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THEORETICAL REVIEW

The Importance of Considering All Attributes of Memory in Behavioral Endophenotyping of Mouse Models of Genetic Disease

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In order to overcome difficulties in evaluating cognitive function in mouse models of genetic disorders, it is critical to take into account the background strain of the mouse and reported phenotypes in the clinical population being studied. Recent studies have evaluated cognitive function across a number of background strains and found that spatial memory assayed by the water maze and contextual fear conditioning often does not provide optimal results. The logical extension to these results is to emphasize not only spatial, but all attributes or domains of memory function in behavioral phenotyping experiments. A careful evaluation of spatial, temporal, sensory/perceptual, affective, response, executive, proto-linguistic, and social behaviors designed to specifically evaluate the cognitive function each mouse model can be performed in a rapid, relatively high throughput manner. Such results would not only provide a more comprehensive snapshot of brain function in mouse disease models than the more common approach that approaches nonspecific spatial memory tasks to evaluate cognition, but also would better model the disorders being studied.

Keywords: behavioral endophenotype, mouse model, multiple memory systems, attributes, behavioral genetics

In the evaluation of behavioral phenotypes in mouse models of genetic disorders, the background of the mouse provides a major contribution to the interpretation of any behavioral results (Moy et al., 2008a). This is not a trivial point as the FVB/N strain is commonly used for the creation of mouse models of genetic disorders, and the SJL/J mouse has been used in studies evaluating neurotoxicological effects on neurocognition (cf., Berman, Pessah, Mouton, Mav, & Harry, 2008; Hornig, Chian, & Lipkin, 2004). The SJL/J and FVB/N strains, however, are prone to early onset blindness, precluding many researchers from evaluating any behavioral phenotypes of founder generations of novel mouse models (Errijgers et al., 2007). This is problematic because it is highly impractical for researchers to backcross a newly developed genetic model mouse with C57BL/6J mice until congenic prior to being able to determine if the mouse serves as a valid model for the disorder being studied.

As a step toward ameliorating this difficulty, Farley, McKay, Disterhoft, and Weiss (2011) applied a collection of behavioral tasks emphasizing nonspatial information processing to evaluate memory in FVB/N mice. Their focus was on the use of common behavioral paradigms that do not require visual function to demonstrate that FVB/N mice do not show poor memory or impaired hippocampal function, just poor vision. The primary strength of this article was that most of the tasks they used can easily be applied by most laboratories set up for behavioral analysis. What remained overlooked, however, was the applicability of the tasks they used as de facto models for human cognitive tasks evaluated in mouse models of disease as well as what specific domains beyond "memory" were being tested by each of the tasks they employed.

Research into mouse models of genetic disease tend to use the water maze, passive/active avoidance, or contextual fear conditioning as the primary index of "learning and memory" (Llano Lopez, Hauser, Feldon, Gargiulo, & Yee, 2010; Stewart, Cacucci, & Lever, 2011), even though spatial memory is not always analogous to the learning and memory impairments reported in a number of genetic disorders. Furthermore, inherent in the use of the water maze as a measure of memory is the idea that memory has a direct relationship with hippocampal integrity, which is not true across all domains. In addition to spatial processing, the hippocampus has been implicated in temporal processing in humans and rodents (Chiba, Kesner, & Reynolds, 1994; Hopkins, Kesner, & Goldstein, 1995; Fouquet, Tobin, & Rondi-Reig, 2010). This is important because temporal processing deficits, have been linked to damage or impaired function to a number of brain areas, including (but by no means limited to): hippocampus (Fortin, Agster, & Eichenbaum, 2002; Hunsaker, Fieldsted, Rosenberg, & Kesner, 2008), anterior thalamus (Wolff, Gibb, & Dalrymple-Alford, 2006), infralimbic/prelimbic (IL/PL) cortices (Mitchell & Laiacona, 1998), parietal cortex (Marshuetz, 2005), basal ganglia (Coull, Cheng, & Meck, 2011), and cerebellum (Pakaprot, Kim, & Thompson, 2009).

An important consideration in selecting an attribute to study in mouse disease models is to directly model what is being evaluated

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in human clinical populations. Temporal processing has been evaluated explicitly in a number of disorders, even being shown to be prodromal to full disease onset/progression in a number of disorders. For example, temporal ordering or sequencing deficits have been reported in Alzheimer's disease (Bellassen, Iglói, de Souza, Dubois, & Rondi-Reig, 2012), Parkinson's disease (Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988), Huntington's Disease (Pirogovsky et al., 2009), fragile X-associated disorders (Johnson-Glenberg, 2008; Simon, 2011), schizophrenia (Davalos et al., 2003a, 2003b), and autism spectrum disorders (Allman, Pelphrey, & Meck, 2011)—in some cases, in the absence of memory deficits. Behavioral paradigms emphasizing temporal processing, when carefully parameterized, serve as appropriate models for these prodromal deficits seen in clinical populations.

In moving beyond simple memory tests in mice, it is important to evaluate all aspects of brain function in mouse models of genetic disorders, not just simple memory function—because clinical research has moved beyond using solely intelligence testing and into defining collections of quantitative traits that scale with either the severity of disease progression or dosage of the underlying genetic mutation, referred to as "endophenotypes." Endophenotypes are collections of quantitative traits hypothesized to represent risk for genetic disorders at more biologically (and empirically) tractable levels than the full clinical phenotype, which often contains more profound deficits shared across numerous genetic disorders. This behavioral endophenotyping approach this article emphasizes, facilitates the identification of behavioral deficits that are specifically associated with both the specific genetic mutation and the pathological features observed in the clinical populations being modeled (cf., Hunsaker, 2012). When designed to evaluate specific disease-related hypotheses, behavioral endophenotypes model quantitative patterns of behavioral deficits that scale with the size and/or severity of the genetic mutation (Gottesman & Gould, 2003). Importantly, although this behavioral or cognitive endophenotyping strategy does deviate slightly from the strict definition of an endophenotype as outlined by Gould and Gottesman (2006), the basic process and the underlying theory is the same.

To evaluate behavioral or neurocognitive endophenotypes in mice, it is critical to first define what is known concerning neurocognitive function in the population being studied, preferably through direct interactions with clinical scientists directly studying the disorder in question. The second step is to develop a set of mouse behavioral tasks to explicitly model the pattern of cognitive strengths and weaknesses present in the clinical populations in collaboration or consultation with the clinical scientists. The final step is to continue task refinement to evaluate the mouse model across the maximal number of features present in the clinical population to develop either risk prodrome for later disease progression/onset or biomarkers that can be used as outcome measures for interventional studies (cf., Hunsaker, 2012). The resulting data should provide a quantitative pattern of strengths and weaknesses that scale with the dosage of the mutation in question.

This review expands upon Hunsaker (2012) by moving beyond simply providing an underlying theoretical foundation for behavioral endophenotyping of mouse models of genetic disease. This is important because the article from Hunsaker (2012) proposed the theoretical foundation for behavioral endophenotyping in an abstract sense, but the information therein is difficult to apply to all but the highly experienced behavioral phenotyping laboratory. The present article will explicitly outline an intuitive, practical, and readily applicable methodology that can be applied by experienced behavioral neuroscientists, behavioral phenotyping laboratories, as well as molecular biologists in a relatively straightforward manner.

Approaches to Endophenotyping

Since the tacit acceptance of the water maze, passive/active avoidance and contextual fear conditioning as the standard memory tasks for mouse models of disease (cf., Llano Lopez, et al., 2010; Stewart et al., 2011), the development of behavioral tasks to dissect the role of brain regions affected by the mutation for memory processing has stalled—at least in mice. In contrast, during this same period the research into the neural systems underlying learning and memory processes has reached a boon in rats. Quite recently, an effort has been made to translate the paradigms developed in rats into the mouse disease research (Hunsaker, Wenzel, Willemsen, & Berman, 2009, Hunsaker, Goodrich-Hunsaker, Willemsen, & Berman, 2010; Nakazawa, McHugh, Wilson, & Tonegawa, 2004; Rondi-Reig et al., 2006).

What has remained elusive in the field of behavioral genetics is a clear theoretical rationale underlying the choice of experiments performed on each given model (i.e., water maze does not test all types of spatial memory, let alone all types of memory). In order to complete the goal of comprehensively evaluating learning and memory processes across all mouse models, it becomes critical to step back and separate learning and memory into component attributes that can be evaluated in turn (cf., Kesner & Rogers, 2004; White & McDonald, 2002). Such an approach allows the murine researcher to evaluate brain function at a level more sophisticated than previously possible using more standard behavioral tasks not developed with any particular cognitive domain in mind (cf., Hunsaker, 2012).

Before moving into a closer analysis of the proposed approach, it is important to mention the pitfalls with the common memory tasks used in mice: the water maze, passive/active avoidance, and contextual fear conditioning. All of these tasks can be useful as a component of a phenotyping approach, but in themselves, do not allow researchers to specifically determine the nature of impaired memory in mouse models. For all these tasks there are confounding factors relating to anxiety and, more importantly, the use of negative reinforcement as the primary motivation for task performance (cf., Barkus et al., 2010). Additionally, it has been suggested on numerous occasions that the water maze may not be an appropriate task for use in mice, because their performance relative to rats is poorer than would be predicted when compared with performance on nonwater-based paradigms (Frick, Stillner, & Berger-Sweeney, 2000; cf., Whishaw & Tomie, 1997)—and dry land alternatives are often slow to be adopted (cf., Kesner, Farnsworth, & DiMattia, 1989; Llano Lopez, et al., 2010). Furthermore, when negative reinforcement is used for motivation, especially using assays such as contextual fear conditioning to evaluate spatial memory, models demonstrating disorders in affect (i.e., depression or anxiety disorders) may demonstrate memory deficits for reasons other than impaired spatial processing (cf., Banik & Anand, 2011).

Attributes of Memory Processing

Table 1 outlines the first consideration in developing or choosing behavioral experiments to test mouse disease models, which is to consider what type of memory needs to be tested in the mouse. Briefly, one has to consider if the disorder being studied primarily

Table 1
Description of the Memory Systems Used in the Attribute Theory as Applicable to Research Into Mouse Models of Disease

Stage	Event-based	Knowledge-based	Rule-based
Encoding	• Pattern separation • Transient representations • Short-term memory • Intermediate-term memory	• Selective attention • Associated with permanent memory representations • Perceptual memory	• Strategy selection • Rule maintenance
Retrieval	• Consolidation • Pattern completion	• Long-term memory • Retrieval based on flexibility and action	• Short-term working memory

results in an episodic (event-based) memory deficit, knowledge-based memory deficits, or executive function (rule-based) deficits (Kesner & Hunsaker, 2010; Kesner & Rogers, 2004). Knowledge-based memory is often referred to as semantic memory in the human episodic memory literature. This article will use the term knowledge-based memory, because semantic memory has an implicit language component that cannot be evaluated directly in rodents. It is more analogous to the reference memory system proposed by Olton, Becker, and Handelmann (1979). Once that is determined, then the component memory domains can be identified and tested using experiments designed with each disorder and model in mind (Hunsaker, 2012; Simon, 2007, 2008, 2011).

Table 2 outlines a collection of simple tasks based on each component attribute that can be used to test cognitive dysfunction in mouse disease models. Aside from spatial attributes commonly tested, along with the temporal, response, social, and sensory/perceptual attributes tested thoroughly by Farley et al. (2011), it is also critical to evaluate the role of affect, proto-language, and executive functioning attributes in mouse models of neurodevelopmental disorders, because these domains are often profoundly

Table 2
Tasks That can be Used to Evaluate Behavioral Phenotypes in Mice

Attribute	Event-based	Knowledge-based	Rule-based
Spatial	• Metric processing • Topological processing • Magnitude estimation • Delay match to place with variable interference	• Biconditional discrimination • Delay match to place with variable cues • Declarative sequence learning • Cheeseboard	• Covert attention tasks
Temporal	• Trace conditioning • Temporal ordering • Sequence learning	• Sequence completion • Duration discrimination	• 5 choice serial reaction time • Peak interval timing • Time left task
Sensory Perceptual	• Delay match to sample with variable interference	• Biconditional discrimination	
Response	• Ladder walking tasks • Acquisition of skilled reaching • Working memory for motor movements	• Delay match to direction • Direction discrimination • Nondeclarative sequence learning	• Reversal learning • Probabilistic reversal learning • Operant conditioning • Stop signal task • Serial reversal learning
Affect	• Reward contrast with variable reward value	• Classical conditioning • Trace conditioning • Conditioned preference • Anticipatory contrast	• Operant conditioning • Gambling Task • Latent inhibition
	Specific cross-domain tasks important for murine research into neurodevelopmental disorders		
Executive Function	• Contextually cued biconditional discrimination • 5 choice serial reaction time task • Operant conditioning • Covert attention tasks • Reversal learning • Probabilistic (80/20) reversal learning • Serial reversal learning • Stop signal task • Gambling task • Latent inhibition		
Social	• Social transmission of food preference • Social novelty detection		
Proto-language	• Spectrographic analysis of ultrasonic vocalizations		

affected in these populations (Hunsaker, 2012; Simon, 2007, 2011).

An often overlooked, but critical, consideration in choosing behavioral assays is that of the neuropathology associated with any disorder being modeled. It seems an obvious point that one would choose behavioral paradigms that emphasize spatial (and temporal) processing to evaluate disorders with known hippocampal pathology (e.g., Alzheimer's disease) and tasks emphasizing response learning in tasks showing clear basal ganglia pathology (e.g., Parkinson's disease), but unfortunately this is not consistently taken into consideration in experiments using mouse models of genetic disorders (cf., Taylor, Greene, & Miller, 2010; Wesson, Nixon, Levy, & Wilson, 2011).

Table 3 outlines neuroanatomical substrates underlying each attribute in mice that can be consulted to guide the development or application of behavioral tasks for mouse models of disease. Importantly, although these anatomical structures have been shown to underlie the attributes as mentioned in Table 3, this description is more of a blueprint of structures that are critically involved with these processes (for references pertaining to the structures mentioned in Table 3 cf., Arns, Sauvage, & Steckler, 1999; Dere, Huston, & De Souza Silva, 2007; Fischer & Hammerschmidt, 2011; Fukabori et al., 2012; Harvey, Coen, & Tank, 2012; Hunsaker & Kesner, 2010; Johansen, Cain, Ostroff, & LeDoux, 2011; Kargo, Szatmary, & Nitz, 2007; Lalonde & Strazielle, 2003; Madsen, Brown, Short, & Lawrence, in press; Matzel & Kolata, 2010; Simpson, Kellendonk, & Kandel, 2010). Stated another way, when one brain region is shown to underlie or be involved in a process, it is more likely than not that a larger network involving the candidate neuroanatomic structure actually underlies the process, and that the contributions of the larger network is more poorly understood than the role for the single structure. An example is the hippocampus: hippocampal ablations result in profound deficits for spatial and temporal processing (cf., Jerman, Kesner, & Hunsaker, 2006; Hunsaker et al., 2008), but removal of inputs/outputs from the entorhinal cortex and septal nuclei result in qualitatively similar deficits (cf., Hunsaker, Tran, & Kesner, 2008). As such, it can be said the neural networks that include the hippocampus, and not the hippocampus in isolation, subserve spatial and temporal processing.

Application of the Attributes to Behavioral Endophenotyping

Despite the need to move beyond limiting behavioral research to the standard behavioral paradigms (i.e., water maze, contextual fear conditioning), it is by no means necessary to avoid these tasks all together. Rather, it is important to integrate these tasks into more through behavioral analysis necessary for elucidating behavioral endophenotypes.

To begin, it is important to evaluate the basic sensory function in all mice, because any deficits in basic sensation or perception confound interpretations of behavioral results (Crawley, 2007). Sensory deficits do not preclude the behavioral analysis of a mouse model. When a mouse shows sensory deficits, either the model can be bred onto a different background strain over numerous generations—commonly >10 generations backcrossed onto the C57BL/6J strain—or else behavioral tasks can be chosen that minimize the contribution of the particular sensory modality that is not being processed, as Farley et al. (2011) demonstrated in their article emphasizing behaviors not requiring vision in mice that are blind from an early age.

After evaluating basic sensory function in the mouse model, it is critical to determine the pattern of behavioral strengths and weaknesses in the population being modeled by the mouse. With this information from the clinical population, it is important to either create or adopt behavioral tasks to evaluate the same cognitive attributes or domains as tested in the clinical population. For example, if a disorder being modeled shows global memory deficits (measured by intelligence [IQ] and neuropsychological tests) without concomitant impairments for executive function, then the mouse model needs to be tested for memory across a number of domains or attributes evaluated by the neuropsychological tests in order to better dissect cognitive function in the model. In this example, executive function should also be evaluated, but in this case to verify intact executive function in the model.

Table 3
Neuroanatomical Correlates Underlying Each Attribute in Mice

Attribute	Event-based	Knowledge-based	Rule-based
Spatial	Hippocampus	Parietal cortex	IL/PL*
			Retrosplenial cortex
Temporal	Hippocampus	Anterior cingulate	Anterior cingulate
	Basal Ganglia	IL/PL*	IL/PL*
		cerebellum	
Sensory/perceptual	Sensory cortices	TE2 cortex†	IL/PL*
		Perirhinal cortex	
		Piriform cortex	
Response	Caudoputamen	Precentral cortex	Precentral cortex
		Cerebellum	Cerebellum
Affect	Amygdala	Agranular insula#	Agranular insula#
		Amygdala	IL/PL*
Executive	Basal Ganglia	IL/PL*	IL/PL*
Function	IL/PL*	Parietal cortex	Parietal cortex
Social Proto-language	Underlying neural networks still being elucidated		

Note. Murine homologs of † inferior temporal cortex, * medial prefrontal cortex, # orbitofrontal cortex.

More concretely, a general memory deficit may be mediated by an inability to encode new information, consolidate/retrieve encoded information, or understand the rules required to perform correctly on a given test. All of these factors can be tested in mice, and can further be evaluated across domains: Spatial, temporal, and response memory can be specifically evaluated in the mouse, as can the contribution of affect to memory, anxiety, and depressive behaviors. With these data, research into the mouse model may actually serve to inform the clinic as to more specific domains that can be tested in the clinic—emphasizing a direct interaction across the research in the clinic and the behavioral genetics laboratory (cf., Hunsaker, 2012).

A prime example of applying these attributes to develop an appropriate behavioral endophenotype of a mouse model is the elucidation of the BTBR T + tf/J mouse as a putative model of behavior related to autism spectrum disorders (Moy et al., 2008b, 2008a). Autism spectrum disorders are behaviorally diagnosed using three core criteria: aberrant reciprocal social interactions, deficits in social communication, and repetitive perseverative behaviors. As can be imagined, the typical battery of behavioral tasks present in behavioral phenotyping labs were initially unable to model these core features, because memory deficits, profound motor dysfunction, and impaired fear processing are not core criteria for an autism spectrum disorder diagnosis.

Recently, however, these three core features were broken down into component processes and each tested in turn to determine how well the mouse models autistic-like features. Reciprocal social interactions were reduced into social recognition, social anxiety, and sociability domains that can be tested in turn. The evaluation of repetitive perseverative behaviors did not require breaking the behaviors into component attributes, but rather required the development of novel behavioral paradigms to specifically model the results seen in the tests commonly administered to individuals with autism spectrum disorders. The evaluation of abnormal social communication was more difficult, because it required the careful analysis of vocalizations made by mice using tools from other disciplines. In short, ultrasonic vocalizations have been collected and their rate used as a measure of affect or stress (Moy et al., 2008a, 2008b), but it was determined that if the individual vocalizations were analyzed spectrographically, differences among strains were possible, and any systematic differences unique to certain trains may be interpreted as abnormal communication. Altered scent marking behaviors also serve as communication deficits in mice.

To evaluate impaired social interactions, it was not only necessary to evaluate the general sociability of mice, but also to evaluate in more detail the interactions among the mice that model autistic features and mice that do not. It has been demonstrated that the BTBR T + tf/J mouse shows reduced social approach to other BTBR T + tf/J mice, as well as to C57BL/6J mice, and that the BTBR T + tf/J mice show elevated levels of social anxiety and behaviors analogous to gaze avoidance, a commonly reported behavior in individuals with autism spectrum disorders (Bolivar, Walters, & Phoenix, 2007; Defensor et al., 2011; McFarlane et al., 2008; Pobbe et al., 2011; Yang et al., in press). It has also been demonstrated that a BTBR T + tf/J mouse shows abnormalities in proto-linguistic processes as measured using social and nonsocially evoked ultrasonic vocalizations. These vocalizations are both reduced in quantity, and show abnormal structure when evaluated spectrographically (Scattoni, Ricceri, & Crawley, 2011; Scattoni, Gandhy, Ricceri, & Crawley, 2008). Similar findings have been reported in communicative behaviors involving scent marking, an important method of communication among rodents (Wöhr, Roullet, & Crawley, 2011). To evaluate repetitive and stereotyped behaviors, as well as perseverative behavior reported in autism spectrum disorders, a number of paradigms were developed. These range from perseverative, restricted search patterns in the holeboard and impaired response reversal learning on a T maze (Moy et al., 2008a, 2008b). One recent report of intact reversal learning with predictable reward shifts, but impaired probabilistic reversal with 80/20 reward contingencies directly models results of clinical research into autism spectrum disorders (Amodeo, Jones, Sweeney, & Ragozzino, 2012). Motor and cognitive stereotypies have also been reported in a BTBR T + tf/J mouse (Pearson et al., 2011).

As another example of the approach to behavioral endophenotyping, one can use the evolution of the research into one of the fragile X-associated disorders, the fragile X premutation. The fragile X premutation is the result of a tandem trinucleotide repeat on the 5 ft untranslated region of the FMR1 gene that results in excess FMR1 mRNA and slight reductions in the FMR1 protein (FMRP) levels. Initially, it was thought the carriers of the premutation were cognitively unaffected by the mutation (Hunter et al., 2008), but more recently a cognitive phenotype has been evaluated that includes altered hippocampal-dependent episodic learning, reduced affect, and spatiotemporal processing that is negatively modulated by increasing CGG repeat length (Goodrich-Hunsaker et al., 2011a, 2011b, 2011c; Hessl et al., 2011; Koldewyn et al., 2008). There are two mouse models of the premutation, the CGG KI mouse (Willemsen et al., 2003), and the CGG-CCG mouse (Entezam et al., 2007). Both models have been cognitively evaluated using the traditional approach, using the water maze or passive avoidance to evaluate memory function. Despite identifying cognitive deficits and elevated anxiety in the CGG KI (Van Dam et al., 2005) and CGG-CCG mice (Qin et al., 2011), the results are difficult to interpret in light of the phenotypes reported in premutation carriers, who do not consistently show memory deficits or anxiety disorders (Hunter, Rohr, & Sherman, 2010).

More recently, an endophenotyping approach has been applied to the CGG KI mouse, designed to specifically model the spatiotemporal processing results from Goodrich-Hunsaker et al. (2011a, 2011b, 2011c). The approach was to model the modulation of cognitive function seen in carriers of the premutation rather than large-scale deficits, because in these studies there were not consistent group differences between control participants and carriers of the fragile X premutation. The CGG KI mouse shows impairments for spatial processing, temporal processing, and reduced visuomotor function; furthermore, all these impairments worsen as a function of increasing CGG repeat length—suggesting the experimental paradigms may be useful to elucidate a behavioral endophenotype (Diep et al., 2012; Hunsaker et al., 2009, 2010, 2011; cf., Gottesman & Gould, 2003; Gould & Gottesman, 2006; Hunsaker, 2012). What remains untested in the mouse models of the premutation are any contribution of altered affect and executive function as has been reported in premutation carriers (Hessl et al., 2011; Hunter, Sherman, Grigsby, Kogan, & Cornish, in press).

A number of neurodegenerative disorders also have mouse models that have not been thoroughly characterized beyond the

traditional behavioral paradigms. Individuals with Huntington's disease do not only show chorea, but also progressive deficits for cognitive function. More precisely executive functioning deficits worsen across time into a subcortical dementia, as do memory deficits and neuropsychiatric sequelae such as anxiety, depression, and blunted affect (cf., Dorsey, & Huntington Study Group COHORT Investigators, 2012). These features have been modeled in the mouse models (Fielding et al., 2011). However, the neuropathological features associated with Huntington's disease, including reduced frontal-striatal connectivity, suggest the patients should show difficulties with temporal ordering and temporal functioning, and this has been proposed to underlie episodic memory deficits (Pirogovsky et al., 2009). In Huntington's disease, deficits in picture sequencing and sequential motor learning have been reported (Feigin et al., 2006; Foroud et al., 1995; Ghilardi et al., 2008; Snowden, Crawford, Thompson, & Neary, 2002), as well as deficits for a temporal ordering paradigm designed initially for rodents (Pirogovsky et al., 2009). More importantly with the Pirogovsky et al. (2009) article, impaired performance for temporal ordering was correlated with time to symptom onset in individuals with the mutation underlying Huntington's disease—suggesting temporal ordering may be an endophenotype or prodromal feature that can be used to characterize the disease. In fact, temporal processing deficits have been reported in Alzheimer's disease (Bellassen et al., 2012), Parkinson's disease (Sagar et al., 1988), Huntington's disease (Pirogovsky et al., 2009), fragile X-associated disorders (Hunsaker, 2012; Johnson-Glenberg, 2008; Simon, 2008, 2011), schizophrenia (Davalos et al., 2003a 2003b), and autism spectrum disorders (Allman et al., 2011).

Unfortunately, to date, these sequencing/temporal processing features of Huntington's disease (among many others) have not been modeled in the respective mouse models. There are a number of behavioral paradigms that have been used in mouse disease models, which can be used to test temporal processing in neurodegenerative disease, but they have yet to be widely applied in behavioral genetics research (DeVito et al., 2009; Hunsaker, 2012; Hunsaker et al., 2010).

Practical Advice to Apply an Endophenotyping Approach

There are a number of difficult questions that must be answered in the development of a comprehensive behavioral endophenotyping approach, including: How many of these behavioral tests could be conducted on a single cohort of mice? Would multiple tests on the tasks listed lead to potential confounds? What are the potential contributions/confounds of environmental effects, such as housing conditions, on mouse behavior? These are important factors, because small changes in experimental design can make the difference between a successful analysis of a behavioral phenotype and a collection of uninterpretable data.

The question of testing the same group or mice across multiple experiments is sometimes more complicated as it seems, but a solution can be designed if viewed through the attribute model. The most critical aspects that need to be taken into account when performing multiple experiments on the same mice are twofold: any role for negative affect on task performance, and the rule-based memory system succumbing to interference across tasks. It is important to keep in mind the role for negative affect for task performance not only on the present task, but also future tasks performed with the same group of mice. If a mouse is to receive fear conditioning in the middle of an experimental design, it will take a week or so of handling for the mouse to unlearn any associations between the fear conditioning and the experimenter (cf., Rudy & O'Reilly, 2001).

For the rule-based memory system, it is important to remember that mice and rats take a significantly longer amount of time to learn and apply rules to guide behavior than humans. As such, if a researcher wants to perform any experiments that require the mouse to learn a rule or set of rules to guide behavior, and are not just exploiting the natural tendency of mice to explore their environment and behaviorally respond to novelty across domains (i.e., novelty detection), then intervening tasks not requiring rule learning/implementation need to be presented prior to the usage of another task taxing the rule-based memory system. Also important in this case is the use of very different apparatus for each rule-based learning task, or else previously learned rules will have to be explicitly extinguished prior to beginning training on a new task (cf., Cohen & O'Reilly, 1996).

As a rule of thumb, it is best to perform at most a set of experiments evaluating basic sensory function in mice (cf., Crawley, 2007), followed by tasks evaluating each attribute in turn, followed potentially by the water maze/avoidance tasks and fear conditioning as the final task to prevent carryover from experiments interfering with subsequent experiments. In this, most likely more than one experiment tasking executive function/complex rule learning can be performed. More than one of these tasks will result in interference that will confound interpretation of subsequent rule-based tasks. Additionally, aside from the water maze and fear conditioning experiments, it is recommended that series of experiments be counterbalanced across animals and groups, preferably using a Latin square design to reduce the contribution of task order to any observed effects. Additionally, it is often worth testing the ability of mice to perform the behavioral task battery by evaluating a few wild-type mice of the background strain being used to verify that they can perform all the tasks without being overwhelmed by excessive testing.

In addition to genetic background, the treatment of mice prior to and during experimentation is critical. It has been shown a number of times that alterations to the cage environment is an important factor for later behavioral improvement—such that an enriched environment results in better performance on behavioral tasks and increased gray matter and dendritic complexity. As such, mice should preferably be housed in a standard fashion, either with a set number of mice per cage or else singly housed—but it is important to note that mice do not do as well singly housed as rats; they tend to show increased anxiety levels, which may affect task performance (cf., Van de Weerd, et al., 2002). As such, multiple housed is recommended unless precise drug dosing or food deprivation is required that precludes group housing. Furthermore, the amount of stimuli available to the mice within each cage should be uniform across cages. As such, a standard environment needs to be maintained among all mice during experimentation.

Conclusions

An important consideration in the study of mouse models of any genetic disease is how well the behavior of the mouse serves to

actually model the behaviors present in the clinical population being modeled. In order to optimally address this concern is to explicitly develop a behavioral endophenotype of the mouse model in which the mouse is explicitly tested using tasks rigorously designed to explicitly test the cognitive domains affected in the clinical population. To achieve this goal, it is important to not only apply standard behavioral tasks to mouse models of genetic disorders, but also to directly evaluate brain function across all cognitive domains. Furthermore, it is critical for behavioral genetics labs to interact with clinical research laboratories to develop comprehensive behavioral endophenotypes for the disorder being modeled. The strength of behavioral genetics and the mouse models is the ability to apply behavioral paradigms known to be subserved by known anatomical loci to determine not only the behavioral phenotype of the model, but also to elucidate candidate brain regions affected by the mutation (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). When research into mouse models of genetic disorders emphasizes patterns of mnemonic strengths and weaknesses across domains (i.e., the behavioral endophenotype), the results will not only directly model the disorder being studied, but may serve both as risk prodrome for disease onset or progression, as well as outcome measures that can be applied by the clinic in interventional studies.

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