Vol. 20, No. 5, pp. 493–502, 1998
Published by Elsevier Science Inc.

0892-0362/98 $0.00 + .00

ELSEVIER

PII S0892-0362(98)00013-0

Symposium Overview: The Use of Delayed Matching-to-Sample Procedures in Studies of Short-Term Memory in Animals and Humans

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Received 20 February 1998; Accepted 11 March 1998

PAULE, M. G., P. J. BUSHNELL, J. P. J. MAURISSEN, G. R. WENGER, J. J. BUCCAFUSCO, J. J. CHELONIS AND R. ELLIOTT. *Symposium overview: The use of delayed matching-to-sample procedures in studies of short-term memory in animals and humans.* NEUROTOXICOL TERATOL **20**(5) 493–502, 1998.—Behavioral paradigms applicable for use in both human and nonhuman subjects for investigating aspects of working/short-term memory are presented with a view towards exploring their strengths, weaknesses, and utility in a variety of experimental situations. Such procedures can be useful in teasing out specific aspects of mnemonic processes including discrimination, encoding, and retention. Delayed matching-to-position, delayed matching-to-sample (DMTS), and titrating matching-to-sample procedures are highlighted. Additionally, the application of DMTS tasks in preclinical and clinical settings is presented: drug effects on memory processes can be explored preclinically in animal models; normative data have been developed in human populations where they have been used in adults to explore the relationships between mnemonic processes and specific clinical entities such as Parkinsonism, senile dementia of the Alzheimer's type, schizophrenia, and depression. Studies in children indicate that encoding and retention processes improve rapidly in the early years, plateauing prior to puberty. Noninvasive imaging techniques such as positron emission tomography (PET) indicate that activity in specific brain areas is associated with DMTS task performance and may serve to confirm roles for such structures in mnemonic processes. Published by Elsevier Science Inc.

Working memory Comparative psychology Discrimination Encoding Retention

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AT the 1997 Annual Meeting of the Behavioral Toxicology Society held in Palm Beach, FL, attendees were treated to an excellent series of presentations that discussed the finer points of delayed matching-to-sample (DMTS) procedures. What follows are synopses of the six presentations along with an excellent bibliography that will serve as an important resource for all of us interested in these most powerful approaches to the study of memory. Phil Bushnell opened the symposium with an important contribution in which he presented historical and theoretical material.

WORKING MEMORY: PROCESSES AND PROCEDURES

Working memory is a term denoting one of several types of memory that have been identified by cognitive psychologists. Accepted taxonomies of memory typically distinguish among different kinds of remembering depending upon the information that must be remembered. A basic dichotomy distinguishes between the retention of factual or experiential information on the one hand, and the retention of habits and motor skills on the other [e.g., (70)]. Animal psychologists further differentiate this "fact memory" into working and reference memory. As first described by Werner Honig, working memory is required when ". . . different stimuli govern the criterion response on different trials, so that the cue that the animal must remember varies from trial to trial" (31). Thus, in contrast to reference memory, which is used to retain information that remains constant over time, working memory is required to remember information that varies unpredictably in time and/or in content.

Delayed (Non)Matching-To-Sample

In principle, assessing working memory is simple: one presents a bit of information (a *sample*) to a subject, withdraws that information, waits a period of time (a *delay*), then presents that same bit of information along with a comparison bit, and asks the subject to identify which bit of information was presented previously (a *choice*). This process is then repeated across a number of trials. Only two bits of information are needed: working memory will be required as long as the sample bit is selected randomly from trial to trial. This procedure forms the conceptual basis for memory paradigms known as delayed matching-to-sample.

Discrimination, Encoding, and Retention

At least three component subprocesses are needed to perform the operations necessary for successful working memory: discrimination, encoding, and retention (30). Discrimination refers to the perceptual (usually—but not always—visual) processes necessary to identify the information being presented during the sample phase of a trial. Encoding refers to the process(es) by which the perceptual information available in the presence of the sample stimulus is converted into an internal representation of that information. Retention refers to the process(es) that maintain the veracity of that information over time (i.e., during the delay). Under some conditions, accurate retrieval of that information may also be necessary, but the short-term, ephemeral nature of working memory suggests that retrieval plays a minor role in it.

Heise and Milar (30) provided a logical means to measure discrimination, encoding, and retention independently in the context of memory tests. If the sample and the comparison stimuli are presented simultaneously ("no-delay"), then only discrimination will be necessary to identify the comparison stimulus that matches the sample. Reductions in accuracy on no-delay trials thus indicate deficits in discrimination. If the sample is terminated immediately prior to presentation of the comparison stimuli ("zero-delay"), then both discrimination and encoding are required for accurate matching of the comparison stimuli with the sample. Reductions in accuracy on zero-delay trials thus indicates a deficit in either discrimination or encoding, or both. If delays of variable length are interposed between termination of the sample and presentation of the comparison stimuli ("*x*-delay"), then discrimination, encoding, and retention are all required for accurate choice. If retention is impaired, accuracy on *x*-delay trials will fall more quickly as *x* (the length of the delay) increases, leading to a steepening of the slope of the function relating choice accuracy to delay (the retention gradient). Combining the three types of trials in a test can thus allow one not only to quantify mnemonic impairment but also to identify its source.

It may be argued that a deficit in discrimination or encoding differs fundamentally from a deficit in retention, because only retention should be considered a mnemonic process. This definition restricts memory to the rate at which information, once acquired, is lost. A broader definition of memory would include discrimination and encoding, without which "remembering" the correct choice at the end of the delay will fail. This semantic argument should not impede efforts to identify and characterize the logically dissociable cognitive processes underlying working memory and their potential disruption by neurotoxic agents.

Delayed Response vs. Delayed Comparison

As also suggested by Heise and Milar, procedures for quantifying working memory can be distinguished along two dimensions into four basic types. The first dimension differentiates "delayed response" tasks from "delayed comparison" tasks. In a delayed response task, the correct response is defined before the delay, whereas in a delayed comparison task, the correct response is not defined until after the delay. Thus, accurate performance in a delayed response task requires processing information about the response, whereas accurate performance in a delayed comparison task requires processing information about the sample stimulus. Delayed matching-to-position [e.g., (11,16)] and delayed matching-to-sample [e.g., (14,68)] exemplify delayed response and delayed comparison procedures, respectively.

Discrete Trial vs. Continuous Format

Both delayed response and delayed comparison tasks may be administered in either a discrete trial or a continuous format. In a discrete trial format, sample and choice stimuli are paired in a given trial, and a given sample applies only to that trial. Delayed matching-to-sample and delayed matching-to-position tasks are presented in discrete trial format. In a continuous format, each stimulus presentation provides both the comparison stimulus for a given trial and the sample stimulus for the next trial. Continuous spatial alternation (29) and continuous nonmatching-to-sample (46) procedures exemplify the continuous format. In continuous spatial alternation, the correct stimulus on trial n is always opposite to the correct stimulus on trial $n \pm 1$; in continuous nonmatching-to-sample, a response to the stimulus on trial n is reinforced if and only if that stimulus differs from the stimulus presented on trial $n - 1$.

D(N)MTS Advantages

All four types of procedures can adequately assess working memory; however, all of the three trial types (no-delay, zero-delay, and *x*-delay) necessary for logical dissociation of the component processes of working memory (discrimination, encoding, and retention) can be presented only in discrete trial, delayed comparison tasks. Continuous procedures are limited to *x*-delay trials. Whereas zero-delay trials can be approximated in discrete trial delayed response tasks, no-delay trials (sample and comparison stimuli presented simultaneously) can be arranged only using the delayed-(non)matching-to-sample format. Thus, this format provides an analytical advantage over the other formats.

Dealing With Mediating Strategies

An advantage associated with delayed comparison procedures involves their ability to avoid mediating strategies that are commonly observed in delayed response procedures [e.g., (25,27,33)]. That is, because the correct response is defined prior to the delay in a delayed response procedure, the subject can in principle physically "bridge" the delay interval by, for example, positioning himself near the location of the correct response. Because the correct response is not known until after the delay in a delayed comparison procedure, this simple positioning strategy is not effective. However, as shown in the original article describing a delayed matching-to-sample procedure (3), pigeons can develop more complex mediating strategies in this delayed comparison procedure, and these strategies substantially improve their choice accuracy. Thus, no working memory procedure is immune to mediating strategies. A common approach to controlling mediating strategies is to require specific "neutral" behavior (e.g., nosepokes into a central food cup) during the delay (10,16), thus reducing the opportunity for mediation.

The best way to determine whether mediating strategies are being utilized is to measure behavior during the delay interval. These measurements have rarely been made: in one instance, "delay presses" (presses on retracted/inactive levers during delays) were recorded from rats performing a delayed matching-to-position task (9). Contrary to expectation, little relationship was observed between either the frequency or the distribution of the delay presses and accuracy of choice, suggesting that these "rehearsal" responses did not effectively improve working memory. Clearly, more work is needed to clarify the role of mediating responses in working memory tasks and their potential role in determining the nature of the mnemonic processes actually engaged by the test procedures.

Jacques Maurissen followed with a second presentation that focused on one of the specific procedures mentioned previously. Here, in the context of attempting to determine the effects of chemicals on important brain functions in rats, it was posited that such functions (e.g., memory) can only be indirectly studied in animals through a careful evaluation of behavior.

DELAYED MATCHING-TO-POSITION (DMTP): DATA, ANALYSIS, AND INTERPRETATION

Behavior is affected by a number of factors. When studying the effects of a test material on memory, it must be remembered that other chemical-induced effects such as motor dysfunction, sensory disturbance, impaired discrimination learning, and decreased motivation can result in decreased attention and responsiveness and, thus, modify the behaviors under observation in the absence of any specific effect on memory. Some tests allow these so-called "nonspecific" or "performance" effects to be teased apart from mnesic processes. The delayed matching-to-position (DMTP) procedure is such a test. A word of caution here about the term "memory." Some scientists equate "memory" exclusively with "information retention" over time, given that information can only be remembered if it has previously been acquired and you cannot forget what you do not know (17,28). Memory will be defined in this manner for my portion of this article. For others, as mentioned by the previous speaker, "memory" is a more global concept that encompasses acquisition, storage, and retrieval of information over time (31). A common link between these definitions is the passage of time. Typically, in a delayed matching-to-position task, an item of information is presented and retention is tested by having the subject select the same item from several alternatives after a delay. The data are usually expressed in terms of percent correct choice, also known as "matching accuracy." Increasing the duration of the delay results in a decreased percent correct choice, confirming that the procedure constitutes a test of memory (12).

DMTP Interpretation

Typically, a series of "percent correct" data points at two or more delays are plotted with time on the abscissa and the corresponding percent correct on the ordinate. A line can generally be fit to the data. It crosses the ordinate at time zero (*Y* intercept) and has a definable slope. The slope of such a function indicates the rate of decay of information (also known as the "forgetting curve" or "retention gradient" discussed earlier).

The intercept at time zero (which is not a measured data point, but which is extrapolated from measured data) represents nonmnesic processes. The need to extrapolate to time zero comes from the fact that, even in the case of zero-second delays, subjects still generally take a few seconds to perform the task. 1) *Different Slope—Same Intercept:* If the data from the treatment group have a steeper slope than those for the control group, but start at time zero at the same performance level (i.e., percent correct), it can be concluded that the capacity to retain information has decreased (i.e., forgetting rate is increased) in the treated group in the absence of nonmnesic confounders. 2) *Same Slope—Different Intercept:* If the treatment group data have a lower intercept than those for the control group, but they have the same slope, it can be concluded that the retention rate is not affected in the treated group, but that information encoding and/or related processes at time zero were affected by treatment. 3) *Different Slope—Different Intercept:* When treatment significantly affects both the intercept and the slope, the data are hard (if not impossible) to interpret, partly because of the possibility of an interaction between intercept and slope.

DMTP Caveats

Before concluding that a test material affects memory, the investigator should pay attention to the following points: 1) *Single-delay experiments*: Memory is a time-dependent process. A minimum of two delays are needed to derive a slope. In the absence of a slope, no inference can be made about memory (i.e., retention) without the confounding effects of encoding, attention, motivation, etc. [(30), p. 157]. 2) *Correction trials:* If the subject has developed a position bias (i.e., repeatedly choosing the same lever), there needs to be some

correction made for that bias so that the data can reflect a true mnesic process. 3) *Mediating responses or "rehearsals"*: By positioning itself next to the lever to be chosen, the subject can increase the reinforcement density by nonmnesic means. The experimental design should minimize opportunities for such mediating responses and the recording system should automatically quantify their occurrence. Finally, the investigator should verify the effectiveness of the measurement by direct observation of subjects during delays. 4) *"Zero-second delay" data point:* Even though the stimulus indicating the end of the delay coincides with the onset of the occasion for responding in the zero-second condition, there is always a short delay before responding actually occurs. The so-called "zero-delay" data cannot, therefore, be construed as a pure expression of nonmnesic processes (because of the time involved): only the extrapolated percent correct choice at zero seconds can. 5) *Arcsine transformation*: If the data are analyzed in terms of percent correct choice rather than as slope and intercept, their distribution at short delays most likely will not be normal, but will have a binomial form. In this case, an arcsine transformation (also called angular transformation) may be useful before statistical analysis (38). 6) *Ceiling/Floor effect*: If, for example, a group exhibits 95–100% correct choices at several short delays (i.e., there is no slope), and the percentage correct monotonically decreases at longer delays, this is evidence for a ceiling effect. Under such circumstances it can be argued that, even in the presence of delay-dependent data, the exact nature of the effect cannot be resolved without further experimentation. The same concerns arise when the data "bottom out" at the longer delays. 7) *Scaling effect*: To analyze proactive interference effects in choice accuracy (i.e., altered performance on the current trial due to the performance on the previous trial), Dunnett et al. (18) used a DMTP task with two levers. They divided the data into trials in which the response on the previous trial was on the same side or opposite side of the response on the current trial. They noticed that the difference in choice accuracy between previous-response-same and previous-response-opposite trials was much greater in old than in young rats, suggesting that old rats were more susceptible to proactive interference than young rats. However, the young rats performed at a higher level of accuracy than the old ones. In a very astute study, Dunnett and colleagues increased the duration of the delay in the young rats to equate their forgetting curve with that of the old rats. Under these conditions (i.e., when baseline levels of remembering were similar), the difference between young and old rats vanished, demonstrating that they were all equally susceptible to proactive inhibition. In other words, the effects of an independent variable on an endpoint cannot be compared in situations where baseline conditions are dissimilar (scaling effect). As a corollary, it is not possible to draw any conclusion when comparing the effects of a test material on similar tasks, one involving memory, the other not (e.g., cued and noncued tasks), in the presence of a baseline difference (e.g., different accuracy levels in the two procedures). In such a case, the investigator could not differentiate between effects due to memory vs. effects due to task difficulty because these factors are inextricably linked and cannot be separated in the presence of a baseline difference. In summary, DMTP techniques are powerful tools for teasing apart mnesic from nonmnesic effects of chemicals, but caution must be exercised in the design, analysis, and interpretation of the findings.

Our colleague from the University of Arkansas, Galen Wenger, presented data obtained in both pigeons and squirrel monkeys with a little-used variation on the DMTS theme in which the subjects' performance was used to adjust delay durations within sessions.

TITRATING MATCHING-TO-SAMPLE PERFORMANCE IN PIGEONS AND SQUIRREL MONKEYS: BASELINE AND CHEMICAL EFFECTS

As we have heard previously, matching-to-sample performance was first described in laboratory animals over 40 years ago (3,24,58). Briefly, a stimulus (the sample stimulus) was presented to the subject and, following a response to this stimulus, it was extinguished. Following some delay, two or more comparison stimuli, one of which matched the original sample stimulus, were presented simultaneously to the subject. A response to the stimulus that matched the original sample stimulus produced a reinforcing stimulus whereas a response to the stimulus that was not identical to the original sample stimulus resulted in the extinguishing of all stimuli and the initiation of a time-out period. Following the presentation of the reinforcing stimulus or the completion of the time-out period, the next trial was initiated by the presentation of a sample stimulus. Since these original reports, a number of studies have shown that percent accuracy of the matching response is proportional to the length of the delay (13,39). These reports also showed that, in pigeons, matching accuracy approaches chance performance at delay values of 10–12 s.

Procedural Complications

Although the matching-to-sample schedule as just described fulfills many of the criteria of a task measuring short-term or working memory, there are a number of technical problems associated with it. First, subjects frequently develop a position bias evidenced by a majority of the responses to the comparison stimuli being restricted to either the right- or left-hand key of a three-key pigeon chamber. As a result, on approximately 50% of all trials the subject's response to the right-hand key, for example, results in a matching response and is reinforced. Unfortunately, such biases in responding, even when not observed under control conditions, are frequently seen following drug administration, making interpretation of dose–response curves difficult. A second problem observed with the procedure is the frequent occurrence of prominent ceiling and floor effects. With only two comparison stimuli presented following the delay, chance performance will be equal to 50% accuracy: this limits the magnitude of any decrease in accuracy that can be observed and is particularly problematic when accuracy, particularly at the longer delays used, is near this level under control conditions. This is further complicated by the fact that, when stability of responding is achieved following training, the percent accuracy at short delays is usually around 95%. Thus, there is little or no room above the control performance in which one might observe a statistically significant improvement following drug administration. Some investigators have tried to minimize this ceiling effect by lengthening the delays, resulting in a lower percent accuracy in control performance. However, even with such an approach, no consistent improvements in accuracy have been reported following drug administration in pigeons. This raises the issue of whether a drug can improve control performance that may represent the limit of the organism's abilities.

Delay Titration and Choice Position Randomization

As a result of these issues, our laboratory began a series of experiments with pigeons and modified the procedures de-

scribed above in several significant areas. First of all, the ceiling and floor effects were minimized by allowing the length of the delay to change as a function of the subject's performance. Thus, the dependent variable becomes the length of the delay rather than percent accuracy. Similar titration procedures have been reported previously and appeared to have potential for the study of drug effects on memory function (13,40,57). In our experiments with pigeons, the delay value on the first five trials of the session was fixed at 3 s. On the sixth and all subsequent trials the delay value was either increased, did not change, or decreased depending upon whether accuracy on the previous five trials was >80%, 80% or <80%, respectively (66,67). Control performance was characterized by choice accuracies of 80% or higher at much longer delays than those that have been reported using fixed delay procedures. Effects on accuracy were only observed when drug-induced changes exceeded the ability of the titration schedule to maintain 80% accuracy (i.e., by further decreasing the length of the delay). A second change in the procedure was to present the two comparison stimuli randomly on all three keys of a three-key pigeon chamber rather than just on the two side keys. This resulted in a 33% probability than any single key would remain dark during the presentation of the comparison stimuli and effectively prevented the development of position biases. We also compared control performance and drug effects in pigeons responding under this titration procedure with those performing in schedules using fixed delay values ranging from 0 to 6 s. The titration schedule was shown to maintain higher percent accuracies at longer delays and provided more graded dose–response curves than those observed in pigeons responding under matching-to-sample baselines using fixed length delays.

Squirrel Monkeys

The same titration procedures and parameters have also been used with squirrel monkeys (32) with generally similar results. However, in squirrel monkeys overall percent accuracy for the session was frequently observed to decrease in the absence of a decrease in the average value of the delay for the session. This suggests that the same titration parameters that worked beautifully in pigeons are not optimum for squirrel monkeys. It should also be noted that recent work using fixed delay values in experiments with squirrel monkeys suggests that matching performance is not as good in squirrel monkeys as it is in pigeons.

In summary, pigeons and squirrel monkeys can be trained to respond under a titrating matching-to-sample procedure. However, as noted, the titration parameters that appear to work fine in pigeons may not be optimum for squirrel monkeys. The titration procedure has several advantages over fixed delay procedures including: the level of difficulty is more constant across subjects, it is easier to change the level of difficulty in a consistent manner, and the prominent ceiling and floor effects are minimized. The disadvantages of the titration procedure compared to fixed delay procedures include: a difficulty in showing interactions between delay length and drug effects, and a smaller historical data base for comparison.

Jerry Buccafusco provided a discussion of his experience looking at drug effects on DMTS performance in both young and old macaques, and reminded us of the utility of the aged monkey model for studying phenomenon shared with humans.

DELAYED MATCHING-TO-SAMPLE PERFORMANCE IN YOUNG AND AGED MONKEYS IN THE ASSESSMENT OF NEW DRUGS FOR THE TREATMENT OF COGNITIVE DISORDERS

The behavioral repertoire of old world monkeys resembles that generated by the human neurobehavioral system more than that of any other laboratory animal, except higher apes (49). Behavioral tasks that tap the higher cognitive abilities of these nonhuman primates may provide information relevant to normal human aging and to the dementias. Aged monkeys display many similar pathologic and neurochemical changes of the central nervous system seen in Alzheimer's patients (4,60,65). We have recently confirmed the presence of numerous ubiquitin-positive senile plaques that colocalize β-amyloid protein in aged macaques (61). Also, these aged animals respond cognitively in a manner similar to impaired humans following administration of memory enhancing or amnestic agents [for review see (15)]. The method most frequently employed to test the sophisticated cognitive repertoire of these monkeys has been one or another variation of delayed response tasks. The delayed matching-to-sample (DMTS) task allows the measurement of abilities that are relevant to human aging, such as attention, strategy formation, reaction time in complex situations, and memory for recent events. A similar version of this task has been employed to demonstrate cognitive impairment in patients with Alzheimer's disease (34). Our data collection system utilizes several variables that relate a monkey's performance to three categories: (a) color preference, (b) position preference, and (c) response latency. For example, the formation of color strategies reflects a category of cognitive ability, which not only is unique to primate species but may be mediated by different neuronal substrates than those that mediate memory recall. The ability to form such concepts very likely relates to human declarative memory (59). This situation is highly appropriate for animal experimentation, and the models to be employed should offer the best available subjects for prehuman trials.

The DMTS Procedure

Our DMTS paradigm is computer initiated, with the experimenter isolated from the animal. However, we determined early on that several animals could be tested simultaneously in their home cage environment with no obvious loss of task stability or predictability (5,23). Test panels are attached to the home cages. Stimuli on the test panels are 2.54 cm diameter colored disks (red, yellow, or green) presented by light-emitting diodes centered behind clear plastic push-keys. A trial is initiated with the illumination of the sample key by a colored disk. A key press extinguishes the sample light and initiates one of four preprogrammed delay intervals, during which no disks are illuminated. Following the delay interval, two choice lights found below the sample key are illuminated. One of the choice lights matches the color of the sample light and these disks remain illuminated until a monkey presses one of them. Key presses of choice stimuli that match the color of the sample stimulus are reinforced by delivery of a 300-mg banana-flavored food pellet. Nonmatching choices are neither reinforced nor punished. Color patterns are fully counterbalanced for side, delay, and matching-to-sample. A new trial is initiated 5 s after the second key press on a preceding trial. Monkeys complete 96 trials on each day of testing. Four possible delay intervals between a monkey's response to the sample light and the presentation of the two choice lights are used: these delay intervals are individually adjusted to produce stable performance levels approximating

the following criteria: zero-second delay (85–100% correct); short delays (75–84% correct); medium delays (65–74% correct); and long delays (55–65% correct). The rationale for this procedure is to normalize performance based on the widely varying capabilities of the monkeys (63). Without this normalization process, intersubject variability is increased, and the more task-proficient animals would be subject to significant ceiling effects.

Age and Drug Treatments

It has been our experience that, although aged macaques are impaired in their performance of the DMTS task, both nonaged adults and aged monkeys respond similarly to most classes of memory-enhancing or amnestic drugs. The model has predicted drug efficacy very well, with doses not unlike those used clinically. In fact, we have examined the cognitive-enhancing potential of a number of drug classes, including, for example, acetylcholinesterase inhibitors, acetylcholine-releasing agents, cholinergic muscarinic and nicotinic receptor agonists, subtype-selective serotonin receptor antagonists, and α_2-adrenergic receptor agonists (7,35,37,63,64). Drugs with clinical amnestic actions, such as scopolamine (62), mecamylamine (23), and nitric oxide synthase inhibitors (47), also disrupt DMTS performance in our monkeys.

Distractability

Variations of the DMTS task have been used to help model other disease states. We instituted a task-relevant distractor that impairs performance only during the distractor-associated trials: on 19% of all trials, a task-relevant distracting stimulus (randomly flashing the sample and cue lights) is presented during either the initial 3 s of delay intervals (early onset) or the final 3 s of delay intervals (late onset). In aged monkeys, both early and late onset distractors impaired task performance on trials with the shortest delays, but did not affect accuracy on trials with long delays. In contrast, young adult monkeys were impaired only by the presence of an early onset distractor, and only for those trials associated with the shortest delays. Methylphenidate (0.005–1.0 mg/kg) reduced distractibility in the young monkeys, but was not effective in this regard in aged monkeys. Thus, attention and recall after brief delays can be impaired following exposure to a task-relevant distracting stimulus in both aged and young adult monkeys, but aged monkeys are more susceptible to distraction and do not receive benefit from methylphenidate administration. We also demonstrated that nicotinic receptor agonists were as effective as methylphenidate in reversing distractor-associated impaired DMTS performance (36,48). Therefore, central nicotinic receptors may be targeted for the treatment of the dementias, as well as for attention deficit disorders; and versions of the DMTS task in young and aged macaques may continue to be useful animal models for these syndromes.

In our transition from animal data to humans, John Chelonis presented findings obtained from a population of normal children, relating changes in DMTS performance to age in a developmental context. These data suggest differential developmental profiles for speed vs. accuracy of performance.

AN ANALYSIS OF DELAYED MATCHING-TO-SAMPLE PERFORMANCE AS A FUNCTION OF DELAY AND AGE IN CHILDREN

As has been discussed repeatedly, delayed matching-to-sample (DMTS) procedures have been used extensively to assess memory in nonhuman subjects (42,69). Often, several delays are used that vary in length from very short (e.g., 0–1 s) to very long (e.g. over 30 s), allowing aspects of both encoding and short-term retention to be measured (10,11). Because DMTS procedures readily lend themselves to use in animals, a variety of studies have been conducted to examine the roles that specific brain areas play in processes associated with performance of these tasks [see (2) for a review] and extensive research has been conducted using these procedures to assess the affects of various psychoactive substances on memory in animals (6,8,26,44). Variations in the DMTS procedure have been used to assess memory in specific populations of human subjects including patients diagnosed with unipolar depression (22) and elderly patients diagnosed with specific disorders that involve an impairment in memory (1,41,56). DMTS procedures have also been used to assess memory in children between the ages of 1 and 3 years (42), and children diagnosed with a variety of behavioral and developmental disabilities (2,45). However, this task has not been used to assess how memory and encoding develop in normal children as they mature.

Developmental Aspects of DMTS Performance

The present experiment assessed DMTS performance in 535 children between the ages of 4 and 12 years with no known psychological problems. Six delays, ranging from 1 to 32 s, were used to determine how normal development affects response latency, encoding, and retention. The results indicated that overall accuracy on this task increased as children grew older and variability simultaneously decreased with the largest decreases occurring at ages 7 and 9 years. Mean observing response latency (the amount of time that a subject takes to press the sample stimulus and, thus, initiate the delay), and the variability in this measure decreased as age increased: fewer children exhibited extremely long observing response latencies as age increased. Mean choice response latency (the amount of time a subject takes to make a choice response, i.e., select from one of three comparison stimuli, after a delay), and the variability in this measure also decreased as age increased. Unlike observing response latency, however, there appeared to be a stepwise decrease in variability with the most dramatic decreases occurring at ages 5.5 and 8 years. Also, there were not any extreme outliers like those noted in the observing response data.

Accuracy

The rate of decay in accuracy was greater for younger children, indicating decreased retention: for 4-year-old children accuracy decreased by 20% from the shortest (1 s) to longest (32 s) delay, but for 11-year-old children the decrease for the same delays was only about 3%. Additionally, older children were more accurate in recalling the correct stimulus at 1-s delays than younger children, indicating better encoding of the stimuli in older children.

Choice Response Latency

Choice response latency at each delay was also influenced by age. Specifically, choice response latency did not change much as a function of delay for the older children, but increased dramatically as delay increased for younger children. For example, the choice response latency for 4-year-old children increased by 3.6 s from the shortest to longest delay, but for 11-year-old children this increase was only 0.4 s. Also as

children became older, the choice response latency curve shifted downward (latencies decreased). If we believe that choice response latencies are a function of attentional processes, then the data suggest that younger children are less able to attend to the task, and this attentional difference is magnified as delays increase.

Performance of a delayed matching-to-sample task is clearly dependent on age, with accuracy improving as children mature: the rate of improvement was greatest at younger ages and decreased as children grew older. Both observing and choice response latencies decreased as children grew older and the rate of decrease was also greatest in younger children. The data indicate that there are differences in aspects of encoding and retention in children of different ages. Specifically, young children appear to have more difficulty encoding information than do older children and they also appear to have more difficulty retaining information once it is encoded.

Normative DMTS Data

This research provides normative DMTS data for children that will be useful for designing research utilizing this and perhaps other operant procedures to assess important aspects of brain function in children. Additionally, these data can be compared to similar data obtained from children with various physiological and/or psychological problems to determine if such children differ significantly from normal subjects in DMTS performance. Preliminary data suggest differences in DMTS performance between normal children and children with attention deficit/hyperactivity disorder.

Our colleague from the UK, Rebecca Elliott, presented recent findings on the utility of DMTS procedures in several clinical populations and in cases where attempts have been made to visualize specific brain areas in humans thought to be associated with DMTS performance.

DMTS PERFORMANCE IN NEUROLOGICAL AND PSYCHIATRIC PATIENTS

The data discussed were obtained using a computerized visuospatial version of a delayed matching paradigm. This test forms part of the "CANTAB" battery of neuropsychological tests that was developed in Cambridge, UK, in parallel with analogous tests for experimental animals (50,53,54). The CANTAB delayed matching-to-sample (DMTS) paradigm uses complex patterns made up of four subelements with different colors and shapes. The sample stimulus is briefly presented, then after a variable delay subjects are presented with a choice of four test stimuli and must select the one that matches. There are four delay conditions: simultaneous, where the sample remains on the screen while the choices are presented (essentially a perceptual and attentional control), and three delay conditions (memory conditions) where the sample disappears 0, 4, or 12 s before the choices are presented. Subjects respond by physically touching the appropriate stimulus on the touch-sensitive computer screen. Both accuracy and latency of performance can be measured but only accuracy data will be discussed here.

Task Standardization

The DMTS paradigm has been standardized in a large group of normal volunteers (n = 787) to determine how performance varies with age and IQ (50). In adults, accuracy of performance declined with increasing age. Performance at the longer delays was affected first but the deterioration then spread to shorter delays. There was also an effect of IQ variation, with subjects in the highest of three IQ bands performing significantly better. These results stress the importance of comparing patient groups to age- and IQ-matched controls.

Lesion Studies

Patients with frontal lobe lesions did not show significant impairments on the task whereas patients with temporal lobe lesions or amygdalo-hippocampectomies showed impairments at all delays (43). Their performance on the simultaneous matching condition was normal, suggesting that their delay impairments were truly mnemonic rather than secondary consequences of attentional or perceptual impairments. These results confirm the consensus from the animal literature that DMTS performance depends crucially on intact temporal lobes but, certainly at relatively short delays, is less dependent on prefrontal cortices.

Parkinson's Disease (PD) and Dementia of the Alzheimer Type (DAT)

Patients with PD or DAT were studied by Sahakian et al. (55) and both these groups showed deficits in task performance. There were, however, subtle differences in the nature of these deficits, suggesting distinct cognitive mechanisms of impairment. Patients with DAT showed pronounced delay-dependent impairments with intact simultaneous matching. By contrast, the patients with PD were more impaired at the simultaneous condition, suggesting a fundamental perceptual or attentional impairment, which in more severe cases led to a secondary "memory" deficit in the delay conditions. For DAT, but not PD, the DMTS task was especially sensitive even early in the course of the disorder when cognitive impairment is relatively mild.

Psychiatric Disorders

The DMTS test has also proved particularly sensitive to psychiatric disorders (20,22). Patients with schizophrenia or unipolar depression showed performance deficits on this task that were disproportionate to their overall level of cognitive impairment. Again, there were subtle and interesting differences in the pattern of DMTS impairment between these two patient groups: in schizophrenic patients, there was no impairment at simultaneous matching but there were dramatic delay-independent DMTS deficits. Depressed patients, on the other hand, showed deficits on simultaneous and delayed matching but, unlike patients with PD, their deficit in the delay conditions could not be fully accounted for by a perceptual/attentional deficit but implicated an additional mnemonic impairment.

Longitudinal Studies

In an important extension of the clinical use of this paradigm, patients with DAT and with depression have been studied longitudinally, allowing the DMTS deficits to be related to the clinical course of these disorders (21,51). Patients with DAT showed a progressive deterioration in DMTS performance and, as seen with normal ageing, deficits became apparent at longer delays first and then spread to shorter delays. By contrast, the study of depression looked at the relationship between performance and clinical improvement. Performance on simultaneous matching returned to normal with clinical re-

mission but some slight residual deficits were seen in the delay conditions.

Drug Studies

The complex patterns of deficits associated with these various disorders and the dissociations in the nature of deficits between populations raises interesting questions about the neural substrates of the DMTS task and its component processes. Recent data have begun to address these questions. Pharmacological studies have been used to show how DMTS performance is affected by psychoactive drugs. In a study of the cholinergic receptor antagonist, scopolamine, with normal volunteers (52), the drug caused significant dose- and delay-dependent impairments resembling those associated with normal ageing and DAT. The benzodiazepine, diazepam, did not impair performance, suggesting that the effects of scopolamine were genuine selective short-term memory effects rather than secondary consequences of sedation.

Imaging Studies

An alternative approach to considering the underlying neural mechanisms of human DMTS performance is to use functional imaging. A recent PET study (19) using a version of this DMTS paradigm with a 5-s delay showed that, compared to a perceptuomotor control task, DMTS task performance was associated with activations in regions of the posterior perceptual cortex, thalamus, anterior cingulate, and cerebellum. There were also significant deactivations in the temporal lobes bilaterally, confirming an important role for these structures. This brief discussion of findings from a number of studies using a variety of complementary approaches shows how a single task has been used to characterize normal and abnormal visual short-term memory, significantly advancing our understanding of this process.

CONCLUSION

Delayed matching-to-sample procedures provide robust behavioral measures thought to provide insight into aspects of processes associated with short-term memory and attention. They can be easily automated, circumventing the need for—and, thus, the problems associated with—tester–testee interaction. They are readily applicable in a variety of species allowing for direct interspecies comparisons. Performance of them by humans is associated with other important measures of brain function such as IQ. Subjects can perform these tasks repeatedly, allowing for the conduct of important longitudinal studies. Although they are noninvasive, they provide important insight into the workings of the central nervous system. Coupled with powerful brain imaging techniques, it is not beyond comprehension that someday we will come to know which brain structures subserve the varied aspects of behavior knowable through the use of DMTS procedures.

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