Learning about Cognition Risk with the Radial-Arm Maze in the Developmental Neurotoxicology Battery

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Abstract

Cognitive dysfunction has been found in epidemiological studies to be among the most sensitive impairments associated with developmental exposure to a variety of environmental contaminants from heavy metals to polyhalogenated hydrocarbons and pesticides. These chemicals have been also shown to impair cognitive function after developmental exposure in experimental animal models. The radial-arm maze (RAM) has proven to be a sensitive and reliable way to assess both learning and memory in a variety of species, most often in rats and mice. The RAM is a very adaptable test method that takes advantage of rodents' instinct to explore new places in the environment to forage. That is, rodents do not need to be trained to run through the maze; they will normally do this from the initial session of testing. Training with differential reinforcement for arm choices provides a more rigorous test of learning and memory. The RAM is quite adaptable for assessing various aspects of cognition. Although the RAM has been mostly used to assess spatial learning and memory, it can be configured to assess non-spatial memory as well. Both working and reference memory can be easily distinguished. The RAM can be run with both appetitive (food reinforced) and aversive (water escape) motivators. The RAM has been found to be sensitive to a wide variety of developmental toxicants including heavy metals such as mercury and pesticides such as chlorpyrifos. There is an extremely rich literature especially with rats showing the effects of many types of brain lesions and drug effects so that the participation of a wide variety of neural systems in RAM performance are known. These systems, notably the hippocampus and frontal cortex, and acetylcholine and glutamate neurotransmitter systems, are the same neural systems that have been shown in humans to be critical for learning and memory. This considerably aids the interpretation of neurobehavioral toxicity studies.

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Introduction

Cognitive dysfunction is one of the most common findings of developmental environmental neurotoxicity in epidemiological studies, most notably seen in studies of lead, polyhalogenated hydrocarbons, and pesticides (Eskenazi et al., 2007; Lanphear et al., 2005; Rauh et al., 2006). Cognitive impairments from developmental exposure to these chemicals have also been documented in experimental animal studies, with species ranging from zebrafish to rhesus monkeys, of course also including the widely use rodents as well (Levin et al., 2001; Levin et al., 2002; Schantz et al., 1991). Experimental animal testing demonstrates the cause-and-effect relationship in a rigorous way not possible with epidemiological studies. Experimental animal studies also provide important brain-based complex mechanistic information about cognitive effects of developmental neurotoxicity unavailable with *in vitro* studies. Inclusion of cognitive tests in the developmental neurotoxicology screening battery provides information critical about an important adverse outcome of developmental neurotoxic exposure in humans. The radial-arm maze (RAM) provides a sensitive and readily adaptable technique with which to determine developmental neurotoxic effects on cognition.

Protecting Against Developmental Neurotoxic Risks of Cognitive Impairment

Cognitive testing is important for risk assessment. However, the way in which cognitive tests are currently used in screening is not as useful as it should be. Given that cognitive impairment is a sensitive indicator of developmental neurotoxicity in human studies, the fact that cognitive tests as currently performed in experimental animal developmental neurotoxicology screening test batteries are not very sensitive, is an indictment against how those tests are currently used, not against the importance of conducting cognitive tests in the screening battery. (see the overview article in this special issue). Screening for cognitive impairments with animal models using insensitive tests will not be very informative and will not provide sufficient protection against toxicant induced cognitive impairments occurring in people. The answer is not to abolish cognitive testing in the developmental neurotoxicity test battery, but to use efficient cognitive tests that are more predictive of cognitive impairment in people. Improving the sensitivity of cognitive testing will not only help in the prediction of cognitive effects of particular compounds in people, it will provide important information about the functional mechanisms of toxicity of a wide variety of chemicals. It is important to use cognitive tests that are not only efficient and sensitive, but that are informative about the neural processes disrupted by toxicant exposure.

Cognitive tests range from very simple quick tests to much more complex tests that take considerable amounts of time to perform. Tests also range in sensitivity. All cognitive tests also involve other neurobehavioral functions, from sensory and motor processes, to motivational and emotional function. For example, active or passive shock avoidance tests of learning and memory are also sensitive to simple changes in locomotor activity and to changes in sensitivity to shock as a motivating influence. Many spatial navigation learning and memory tests rely on visual cues; visual disturbances would affect performance on these tests.

Sensitivity can be lessened in several ways. If the motivating influence is substantial, such as in shock-motivated tests, sensitivity can be diminished. The source of this lessened sensitivity may occur because maximum motivation may bring into use the maximum cognitive resources to solve the task. This would measure peak cognitive performance, but the generalizability of these findings to the more common expression of cognitive function under more modest motivation would be limited. Also, shock induces emotional responses which rather than serving to motivate the subject to learn or remember more accurately could disrupt these processes, again diminishing from the tests' interpretability as well as sensitivity. There is a window of sensitivity to the effects of exposure dependent on the overall sensitivity of the test. If a test is too easy, then it would take a substantial neurobehavioral impairment to influence the outcome of the test, decreasing the sensitivity of the test. If the test is too difficult then the controls would fail, decreasing the sensitivity of the test.

Integrity of controls is essential to a sensitive test. Tests can become quite insensitive even to exposures causing substantial impairment if the performance of the control group is disrupted or made quite variable due to co-exposures, problems with husbandry or variability in test conditions. Like biochemical tests, there need to be regular positive controls to confirm test integrity, that is, a test of the test. These can include positive controls of known amnestic drug treatments such as scopolamine or dizocilpine, internal dynamics of the test such as acquisition curves or forgetting curves or the effects of brain lesions impairing accuracy on the test.

Spatial discrimination is an important cognitive function shared by great variety of species from honeybees to humans. Simple tests of spatial discrimination such as the RAM are sensitive to toxicant exposures such as developmental exposure to lead and chlorpyrifos as well as antagonists of transmitter receptors critical for cognitive function such as scopolamine (muscarinic acetylcholine antagonist) and dizocilpine (NMDA glutamate antagonist). Rats and mice normally run in the RAM in an efficient food foraging pattern and chose different arms above chance rates even with minimal training. With training they learn in a reproducible fashion improving accuracy over a small number of sessions to an asymptote of performance to index memory. Working and reference memory can be differentiated by selectively baiting some arms, but not others. Response speed can be measured in a manner orthogonal to choice accuracy since the same effort is required to make correct or incorrect choices. Of course the set of paradigms in the RAM is only one of many different ways in which cognition can be tested in an efficient and sensitive manner. These tests include T-maze alternation, novel object recognition, operant conditioning and the Morris and other water maze tasks. The other articles in this series provide excellent discussions of those methods.

Using the Radial-arm Maze to Assess Learning and Memory

The RAM is a widely used apparatus to assess spatial working and reference memory. David Olton pioneered its modern use and provided much of the early literature concerning the neural and behavioral systems necessary for accurate performance in the RAM (Olton and Samuelson, 1976). Olton and co-workers adapted previous tests with simultaneous multi-

choice configurations that were developed by Hamilton, Tolman and others in the early (Hamilton, 1911; Hamilton, 1916) and mid- (Tolman et al., 1946) 20th century. Earlier reviews have covered the historical use of the radial-arm maze for addressing the memory effects of drugs (Levin, 1988) and neurotoxicants (Olton, 1983; Walsh and Chroback, 1987), particularly the persistent cognitive effects of developmental neurotoxic exposure. The radial-arm maze has become a very widely used method for the examination of spatial learning and memory in rats, mice and other animals including monkeys and humans. RAM methods have been developed for human testing as well (Braun et al., 2012).

The RAM is quite versatile with a variety of different procedures providing assessment of learning and memory. The win-shift task is the most common way of using the RAM. With this procedure all of the arms are baited at the beginning of the test session and then allow the subject to freely choose arms and retrieve the baits until all the different arms had been chosen. The optimal strategy for this task is to shift response choice after a reinforced entry (win-shift). Working memory is tested by counting the errors, which are re-entries into previously baited arms. The difficulty of the task increases as the session progresses. If all the arms are baited then the first choice is always reinforced. Then as each new arm is chosen the subsequent choice is more difficult. Working and reference memory can be distinguished in the RAM. This test can be run with some of the arms baited but others never baited, such that the first entry into the baited arms is reinforced but not subsequent entries and the never-baited arms are not reinforced at all. The never baited arms stay constant throughout testing. Re-entries of the subject into formerly baited arms is the test of working memory while any entry into a never-baited arms is the test of reference memory. Typically, we have found that 18 sessions of training is sufficient to reach asymptotically good performance on the win-shift radial arm maze task. Delayed matching to sample can be run with the maze initially configured to force the subject to enter one particular arm. Then the subject is allowed access to all of the arms. Errors are counted with the number of arm entries until the subject returns to the initially sampled arm. Learning can be assessed with the repeated acquisition procedure developed by Peele and Baron (Peele and Baron, 1988). In any given session three different arms are rewarded. The subject is given five trials to solve the new problem. The number of errors per trial are counted and the decrease in errors per trial is the index of learning. Non-spatial memory can be assessed by pairing reinforcement with visual or textural cues.

A great many studies have been conducted investigating the effects of various brain lesions, drugs and natural phenomena such as aging on RAM performance. Mazes containing from three to 24 arms have been used in these studies. Because every alternative arm choice is possible every time a choice is made, the radial-arm maze is particularly amenable to computer modeling. Spetch and Wilkie (Spetch and Wilkie, 1980) and Eckerman (1980) have previously designed computer programs to simulate choice behavior in radial arm mazes. The author has written a Monte Carlo computer randomization program which produces random chance accuracy scores for several measures for mazes of different sizes as well as the effect of different levels of memory or response bias (see supplemental file tables).

Lesion studies have provided information concerning brain areas important for memory function as measured by the RAM. As has been seen with numerous other tests, the hippocampus and related structures are of critical importance for memory function in the RAM (Becker et al., 1980). In addition, other limbic structures such as the septum, amygdala and mammillary bodies have been shown to be important for optimal memory function in the RAM (Becker et al., 1980; Taghzouti et al., 1986; Vann and Aggleton, 2003). Lesions of the frontal cortex and the directly connected mediodorsal thalamic nucleus significantly impair memory function as measured by RAM choice accuracy (Becker et al., 1980; Stokes and Best, 1988).

There are a plethora of studies characterizing the involvement of various neurotransmitter systems for proper memory function. This is important for neurotoxicology studies because this substantial background literature provides a basis for interpreting neurobehavioral effects. Many neurotoxicants have demonstrated effects on these transmitter systems and thus would be expected to impact memory function. Screening is more than just detecting the endpoint of a threshold for adverse outcome; it is the beginning of developing understanding of the adverse outcome pathway. The lowest threshold test on a screening battery is unlikely to be the true threshold for adverse effects because by necessity a screening battery is constituted by a small set of tests. Critical to determining the most sensitive tests is knowledge of the biologic pathways underlying the adverse outcome pathways.

Acetylcholine has been the most well characterized neurotransmitter system important for memory. Impairments with both nicotinic and muscarinic acetylcholinergic antagonists have been found to impair memory in the radial-arm maze (Levin, 2001). Glutamate is the second most well characterized transmitter system important for memory function. In particular, NMDA glutamate receptor systems have been shown to be essential components of the neural systems involved in memory. The NMDA glutamate antagonist dizocilpine (MK-801) has been repeatedly shown to significantly impair working memory function as measured by RAM choice accuracy (Levin et al., 1998). Certainly acetylcholine and glutamate are not the only neurotransmitter systems that have been shown to be involved in memory function as assessed by the RAM. It has long been known that other transmitter systems such as dopamine, norepinephrine, serotonin and GABA are also involved in the neural circuits underlying memory function indexed by choice accuracy on the RAM (Levin, 1988). Our experience is that group sizes of 10–15 are sufficient for detecting moderate effects with these classic amnestic drugs.

Developmental Toxicant Exposure and Long-term Effects on RAM Accuracy

The RAM has been used for neurotoxicology studies for several decades. The early work with the use of the RAM in neurotoxicology was ably reviewed by Walsh and Chroback (Walsh and Chroback, 1987). The RAM has been found to be sensitive to the long-term memory impairing effects of developmental exposure to a variety of toxicants including pesticides, metals and other neurotoxicants. Following are some examples of studies that

have found the RAM useful in characterizing long-term cognitive effects of developmental neurotoxicity.

The RAM has been shown to be particularly useful in determining the long-term effects of pesticide exposure during pre and postnatal development. Sex and age-related effects have been found. The organophosphate (OP) pesticide chlorpyrifos caused a significant sex-selective effect on radial-arm maze accuracy with a reversal of the normal male female difference in RAM choice accuracy (Aldridge et al., 2005; Levin et al., 2001). This sort of sex difference with chlorpyrifos induced RAM working and reference memory impairments in males and facilitated performance in females has been also seen in another laboratory (Johnson et al., 2009). Postnatal parathion caused significant RAM memory impairments in adult rats (Stamper et al., 1988). The deleterious sex-selective working and reference memory impairment of developmental parathion exposure appear to become more expressed with the process of aging with older males showing impairments (Levin et al., 2010). Low dose exposure during the early postnatal period with another OP pesticide diazinon also was found to cause long-term working memory impairment in the RAM (Timofeeva et al., 2008).

The RAM is sensitive to the long-term neurobehavioral toxicity of developmental exposure to a variety of metals during development. Mercury given either bolus mid-gestational doses or chronically throughout gestation was shown to significantly impair RAM accuracy in mice (Liang et al., 2009). Either trimethyltin or tributyltin administration in developing rats has been found to impair RAM working memory performance (Gardlund et al., 1991; Miller and O'Callaghan, 1984). Bushnell and Levin (Bushnell and Levin, 1983) found that post-weaning administration of lead or deprivation of zinc impaired working choice accuracy in an 8-arm radial maze. Developmental manganese exposure had persisting effects on RAM (Pappas et al., 1997). Gestational exposure to low levels of the metalloid arsenic in mice significantly impaired RAM accuracy later in life (Martinez-Finley et al., 2009).

It is not just pesticides and metals. The RAM has been shown to be sensitive to the long-term effects of a variety of other developmental neurotoxic exposures on memory as well. Developmental exposure pre or postnatally to the marine toxin domoic acid caused impairments in radial-arm maze performance (Levin et al., 2005; Levin et al., 2006). Prenatal domoic acid exposure significantly attenuated the normal sex difference in this spatial task where male rats typically perform more accurately than female rats (Levin et al., 2005). Gestational bisphenyl-A (BPA) impaired working memory in the RAM (Wang et al., 2014), however not all studies have seen this effect (Sadowski et al., 2014). Developmental PCB exposure caused significant impairments in working memory in the RAM in adult rats (Corey et al., 1996). We showed that developmental halothane treatment, which retards synaptogenesis in the hippocampus impaired 8-arm maze exploration and learning when the rats are adults (Levin and Bowman, 1986; Levin et al., 1987; Levin et al., 1991). These studies show that RAM choice accuracy is sensitive to the cognitive impairments caused by a variety of toxicants.

Cognitive Testing in Screening

A screen serves multiple purposes. Most obviously, the purpose of a toxicant screen is to determine the dose threshold for toxic effects. Thus, within a test battery those measures that detect the lowest effects of a chemical are most valued for they provide the information needed for determining thresholds of toxicity. For this purpose, if a test does not have sensitivity for detecting the lowest dose effect for at least some of the chemicals tested, it is not a useful part of the battery. However, this is only one of the purposes of a screen. A screen of a chemical should not just be considered as a single test of a single chemical, to be judged without regard to its relationship to screens of other chemicals and multiple ways in which the screen can inform for further study. We should derive as much information as possible from screens, not just the single number indicated by the lowest dose than is effective in causing a significant change.

Consideration should be made that the purpose of screening tests is not to provide only endpoints of toxicity. Even these endpoints are necessarily interim. As our understanding of biologic processes vulnerable to toxicity improves and our tests of impacts on these processes improve, the same compounds will need to be retested again and again to determine the thresholds of effect on these newly discovered biologic processes and more sensitive tests. For example, chemicals screened before the discovery of important epigenetic mechanisms would need to re-screened later with these mechanisms in mind. Thus, screens should not only provide endpoints, but starting points as well. Biologic effects of chemicals detected in screens need to serve as starting points for further investigation to determine where these threads of evidence lead into the fabric of physiology. For this purpose, we need to consider not just the initial endpoint that shows effects at the lowest dose effect in the screen. That lowest dose effect may only have that characteristic of sensitivity for the limited tests used by the screen. Other effects in the initial screen, which are only clearly seen at higher doses need to be followed-up to determine where more sophisticated analysis would determine whether damage to these systems would be seen at even lower dose levels in subsequent tests. We always need to keep in mind the limitations of any particular test, especially screening tests, which are often chosen for economy and speed of throughput rather than sensitivity.

There are certainly limitations of our understanding of the neural bases of behavioral function. Because we are always screening under conditions of incomplete information not only of the effects of the chemicals being screened, but also of incomplete understanding of the physiological functions of concern, we need to include in the screen tests of complex functions of concern. For example, we know some of the neurobehavioral systems underlying cognitive function, such as the hippocampus and frontal cortex, as well as cholinergic and glutamate transmitter systems. However, there are most likely many neurobehavioral systems that we do not currently understand that are important substrates of cognitive function and could be vulnerable to neurotoxic actions. Since we cannot comprehensively conduct a mechanism-based assessment, we need to continue to take an end run around our ignorance and test the integrated function of concern.

Screens have value in providing information across chemicals and chemical classes, rather than only for a particular chemical. A comprehensive screen covering a range of neurobehavioral functions of concern over a wide variety of chemicals can provide important understanding of the patterns of neurotoxic effects, which would facilitate further predictability of toxicant actions. This increased knowledge can help with the discovery of new mechanisms of toxicity to improve the comprehensiveness of our understanding of the full variety of critical toxic pathways affecting cognition. We need to develop process oriented screening, rather than just endpoint driven screens, that is, we need to understand the biologic processes underlying the functional impairments caused by neurotoxicants. For example knowledge of the involvement of hippocampus to memory function can help with the understanding of how trimethyl tin can cause memory impairments (Miller and O'Callaghan, 1984). Screens need to be both informed and informing, designed to assess functions of concern and provide information about how those functions are perturbed.

It is important to recognize that at the bottom of the dose effect function not all changes detected are important indicators of functional neurotoxicity. In addition to chemical effects that are the initiating events leading to functional impairment, there are some exposure-induced changes that are relatively unimportant to processes of persisting neurotoxicity. In addition, some exposure-induced changes may be relatively silent until other challenges unmask the effects, such as neonatal parathion effects not seen until aging intervenes. Unless, we have information about how those low dose changes are related to functional impairment seen more clearly at higher doses, we will not know how to interpret their toxicological meaning.

Conclusions

To achieve further progress we need to develop cognitive tests that have predictive validity, mechanistic validity, interpretative literature and economy. Sensitivity is only one aspect needed. The need to quantitate the risk of individual chemicals is one goal of screening. Another goal is to add to the overall knowledge base across many chemicals to determine the variety of ways by which chemical exposure during development can cause behavioral dysfunction.

Subtle toxicant-induced impairments can be unmasked by aging, illness, toxicant co-exposure or genetic vulnerabilities. Screening for cognitive effects in the developmental neurotoxicology test battery is necessary because cognitive impairments are quite commonly the most sensitive neurotoxic effect seen in epidemiological studies and we do not have sufficiently complete understanding of all the neurotoxic pathways that lead to cognitive impairment to adequately model this risk in more elementary systems. Just because the currently used animal model cognitive tests are relatively insensitive does not indicate that cognitive function should not be included in the neurotoxicology test battery. Rather, this indicates that more sensitive tests should be used instead. In addition to providing critical functional information about cognitive effects of individual chemicals, having the requirement for cognitive testing in the developmental neurotoxicology battery will provide important information across and within classes of compounds that will be greatly useful in developing a more complete understanding of the vulnerable neurodevelopmental processes

that underlie adverse cognitive effects of developmental toxicant exposure. There are currently available cognitive tests such as the RAM discussed here, T-maze alternation, novel object recognition, operant conditioning and the Morris and other water mazes that can be immediately used in the developmental neurotoxicology screening battery. Further innovation should develop additional sensitive, reliable and informative cognitive tests for screening. New more efficient and more sensitive tests of cognitive function can be vetted against benchmark amnestic treatments such as acute effects of drugs such as the muscarinic acetylcholine antagonist scopolamine or the NMDA glutamate antagonist dizocilpine (MK-801) or long-term effects of developmental exposure to environmental toxicants such as lead, mercury, PCBs or chlopyrifos. The degree to which early changes in choice accuracy predict later cognitive impairment can help hone the efficiency of higher throughput cognitive screening tests in which the values of sensitivity, specificity and reproducibility can be combined in a low cost test. All this will help avoid first discovery of cognitive impairments caused by developmental toxicant exposure in humans. Even negative data where no cognitive impairments are seen can be valuable in the context of the other in vitro and in vivo results, helping to define what systems are and which are not closely linked to producing cognitive dysfunction.

Cognitive effects are unlikely to be the most sensitive indicator for screening in many cases, but screening needs to be constituted by more than only the leading edge of sensitivity. Just as the edge of the blade is only part of a sword; there must be heft behind the leading edge to make the edge cut effectively. Complex biologic functions like cognition result from simpler biologic events. Important complex functions like cognition are likely to have levels of redundancy in their constituent events so that they are robust to changing internal milieu. Testing for those simpler biological effects should be more sensitive indicators of intoxication than the complex effect for which there is redundancy. However, the trick is to understand which simpler events are key for the complex function, in this case cognition. Because of this incomplete biological understanding we need to include cognitive tests in the screening battery, because it is important and we need to determine which toxic events can lead to cognitive dysfunction. In the big data endeavor we need to gather and attend to the full body of toxicology to not only detect effects but also properly interpret them to determine functional neurotoxic risks. The relationship of cognitive impairments at higher doses to the effects on more elementary processes at lower doses can help in our understanding of the ways by which cognition can be impaired by intoxication. Performing cognitive tests in the developmental neurotoxicology screening battery does add expense, but toxicant induced cognitive impairments in humans are much more expensive and detecting them with epidemiological studies is also quite expensive. The RAM is very easily to use and quite flexible. It is sensitive to neural damage in a variety of systems. The RAM is an excellent addition to the armamentarium of cognitive tests for developmental neurotoxicology screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

Cognitive assessment is important for the developmental neurotoxicology screening battery.

The radial-arm maze is a good test to include in the screening battery.