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ASSESSING COGNITIVE FUNCTION IN ANIMAL MODELS OF MENTAL RETARDATION

Barbara J. Strupp* and Adele Diamond

Division of Nutritional Sciences & Department of Psychology, Cornell University, Ithaca, New York (B.J.S.)
and Department of Brain and Cognitive Sciences, MIT, Cambridge, Massachussetts

Recent advances in the development of animal models of human mental retardation (MR) syndromes offer exciting possibilities for understanding the pathogenic processes in these disorders. However, because MR is, by definition, a disruption in "cognition," the potential offered by these models can only be fully realized if the attention devoted to the cognitive assessment of the animals is equal to that given to the genetic manipulation that created them. Accordingly, this paper provides guidelines for assessing cognitive function in animal models of human cognitive pathology, with an emphasis on MR syndromes. One of the major issues considered is task selection. Because different cognitive processes depend on different brain systems, the nature of the brain damage will determine the tasks that will be most sensitive in any given disorder. Tasks that are most sensitive to one disorder will often reveal no dysfunction in a different disorder. It is therefore imperative that task selection is guided by knowledge, or hypotheses, about (a) the neural systems disrupted in the target disorder; and/or (b) the specific cognitive abilities impaired in the target human syndrome. For example, a hallmark deficit in many MR syndromes is an impaired ability to transfer learning from one situation to another. Because this process has rarely been tested in animal models of MR, it is likely that the degree of impairment in the animals has been significantly underestimated. When devising tasks for animals based on the human data, however, there are dangers in developing analogous tasks, and even in using identical ones. These problems are discussed, along with potential solutions. A second major theme of the paper is that critical information can be gleaned by analyzing the details of subjects' performance, rather than by examination of success and failure rates alone. These types of in-depth analyses can aid in specifying the nature of the impairment, and in illuminating the neural bases of the dysfunction. Examples of useful techniques for analyzing behavior and understanding brain-behavior relationships are provided.

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Recent advances in the development of genetic animal models of human mental retardation (MR) syndromes offer exciting possibilities for understanding the pathogenic processes in these disorders. This information will further understanding of brain-behavior relationships, and is crucial for developing treatments that can ameliorate or prevent the cognitive dysfunction. These models can only be successful, however, if equal consideration and attention are devoted to the assessment of cognitive functioning—the crucial outcome variable. This paper details some issues central to assessing cognitive function in studies using animal models to study human cognitive pathology, with an emphasis on MR syndromes. We illustrate these issues with specific examples, drawing in large part from our respective research programs.

TASK SELECTION

Two types of information have proven useful in guiding the selection of tasks for animal models of human cognitive pathology [see Strupp and Levitsky, 1995]. The first type of information is the cognitive profile of the human condition being modeled, i.e., a delineation of the impaired, and the preserved cognitive processes. Tasks can then be selected that tap these same processes in the animal model being studied. Ample data now support the conclusion that the biological bases of specific cognitive processes are similar across mammals. Because the new genetic MR models are rodent models, it is of particular relevance that this type of correspondence has been demonstrated between humans and rats in cases of damage to the hippocampus [e.g., Rothblat et al., 1993; Kesner, 1990; Eichenbaum et al., 1986; reviewed in Squire, 1992], prefrontal cortex [e.g., Dunnett, 1990; Murphy et al., 1996; Kesner, 1990; Shaw and Aggleton, 1993; reviewed in Kolb, 1984], amygdala [e.g., Cador et al., 1989; reviewed in Aggleton, 1992], posterior parietal cortex [e.g., Kesner et al., 1989; Kesner and Gray, 1989], and the coeruleocortical noradrenergic system [e.g., Bunsey and Strupp, 1995; reviewed in Clark et al., 1987; Robbins et al., 1985], to name just a few. A second type of information that can guide task selection is the nature of the neuroanatomical, neurophysiological, and/or neurochemical changes seen in the brains of individuals with the target MR syndrome. With growing knowledge of the cognitive functions linked to specific brain systems, it is increasingly possible to use neuropathological information to identify tasks that would be expected to show dysfunction in the target syndrome.

Before discussing each of these approaches in more depth, it may be necessary to explain why all of this is necessary. If an animal is impaired, will that not be evident on any learning task? The answer to that question is, unfortunately, a resounding "no," as illustrated by the many tasks that have failed to detect impairment in animal models of phenylketonuria (PKU) or hypothyroidism, conditions that produce profound MR in

*Correspondence to: Dr. B.J. Strupp, 109 Savage Hall, Cornell University, Ithaca, NY 14853. E-mail: bjs13@cornell.edu

humans (see Fig. 1, left column). The absence of any impairment on these tasks cannot be attributed to inadequacies in the experimental models themselves because many other cognitive tasks have revealed significant cognitive impairments with these same treatment regimens (see Fig. 1, right column). A major reason arbitrarily choosing a learning or memory task will not provide an accurate assessment of cognitive functioning is that different cognitive processes are biologically distinct—they depend on different neural systems. It follows that a particular disorder that damages only certain brain systems will alter certain cognitive processes but leave others intact. Consequently, performance will be altered on certain tasks but not others.

This point can be illustrated by the cognitive effects of damage to the hippocampus and surrounding cortical tissue (entorhinal, perirhinal, and parahippocampal cortices), often collectively referred to as the medial temporal lobe. Despite a profound impairment in explicit memory (memory for facts, events), other cognitive functions are relatively preserved, including attention, perception, and implicit memory (memory for skills, priming). Indeed, individuals with this type of brain damage experience little decrement in IQ despite anterograde amnesia so profound that they have little knowledge of events that have occurred since their injury [Milner, 1966; Corkin, 1984; reviewed in Squire, 1992]. The implications of this analysis are clear. First, it is easy to miss dysfunction if the tasks are not carefully selected. For example, if the task taps a specific domain of processing, the dysfunction may be missed because the task does not tap the particular processes affected in the syndrome of interest. On the other hand, if a general task is used that does not depend heavily upon the specific cognitive processes affected, performance on that task may not be significantly altered. A second implication is that one cannot rank all cognitive tasks along a unidimensional "sensitivity" scale. The nature of the brain damage will determine the type of cognitive dysfunction that will be produced in any given disorder and, therefore, the type of task that will reveal that impairment. Task selection for animal models of MR must, therefore, be "informed" rather than arbitrary.

Differential task sensitivity in models of PKU and Hypothyroidism

Not Impaired	Impaired
Active avoidance	Maier 3-table test
Lashley III maze	Hebb-Williams maze
Simple discrimination tasks	Social transmission of food preferences
DRF operant schedule	Complex water maze
DRL-12 operant schedule	Learning set formation
Acquisition	Latent learning
Extinction	Delayed Spatial Alternation
Re-learning	Reversal of discriminative active avoidance
Long-term retention	*DRL (if preceded by CRF)
DRL-12	*Operant switching discrimination
Object discriminations	*Pattern learning task
Social learning	
Discriminative active avoidance	
Simple water maze	
Elevated T-maze	
Progressive ratio	
Spatial discrimination	*due to emotional/motivation effects
Runway discrimination	
Nonspatial discrimination	

Fig. 1. Tasks that have not revealed deficits in animal models of hypothyroidism or PKU (left column), in contrast to those that have revealed dysfunction (right column).

Modeling the Cognitive Profile

One useful approach, as noted above, is to review the human literature on the specific MR syndrome being modeled and attempt to delineate the cognitive functions that are impaired and those that are intact. This type of information is particularly crucial when modeling MR syndromes (as opposed to some other cognitive disorders) because a low IQ score can result from disturbances in many different cognitive processes. Although no one cognitive profile characterizes all individuals with MR, due primarily to the heterogeneity of conditions that produce MR, it is possible to identify some processes that are commonly affected in MR syndromes [reviewed in Hale and Borkowski, 1991; Brooks et al., 1984, 1987; McIlvane and Cataldo, this issue]. Some processes that can readily be modeled in rodents include: (1) transfer of learning [e.g., Campione and Brown, 1984; Campione et al., 1985], (2) selective and sustained attention [Tomporowski et al., 1990; Tomporowski and Allison, 1988; Nettelbeck et al., 1984; Hale and Borkowski, 1991], (3) inhibitory control [Cha and Merill, 1994; Costantini and Hoving, 1973; Ellis et al., 1989; Ellis and Dulaney, 1991; Harnishfeger and Bjorklund, 1994], (4) working memory [e.g., Elliset al., 1985; Hale and Borkowski, 1991], and (5) speed of information processing [Sperber and McCauley, 1984]. Processes that are generally not affected include long-term memory and the rate of learning simple discriminations [Brooks et al.,

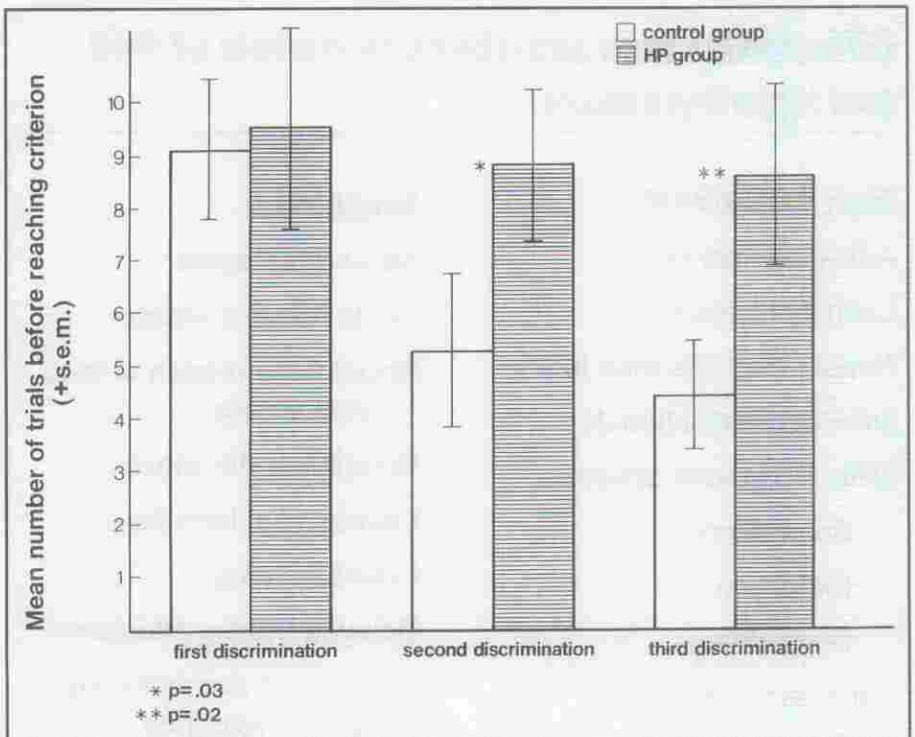

Fig. 2. Results of a learning set task administered to rats exposed to neonatal hyperphenylalaninemia (a model of PKU) and controls. The learning set task was comprised of three 2-choice olfactory discrimination tasks, administered sequentially. Although the PKU rats (the HP group) did not differ from controls in the rate at which they learned the initial discrimination, they did not improve across the three tasks, contrary to the controls. As a result, the HP group was significantly impaired relative to controls on both the second and third discriminations [from Strupp et al., 1990].

1987]. When using an animal model to study an MR syndrome, it is best to include tasks that tap both the impaired and the intact processes in the analogous human condition. Including both types of tasks aids in determining the specificity of the impairment and the validity of the animal model. Rodent tasks designed to assess transfer of learning are described below to illustrate this approach.

Deficient Transfer of Learning in an Animal Model of PKU

An impairment in the transfer of learning across situations is frequently cited as a major impediment to normal functioning in individuals with MR, and a hallmark of MR syndromes [e.g., Campione and Brown, 1984; Campione et al., 1985]; yet this process is rarely tested in animal models. In fact, it is most common to test experimentally-naive animals on a single learning task. We [Strupp and colleagues] reasoned that because this testing situation does not assess the animals' ability to benefit from prior relevant learning experiences—a process that is profoundly affected in human MR—it is likely to result in an underestimation of the cognitive impairment in models of MR [discussed in Strupp and Levitsky, 1990]. This prediction proved to be true in rat models of both classic [Strupp et al., 1990] and maternal [Strupp et al., 1994] PKU, conditions known to produce MR in humans. In these studies, the animals were given a series of related olfactory discrimination tasks designed to permit positive transfer of learning between tasks. The study with classic PKU used a three-problem learning set task; the later study with maternal PKU used a nine-problem series of related tasks, comprised by three different types of task, with three exemplars of each. Learning transfer was defined as significantly faster learning of a given task by animals having mastered the earlier tasks in the series, relative to experimentally naive animals given only that one task.

In both models, the PKU group benefitted significantly less than controls from experience with similar discrimination problems, with the consequence that their impairment relative to controls increased across successive problems (see Fig. 2). It should be emphasized that none of the tasks that comprised the sequence, when given as a single task to experimentally naive rats, revealed an impairment in the PKU group in either study. In contrast, each of these tasks revealed significant impairment when administered in the task sequence after the animals had mastered a similar task. Thus, a task series designed to allow positive transfer of learning between tasks revealed impairments in these MR models that would have been missed if any of the tests had been administered singly. These findings support the importance of including assessments of learning transfer in studies of MR syndromes. They also illustrate the more general principle that task selection for animal models of human cognitive pathology should be guided by an analysis of the cognitive profile of the target human disorder.

Neuropathologic Data as a Guide for Task Selection

Information concerning the nature of the underlying brain damage can also be very useful in guiding task selection when studying animal models of MR syndromes. Tasks can then be selected that are sensitive to damage in the neural system hypothesized to be disrupted in the MR syndrome. This approach can serve several functions, each of which is discussed below. First, it can suggest tests that are likely to be sensitive to dysfunction in the animal model. As noted above, if one selects tasks arbitrarily, without knowledge of the target syndrome, an impairment can easily be missed because the affected cognitive processes were not tapped. To illustrate this approach, consider a hypothetical syndrome in which pathological studies have revealed abnormalities in hippocampal structure. Based on the substantial database linking hippocampal damage in rodents to impaired memory in the radial arm maze [see Squire, 1992], this task would be an excellent candidate for revealing dysfunction in the syndrome of interest.

Information about the locus of the neural damage in the MR syndrome also provides a means of using the cardinal cognitive impairment in the target syndrome to guide task selection for the animal model, in cases where this function is not readily modeled in the animal. For example, in Williams syndrome, the most severe impairment is found in the area of visuoconstructive spatial abilities, reflected by extremely low scores on the pattern construction subtest of the Differential Abilities Scales [Bellugi et al., 1988, 1992, 1994]. It is not at all clear how to devise a similar task for rodents, and if one attempted to do so, it is very possible that the brain region(s) on which the tasks depend would be different in rats and humans. Under these circumstances, one useful approach would be to identify the neural system whose damage is thought to underlie the visuospatial constructive

deficits seen in the Williams patients, and then select a task for rodents known to be sensitive to damage to that brain region. As the pattern of deficits implicates dysfunction of parietal cortex, a rodent model of Williams syndrome should include tasks sensitive to parietal cortical damage in that species; examples include the cheeseboard task [Kesner et al., 1989] or the item memory task [Kesner and Gray, 1989].

A third function served by this approach is to test hypotheses about the basis of the cognitive impairment. Often an investigator has a hypothesis about which neural system is affected in a given disorder. This may be based on biologic considerations or on similarities between the cognitive deficits seen in persons with the disorder and the deficits seen when a particular neural system is not functioning properly. Tasks can then be selected that are known to be sensitive to disruption of this brain system. As always, it is important to include control tasks that allow one to eliminate competing hypotheses about why subjects have performed as they have. Preserved performance on such control tasks makes it more likely that the disorder affects only the specific aspects of cognition and the specific neural systems hypothesized to be affected. It is also important to use more than one task dependent on the neural system in question so that one can obtain converging evidence. No task is perfect. There may be a plausible alternative hypothesis for why a particular result was obtained with one task, but it is unlikely that an alternative hypothesis can also account for converging evidence from multiple tasks. The cognitive profile on these various tasks can shed light on the neural system(s) affected, and more finely delineate the nature of the cognitive impairment in the MR disorder of interest.

Prefrontal Dopamine Deficiency in Early-Treated PKU

The utility of this approach is illustrated by our [Diamond and colleagues] research on PKU. PKU is a genetic disorder in which the ability to convert the amino acid, phenylalanine (Phe), into another amino acid, tyrosine (Tyr), is impaired [Woo et al., 1983; Lidsky et al., 1985]. Levels of Phe in the bloodstream rise to at least ten times normal and levels of Tyr in the bloodstream usually fall [e.g., Krause et al., 1985], resulting in widespread brain damage that causes severe MR [e.g., Cowie, 1971]. When PKU is moderately well controlled by a diet low in Phe (thus keeping the imbalance between Phe and Tyr in the bloodstream within moderate limits) severe MR is averted, but deficits remain in certain cognitive functions [Krause et al., 1985; Pennington et al., 1985; Faust et al., 1986; Brunner et al., 1987; Smith and Beasley, 1989; Welsh et al., 1990]. For example, in our 4-year longitudinal study of children treated early and continuously for PKU we found that children with PKU whose plasma Phe levels were moderately elevated (3–5 times normal), failed all six tasks that required both holding information in mind (working memory) and acting counter to one's initial tendency (inhibitory control)—cognitive abilities dependent on dorsolateral prefrontal cortex. In contrast, these children generally performed normally on the control tasks, most of which tapped the functions of either the medial temporal lobe or posterior parietal cortex. These results suggest that the cognitive impairment of children with PKU who are treated early and continuously may be specific to the dorsolateral prefrontal cortical system.

The potential offered by these models can only be fully realized if the attention devoted to the cognitive assessment of the animals is equal to that given to the genetic manipulation that created them.

We [Diamond, 1994; Diamond et al., 1994, submitted] reasoned that the moderate imbalance in the plasma Phe to Tyr ratio in these children causes a modest reduction in the amount of Tyr reaching the brain due to the competition between Phe and Tyr at the blood-brain barrier [Oldendorf, 1973; Pardridge and Oldendorf, 1977]. Tyr is the precursor of the neurotransmitter, dopamine. Most dopamine systems in the brain are unaffected by modest changes in the level of Tyr. However, the prefrontally-projecting dopamine neurons differ from most other dopamine neurons in the brain in that they have higher rates of firing and of dopamine turnover [e.g., Thierry et al., 1977; Bannon et al., 1981; Tam et al., 1990]. This makes prefrontal cortex acutely sensitive to even a small reduction in Tyr. Indeed, moderate reductions in CNS levels of Tyr that have little effect on dopamine synthesis in other neural regions (such as the striatum), profoundly reduce dopamine synthesis in prefrontal cortex [Bradberry et al.,1989]. Moreover, reducing dopamine in prefrontal cortex produces deficits in the cognitive abilities dependent on prefrontal cortex which can be as severe as those found when dorsolateral prefrontal cortex is removed altogether [Brozoski et al., 1979]. For these reasons it seemed plausible that the mild imbalance in the plasma Phe:Tyr ratio of children treated early and continuously for PKU might well result in deficits in the cognitive abilities dependent on prefrontal cortex, without other cognitive abilities dependent on other neural systems being affected. To test this hypothesis, we had to turn to an animal model because, while cognitive performance and plasma Phe and Tyr levels can be measured in children, regional variations in neurotransmitter levels in the brain cannot.

How might one use this prefrontal-dopamine hypothesis to guide the selection of behavioral tasks for studies designed to test this hypothesis using an animal model of early-treated PKU? We chose the delayed alternation task because successful performance on it has been linked to the integrity of prefrontal cortex in both monkeys [Jacobsen and Nissen, 1937; Battig et al., 1960; Kubota and Niki, 1971] and rats [Wikmark et al., 1973; Larsen and Divac, 1978; Bubser and Schmidt, 1990]. On this task, the animal must remember which goal arm was entered on the previous trial, and the animal is rewarded only for *alternating* goal arms (i.e., selecting the goal arm *not* selected on the previous trial). By varying the delay, the experimenter can vary the amount of time the target information must be held in mind. The hallmark of the sequelae of prefrontal cortex ablation is that subjects fail when a delay is imposed between trials, although they are unimpaired at learning the task, or when no delay is imposed. Thus, they are impaired when they must hold in mind which arm of the maze they have just entered and when they must inhibit repeating that response in order to alternate. In our study of an animal model of early-treated PKU [Diamond et al., 1994], the rats with moderately elevated plasma Phe levels learned the delayed alternation task normally and performed well when there was no delay between trials, but failed when there was a delay between trials. That is, they showed the pattern of error associated with prefrontal

cortex dysfunction. Moreover, the neurochemical variable that was most strongly related to performance on the delayed alternation task was prefrontal cortical levels of the dopamine metabolite, homovanillic acid (HVA). This work is continuing with the genetic model of PKU in mice, developed by McDonald and Shedlovsky [McDonald et al., 1990; Shedlovsky et al., 1993]. It will be important to see if these results are confirmed by evidence of impairments on other tasks dependent on prefrontal cortex and by evidence of no impairment on tasks dependent on other neural systems.

If prefrontal cortex is selectively affected by moderate plasma Phe elevations because of the special properties of the prefrontally-projecting dopamine neurons, then any other dopamine neurons that also have those properties should also be affected. Retinal dopamine neurons share these properties; they, too, fire rapidly and turn over dopamine rapidly [Kupersmith et al., 1982; Regan and Neima, 1984; Skrandies and Gottlob, 1986; Bodis-Wollner et al., 1987; Bodis-Wollner, 1990]. Like the prefrontally-projecting neurons, retinal neurons are extremely sensitive to small changes in Tyr availability [Fernstrom et al., 1986; Fernstrom and Fernstrom, 1988]. Moreover, the competition between Phe and Tyr at the blood-retinal barrier is comparable to that at the blood-brain barrier [Rapoport, 1976; Tornquist and Alm, 1986]. Therefore, we predicted that retinal functions dependent on dopamine should also be affected in children with PKU with plasma Phe levels 3–5 times normal; this prediction has recently been confirmed. If the retina is depleted of dopamine, one finds an impairment in sensitivity to visual contrast. For example, patients with Parkinson's disease, who have reduced levels of dopamine, have impaired sensitivity to contrast [Regan and Nemia, 1984; Skrandies and Gottlob, 1986; Bodis-Wollner et al., 1987; Bodis-Wollner, 1990]. Contrast sensitivity reflects the threshold below which black lines (sinusoid gratings) are too dim to be detected. We [Diamond and Herzberg, 1996] found that children treated early and continuously for PKU, whose plasma Phe levels were 3–5 times normal, were impaired in contrast sensitivity across all five spatial frequencies tested. This novel finding of a visual defect in children treated early and continuously for PKU illustrates the utility of using neurochemical hypotheses to guide the selection of cognitive tasks.

Dangers and Possible Pitfalls When Selecting Behavioral Tasks

Using Analogous Tasks

Suppose there is evidence demonstrating that success on a certain task depends upon a particular neural system, but that task is inappropriate for the species or age group being studied. There are many instances where a behavioral test used with human subjects cannot be used with non-human animals, or vice-versa, or a test used with adults cannot be used with children. In this case, experimenters sometimes use a task that appears to be similar, and that they hope requires the same cognitive abilities and the same neural system. There are dangers here. Even though two tests may look very similar, they may, in fact, require different cognitive abilities and different neural systems. If you must modify a behavioral task, then you need empirical evidence that this new task (however similar to the old task it may appear) actually does depend upon the same neural system. This issue can be illustrated by attempts to develop tasks of medial temporal lobe function for nonverbal subjects. Damage to the medial temporal lobe impairs subjects' ability to recognize or recall previously presented material. The classic tests used to assess explicit recognition or recall require subjects to verbally respond to the experimenter. One might think that an analogous measure that could be used with nonverbal subjects (animals or infants) is the rate at which subjects learn material when it is presented for a second time; recall would be indicated by a rate that is faster than seen for original learning. Another apparently similar test might determine whether subjects recognize a degraded form of the target material when it is presented for a second time, under conditions in which they are unable to identify new material presented in a similarly degraded form. However, these examples of facilitated performance based on prior exposure, termed "priming," do *not* depend on the medial temporal lobe [e.g., Schacter, 1985; Graf et al., 1985; Schacter and Graf, 1986; Shimamura, 1986]. It would have been reasonable to think that a priming task might be a good non-verbal analogue of a verbal-recognition or recall task, but that inference would have been wrong.

One cannot rank all cognitive tasks along a unidimensional "sensitivity" scale. The nature of the brain damage will determine the type of cognitive dysfunction that will be produced in any given disorder and, therefore, the type of task that will reveal that impairment.

Using the Same Task With Different Species or Age Groups

Given the dangers involved in creating analogous tasks when testing different species or different age groups, one might think that the solution is to use exactly the same task. There are dangers here, too, however. The task may not be appropriate for the subjects. For example, tasks that require the exquisite visual abilities of primates can be inappropriate for rodents who rely heavily on olfaction and have poorly developed visual abilities. A second concern is that the same task may be approached differently, or solved differently, by subjects of different species or ages. Because a task that appears to be outwardly the same may be solved differently by different species or age groups, it is important to obtain evidence that the task you are using depends upon the neural system of interest in the subject population you are studying, as illustrated below.

Almost every task requires multiple abilities, and hence can be failed for several different reasons. For example, monkeys with medial temporal lobe lesions [Zola-Morgan et al., 1989; Meunier et al., 1993; O'Boyle et al., 1993] fail the delayed non-matching to sample task because of impaired visual recognition memory. However, human toddlers and infant monkeys, who also fail the task [Overman et al., 1992; Diamond et al., 1994], appear to do so for a different reason. One can see that the causes for failure on the very same task are different in the different subject populations by looking at the conditions under which these different subjects fail. Adult monkeys with lesions of the medial temporal lobe perform well when the delays are brief (10–15 seconds) and perform progressively worse at longer and longer delays. They fail because they have difficulty remembering over long delays. Toddlers of 12–18 months, in contrast,

fail even at the shortest delay (5 seconds). Their failure is almost surely not due to poor memory because (a) toddlers of the same age can remember a variety of things for 5 seconds, and (b) when they get older and finally succeed at the short delay, they also succeed at longer delays (e.g., 30 seconds). Hence it would be incorrect to infer that the developmental progression in children's or infant monkeys' performance on the delayed nonmatching to sample task tracks the maturational development of the memory ability dependent on the medial temporal lobe. This illustrates that the same task can be failed by different subject groups for different reasons. It is important to pay close attention to the conditions under which subjects succeed or fail and to the nature of the errors to better understand the underlying reason for those errors.

Experimental Design and Data Analysis

It is critically important to look at *why* subjects perform poorly on a task: Under what conditions do they succeed and under what conditions do they fail? How do changes in task parameters affect performance on the task? Answers to these questions can aid substantially in delineating the impaired versus preserved cognitive functions in the target syndrome of interest.

Case 1: Assessment of Attentional Function in a Rat Model of Childhood Lead Exposure

This point is illustrated by our [Strupp and colleagues] research in which we have examined cognition in a rat model of childhood lead exposure [Strupp et al., 1995]. In the study described below, lead was administered in the drinking water (0, 75, or 300 ppm lead acetate), initially to the pregnant dams and then directly to the offspring after weaning. These regimens were designed to produce steady-state blood lead levels that correspond to those frequently seen in urban children exposed to dust from lead-based paint, the most common source of childhood lead exposure in the United States. These three regimens produced steady state blood lead levels of <5, 20, and 40 μg/dl, respectively, all levels that are not associated with overt toxicity in either rats or children. Notably, the levels produced by the 75 ppm regimen were considered safe for children until 1991. Recent epidemiological data, however, indicate that levels as low as 10–25 μg/dl in the first few years of life are associated with IQ deficits at both 5 [e.g., Bellinger et al., 1991] and 10 [e.g., Bellinger et al., 1992] years of age. To verify that cognitive deficits are indeed produced by these very low exposures, and to learn more about the specific cognitive processes affected, we tested these lead-exposed rats on a variety of cognitive tasks. One task selected for the battery was a vigilance task, based on reports suggesting that children exposed to lead exhibit a mild form of Attention Deficit Hyperactivity Disorder [Needleman, 1982]. In this task, a brief (700 msec) light cue was presented over one of three funnel-shaped ports either 0, 3, 6, or 9 seconds after trial onset, with the different prestimulus delays being presented quasi-randomly across trials. The animals were rewarded for making a 1-second nosepoke into the port under which the cue had been presented. Because responses made prior to the light cue were considered incorrect and terminated the trial, the task assessed inhibitory control as well as sustained attention across the 9-second interval during which the light cue could be presented [see Bunsey and Strupp, 1995 for additional task details].

Even though two tests may look very similar, they may, in fact, require different cognitive abilities and different neural systems.

Chronic low-level lead exposure did not alter performance at the 0-second delay; however the lead-exposed animals (both the 75 and 300 ppm groups) were significantly impaired at each of the longer delays, with the magnitude of the deficit increasing with increasing delay. An analysis of the conditions under which the lead-exposed animals were, and were not, different from controls helped to illuminate the nature of the impairment. Because the lead-exposed and control rats did not differ at the 0-second delay, it was possible to exclude differences in motivation, visual acuity, and motor function as the basis of the impairment at the longer delays. Lead exposure also did not alter the tendency of the animals to respond to the port chosen on the previous trial, thus excluding spatial perseveration as a basis for the impairment. A reduction in the speed of information processing, another potential source of errors in this task, could also be excluded as a cause of the impairment. This conclusion was based on an analysis of reaction time in a similar visual discrimination task also administered to these animals, in which the light cue was presented immediately after trial onset rather than after a variable delay. Lead exposure did not alter information processing speed, based on reaction time during the criterial phase of performance. Because performance was, by definition, at least 80% correct, it could be assumed that the cue had been processed prior to the response. The fact that a speed-accuracy trade-off was observed (the fastest responses were least accurate) supports the conclusion that the measure was sufficiently sensitive to have detected an effect of lead exposure, had one existed.

Several types of errors did, however, differentiate the control and lead-exposed rats. First, the exposed animals made significantly more responses prior to the presentation of the light cue than controls, indicative of impulsivity or a deficiency in inhibiting prepotent responses. To determine if this latter defect was the sole locus of the impaired performance of the lead-exposed animals, we also examined accuracy on trials in which the animal did not respond prior to cue presentation (termed, post-stimulus percent correct). The post-stimulus percent correct decreased with increasing pre-stimulus delay, suggesting that this measure tapped sustained attention. A significant interaction of lead treatment and delay was found, reflecting the fact that the relative impairment of the lead-treated animals increased with increasing delay. This pattern of findings points to an impairment in sustained attention as a second locus of impairment in these animals. These findings support suggestions that lead-exposed children exhibit symptoms reminiscent of attention deficit hyperactivity disorder. The findings also support the more general point that an examination of the pattern of group differences across a range of responses allows one to go beyond merely noting that the groups differ, to a delineation of the specific cognitive processes that are altered.

Case 2: Errors in the A-not-B and Object Retrieval Tasks Following Damage to Specific Brain Systems

Identifying the ways in which subjects fail can also be helpful in identifying what system or systems in the brain may have been disrupted. Consider the different patterns of errors seen in the

A-not-B and object retrieval tasks following damage to different neural regions. In the A-not-B task, there are two hiding wells, one to the left, the other to the right. On each trial, the subject sees the reward being hidden in one of the wells. After a delay, the subject is free to try to find the reward by searching one of the wells. The reward is hidden in the same well until the subject is correct on two consecutive trials; then the side of hiding is reversed. Monkeys with prefrontal cortical lesions err primarily on reversal trials and on the trials immediately following reversals [Diamond and Goldman-Rakic, 1989]. On the other hand, monkeys with lesions of the medial temporal lobe do not err primarily on reversal trials, although after they have made an error, they, too, tend to repeat that error on the following trial [e.g., Squire and Zola-Morgan, 1983; Diamond et al., 1989]. On the object retrieval task, where the reward must be retrieved from a small transparent box open on one side, monkeys with prefrontal cortical lesions err when they see the reward through a closed side of the box. They keep trying to reach directly for the reward through that closed side, rather than detouring around to the opening [Diamond and Goldman-Rakic, 1985; Diamond, 1991]. Monkeys with lesions of posterior parietal cortex, on the other hand, try to detour around to the opening. When they err it is because their reach is mis-aimed [too high, too far, or too close; Diamond and Goldman-Rakic, 1985; Diamond, 1991]. By comparing the results one obtains with an MR animal model to the pattern of deficits seen following specific brain lesions, one can make inferences about the locus of the underlying brain damage.

In contrast to these examples, it should be acknowledged that the brain damage in many—if not most—MR syndromes appears to be diffuse rather than localized. This situation is further complicated by the fact that the brain damage in these syndromes occurs, by definition, during development of the brain, with the consequence that some reorganization and/or recovery of function may occur. This factor may partially underlie the frequent observation that the functional effects of a focal brain lesion sustained during early development are often different from the sequelae of this same lesion when sustained during adulthood [e.g., Kolb, 1990; Bates, 1996]. Both of these factors—the diffuse nature of the brain damage coupled with the potential for reorganization of the brain following early injury—significantly complicate the strategy of using the cognitive profile in specific MR syndromes to guide hypotheses about the nature of the underlying brain damage. This approach has proven useful, however, and would be substantially facilitated by additional research on the cognitive effects of focal brain lesions sustained during early development. At present, this type of inferential approach is hampered by the fact that the vast majority of lesion data that can serve as a reference point pertain to adult lesions.

Case 3: Analysis of Reversal Learning Deficits in Lead-Exposed Rats

In the examples cited above, insight into the nature of the brain damage and the specificity of the impairment was provided by examining the types of errors committed. Another technique that has proven useful in attaining both of these objectives is to examine group differences in distinct phases of the learning process. We [Strupp and colleagues] used this technique to analyze the data from a serial reversal learning task, administered in our study on low-level lead exposure, described above. In this task, the animals were first tested on a two-choice simultaneous olfactory discrimination task, in which two different odors were presented on each trial from two funnel-shaped ports. A 1-second nosepoke into the port from which the correct odor emanated was rewarded. After mastery of this task, each animal was administered five successive reversals in which the valences of the two cues were reversed; i.e., the previously incorrect odor became correct on each successive reversal [Hilson and Strupp, submitted; Strupp and Hilson, 1996]. This type of task taps the ability of the animal to flexibly change its behavior with changing environmental contingencies, and is comparable to reversal tasks used in humans and nonhuman primates. The ability to flexibly change behavior (and avoid perseveration) is often compromised in MR syndromes [see McIlvane and Cataldo, this issue].

Identifying the ways in which subjects fail can also be helpful in identifying what system or systems in the brain may have been disrupted.

In this study, no effect of lead exposure was observed in the rate at which the initial olfactory discrimination task was mastered, but the higher exposure group (300 ppm lead acetate) took significantly longer to learn each of the subsequent five reversals than either the controls or the 75 ppm group (see Fig. 3). The latter two groups did not differ from each other. The fact that lead exposure did not affect the rate at which the initial olfactory discrimination was mastered allows one to exclude performance factors (motivation, malaise, sensory acuity) as the cause of the observed impairment. Instead, the specificity of the deficit suggests that lead exposure alters some process or processes that are tapped to a greater extent by the reversal tasks than by the initial olfactory discrimination task.

The data from the first reversal were analyzed in more depth to gain insight into the basis of the impairment. These in-depth analyses provided insight into the nature of the effect, revealing effects that had been obscured by the analyses of overall learning rate. Perhaps most illuminating, the period of persistent responding to the previously correct cue (the perseverative phase) tended to be shorter for both the 75 ppm ($P = 0.05$) and 300 ppm ($P = 0.06$) groups relative to controls (see Fig. 5), demonstrating that the slower reversal learning in these animals was not due to inflexibility or perseverative responding to the previously correct cue. Instead, the learning deficit was found to be localized to the post-perseverative phase, a period that was significantly longer for both lead-exposed groups relative to controls ($P = 0.008$; see Fig. 4).

An analysis comparing the two components of the post-perseverative phase provided clues concerning the basis of the impairment. This analysis revealed that the treatment effect was not specific to either the "chance" or "greater-than-chance" components (see Fig. 5). One interpretation of this finding is suggested by studies on discrimination learning in individuals with MR. Zeaman and House [1963] proposed that a deficit limited to the chance phase, such as seen in these individuals, reflects an attentional deficit—a difficulty in identifying the predictive cues—rather than an associational deficit. Slower learning in both phases, such as observed in the present study, would instead indicate an associative deficit.

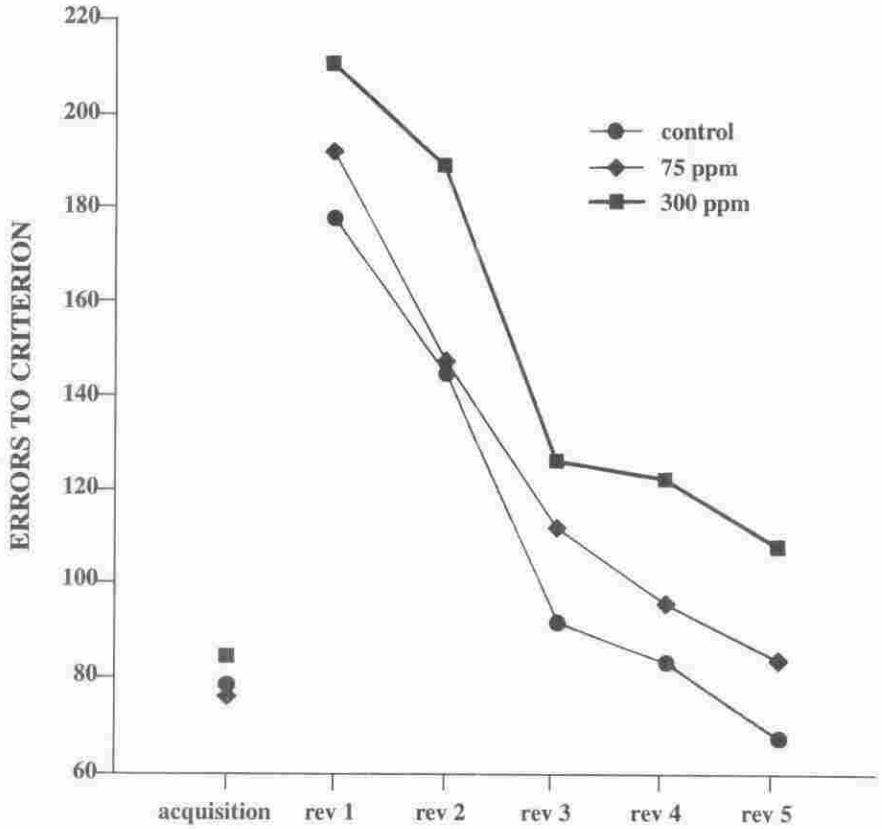

Fig. 3. Errors to criterion for the different tasks that comprised the serial reversal learning task: the original olfactory discrimination, followed by five successive reversals. Whereas lead-exposure did not affect the rate at which the original olfactory discrimination was mastered, the higher exposure group (300 ppm) was significantly impaired on all five reversals, relative to both the controls ($P = 0.0004$) and the 75 ppm group ($P = 0.008$). These latter two groups did not differ from each other ($P = 0.18$) [from Hilson and Strupp, under review].

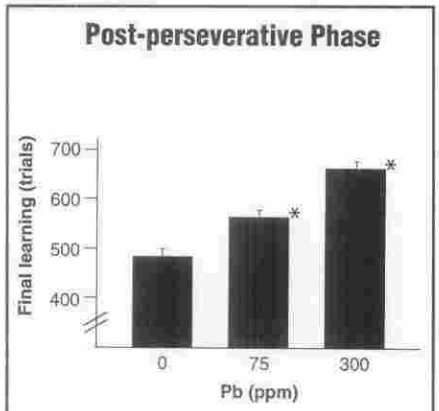

Fig. 4. The duration (number of trials) of the post-perseverative phase was significantly greater for the lead-exposed animals than for controls. This phase started at the point at which the animal ceased to respond persistently to the previously correct cue, and continued until the task was mastered. Contrasts revealed that both the 75 ppm ($P = 0.08$) and the 300 ppm ($P = 0.002$) groups were impaired relative to controls, contrary to the conclusion suggested by the analysis of learning rate (trials to criterion) [from Hilson and Strupp, under review].

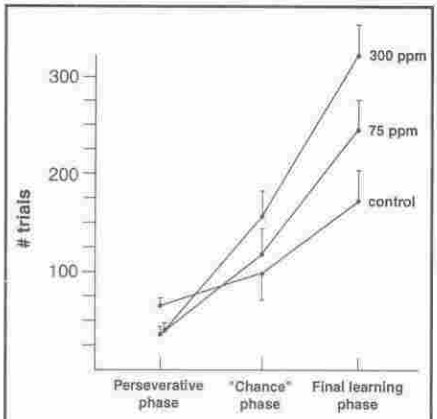

Fig. 5. Comparison of lead-exposed and control rats on the three phases of reversal learning: the perseverative phase, the "chance" phase, and the "greater-than-chance" phase (or final learning phase). Lead exposure tended to shorten the perseverative phase ($P = 0.07$). The post-perseverative phase (comprised of the "chance" and "greater-than-chance" phases), in contrast, was protracted in both lead-exposed groups (see Fig. 4). The lead-induced impairment in the post-perseverative phase was not specific to either of these two component phases (interaction of treatment and phase, $P = 0.75$). (The 200 trials that comprised the criterial block were subtracted from the final learning phase for this graph to provide a more accurate portrayal of the relative number of trials required to master each of the three phases.) [From Hilson and Strupp, under review.]

The hypothesis that an associational deficit underlies the longer post-perseverative phase is supported by the fact that the pattern of reversal learning deficits observed in these lead-exposed animals has also been reported for animals with damage to the amygdala, a brain region thought to play an important role in the process by which environmental stimuli acquire affective or incentive value [Gaffan, 1992; Cador et al., 1989; Everitt and Robbins, 1992]. Amygdaloid lesions have been found to retard the rate at which reversals are mastered, due primarily to an elongation of the post-perseverative phase [Schwartzbaum and Paulos, 1965; Aggleton and Passingham, 1981; Douglas and Pribram, 1966; Jones and Mishkin, 1972]. This same pattern of results has been observed following conjoint damage to the hippocampus and amygdala [Spevack and Pribram, 1973], but not after damage to the hippocampus alone [Eichenbaum et al., 1986; Jones and Mishkin, 1972; Kimble, 1968; Winocur and Mills, 1969], providing additional support for the notion that amygdaloid damage may be instrumental in these observed lead-related effects.

Similar analyses conducted on a three-choice olfactory serial reversal task, administered in a study of early (but not chronic) lead exposure provided an opportunity to test an alternative hypothesis for the longer post-perseverative phase: an impairment in inhibiting responses to the previously correct cue. In this latter task, it was possible to gain more insight into the basis of the impairment in this last phase because two types of errors were possible on each trial: responses to the previously correct cue and responses to the other incorrect cue [Sawyer and Strupp, 1996]. Consequently it was possible to determine whether errors were made specifically to the previously correct cue (indicative of inhibition deficits) or, alternatively, whether errors were made equally to the two incorrect cues, perhaps indicative of impaired learning of the new contingency. This latter pattern was found to characterize the lead-exposed animals, arguing against an inhibitory deficit, and thereby providing indirect support for an associative deficit, as proposed above.

It is noteworthy that, without these analyses of the different components of the learning process in this study, an erroneous conclusion about the basis of the impairment would very likely have been reached: It is often assumed that

slower reversal learning is due to perseveration of the previously correct response, an effect opposite to that observed in this study. This in-depth analysis also proved to be more sensitive than the learning rate measures, revealing an effect in the low exposure group (75 ppm) that had not been evident in these former analyses. The two effects of lead exposure in this task produced opposing influences on learning rate (less initial perseveration coupled with a longer final learning phase), with the result that for the 75 ppm group, no net effect was apparent for learning rate. For the 300 ppm group, in contrast, the duration of the final learning phase was sufficiently increased that an effect was seen in the overall learning rate measure, despite a reduction in the initial perseveration phase. In addition, these in-depth analyses provided insight into the type of brain damage that might be responsible for these alterations. Although damage to the amygdala, orbital frontal cortex, and basal forebrain have all been shown to slow the rate at which reversals are mastered, damage to these latter two structures exerts this effect via increased initial perseveration to the previously correct cue [Butter, 1969; Ridley et al., 1993, Jones and Mishkin, 1972; Roberts et al., 1990, 1992], a pattern very different from that seen in the present study. The fact that amygdala lesions, in contrast, impair reversal learning primarily as a result of an elongated post-perseverative phase, as seen in the lead-exposed animals here, implicates damage to this structure as a viable cause of the behavioral changes. Analyses of learning rate alone would have provided little information concerning the locus of the brain damage, as damage to numerous brain structures impairs reversal learning.

Use of Animal Models to Develop Therapeutic Interventions

Animal models have a pivotal role to play in research on MR syndromes. They provide an opportunity to test hypotheses about the neural bases of cognitive impairments that cannot be tested by studies with human subjects. This knowledge, in turn, can lead to the development of therapeutic interventions, the efficacy of which can also be tested in animal models prior to human application. This potential can easily fail to be realized, however, if the cognitive assessment is not guided by knowledge of the target syndrome. For example, if one or two arbitrarily chosen tasks comprise the testing battery, cognitive dysfunction can easily be missed, and the erroneous assumption made that the animal model does not adequately mimic the analogous human condition. An arbitrary approach to task selection can also lead to problems even if one of the tasks does, by chance, succeed in revealing cognitive impairment in the animals. For example, consider an experiment in which a potential therapy is being tested in the animal model. It is very possible that a particular therapeutic intervention might correct the abnormality in certain neural systems but fail to correct a different problem in other systems, with the consequence that only certain cognitive processes will be ameliorated. Under these conditions, performance on one arbitrarily chosen task that reveals impairment may not be improved by the therapy, leading to the erroneous conclusion that the treatment had no effect. This type of erroneous conclusion could be avoided if a range of tasks was administered, with different tasks designed to tap alternative hypothesized causes, or aspects, of the disorder. In the absence of this type of information, the best approach would be to select tasks that tap a range of cognitive functions dependent on distinct neural systems.

SUMMARY

The goal of this paper was to provide some guidelines for assessing cognitive function in animal models of human cognitive dysfunction, with an emphasis on MR syndromes. Because different cognitive functions depend on different neural systems, the nature of the brain damage will determine which cognitive functions will be most affected in any given disorder, and consequently, which tasks will best reveal that dysfunction. Information about the site(s) of neural damage and/or the cognitive processes affected in the disorder can aid substantially in selecting tasks for the animal model that are optimally sensitive in revealing dysfunction. In addition, the integration of these two sources of information can solve the dilemma of task selection in cases where the cardinal area of dysfunction is one that cannot readily be assessed in the animal model (e.g., visuoconstructive spatial abilities, as discussed above for Williams syndrome). Specifically, the nature of the cognitive dysfunction can implicate damage to a particular brain system; a task can then be selected that is known to be sensitive to dysfunction in that neural system in the animal being studied. A second major theme of this paper concerned the importance of going beyond summary measures of performance (percent correct, trials to criterion) to in-depth analyses of the conditions under which subjects fail and the types of errors they make. This kind of information is crucial for identifying the specific cognitive functions that have been altered, and for elucidating the nature of the underlying brain damage. ■

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