Reversal Learning and Attentional Set-Shifting in Mice

Gregory B. Bissonette[1,2] and **Elizabeth M. Powell**[1,2,3]

[1]Department of Anatomy & Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA

[2]Program in Neuroscience, University of Maryland, Baltimore, MD, USA

[3]Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Schizophrenia is a complex developmental disorder that presents challenges to modern neuroscience in terms of discovering etiology and aiding in effective treatment of afflicted humans. One approach is to divide the constellation of symptoms of human neuropsychiatric disorders into discrete units for study. Multiple animal models are used to study brain ontogeny, response to psychoactive compounds, substrates of defined behaviors. Frontal cortical areas have been found to have abnormal anatomy and neurotransmitter levels in postmortem brains from schizophrenic patients. The mouse model has the advantage of rather straightforward genetic manipulation and offers numerous genetic variations within the same species. However, until recently, the behavioral analyses in the mice lagged behind the primate and rat, especially with respect to test of frontal cortical regions. Current reports of mouse prefrontal anatomy and function advocate the mouse as a feasible animal model to study prefrontal cortical function. This review highlights the most recent developments from behavioral paradigms for testing orbital and medial prefrontal cortical function in pharmacological and genetic models of human schizophrenia.

Introduction

Cognitive rigidity is a common behavior symptom of many developmental disorders, including autism, Tourette syndrome, Rett syndrome and schizophrenia, as well as neurodegenerative disorders of Parkinson's, Alzheimer's and Huntington diseases (Baddeley et al., 2001; Elliott et al., 1995; Gauntlett-Gilbert et al., 1999; Hill, 2004; Josiassen et al., 1983; Pantelis et al., 1999; Traykov et al., 2007; Verte et al., 2005). Patients that suffer frontal lobe deficiencies can easily learn and follow individual rules, but have great difficulty modifying their responses to new rules (Cools et al., 2000; Jacobs and Anderson, 2002; Shamay-Tsoory et al., 2004). For example, schizophrenic patients do not adapt normally to changes in their environments, especially in social and emotional contexts, and they exhibit an inability to modify responses in formal testing situations (Bowie and Harvey, 2006; Elliott et al., 1995; Leeson et al., 2009; Pantelis et al., 1999). Performance deficits are observed on the Wisconsin Card Sorting Test (WCST), in which the subject must sort a

Corresponding Author: Elizabeth M. Powell, PhD Department of Anatomy & Neurobiology University of Maryland School of Medicine HSF II S251 20 Penn St Baltimore, MD, USA Phone: 410-706-8189 Fax: 410-706-2512 epowe001@umaryland.edu.

series of cards dependent upon changing rules, such as suit and color (Berg, 1948; Nelson, 1976). Patients can learn simple rules for sorting the cards, but they are unable to change established behavior once the relevant category changes (Egan et al., 2001; Elliott et al., 1995; Prentice et al., 2008). In addition, these patients are impaired in learning simple reversal tasks, in which the cues signaling correct and incorrect responses are switched (Leeson et al., 2009; Murray et al., 2008; Waltz and Gold, 2007). Thus, patients with different neuropsychiatric disorders display similar impairments in reversal learning and attentional set-shifting, suggesting that multiple neurotransmitters contribute to the common neural circuitry.

The components of the WCST and reversal learning employed in patient studies have been modified and adapted for research animal models. In agreement with the patient data, lesion studies in the primate and rat demonstrated that disruption in prefrontal (dorsal lateral prefrontal cortex) areas reduces the ability to shift between attentional sets (Birrell and Brown, 2000; Dias et al., 1996a, b). Similar conclusions about structural and functional analogies have been drawn about the parallel orbital frontal cortical (OFC) regions in primates and rats (Clarke et al., 2005; McAlonan and Brown, 2003; Schoenbaum and Roesch, 2005). More recently, reports on reversal and perceptual attentional set-shifting tasks in mice support analogous neural substrates in the laboratory mouse (Bissonette et al., 2010; Bissonette et al., 2008; Brigman et al., 2005; Colacicco et al., 2002; Garner et al., 2006). This review will highlight the current literature of evaluating frontal lobe mediated cognition in the mouse, with a special emphasis on the reversal and set-shifting tasks, alterations in neural transmitters and genes associated with human schizophrenia.

Transgenic mice have provided a wealth of information about how individual genes regulate ontogeny and maintenance of the mammalian nervous system. Despite this, linking animal responses to human behavior has been challenging, invoking discussion on parallels of anatomy and behavioral testing and interpretation of the data (Gould and Gottesman, 2006; Nestler and Hyman, 2010). Whether the rodent has a prefrontal cortex has been questioned (Preuss, 1995; Uylings et al., 2003), with the consensus that analogous anatomy and function are present in rat and primate (Brown and Bowman, 2002; Groenewegen and Uylings, 2010; Kolb, 1984; Kolb and Robbins, 2003). Similar cytoarchitecture and chemoarchitecture is described for the C57BL/6J strain of the mouse (Van De Werd et al., 2010). Over the past two decades, behavioral studies in the mouse have demonstrated that although significant strain differences are present, the laboratory mouse appears capable of performing many of the cognitive tasks tested in rats and non-human primates (Owen et al., 1997; Paylor and Crawley, 1997; Rossi-Arnaud and Ammassari-Teule, 1998).

Reversal learning

Reversal learning in mice has been evaluated by modifying methods initially designed for the rat (see (Floresco and Jentsch, 2011) for a current review of the rat literature), including spatial learning with mazes: Morris water, T-maze (Bannerman et al., 2003) and eight-arm maze (El-Ghundi et al., 2003); with a two-choice digging task (Bissonette et al., 2008; Colacicco et al., 2002; Garner et al., 2006); and with operant learning equipment, including the go/no-go (Kruzich and Grandy, 2004; Schoenbaum et al., 2003) and delayed non-match-to-position task (Krueger et al., 2006) or visual discrimination paradigms (Brigman et al., 2005; Bussey et al., 1997b; Chudasama and Robbins, 2003). The two-choice digging task and the touchscreen visual discrimination paradigm have been most popular, especially when assessing both reversal and attentional set-shifting abilities. Both tasks rely on stimulus-reward learning, with the reward being a morsel of food for the food-deprived subject. Reversal learning involves the OFC, dorsal striatum, and amygdala, while set-shifting requires intact medial wall structures (anterior cingulate, prelimbic and infralimbic

cortex), amygdala and dorsomedial striatum (Birrell and Brown, 2000; Bussey et al., 1997a; Bussey et al., 1997b; Kim and Ragozzino, 2005; McAlonan and Brown, 2003; Ragozzino, 2007; Schoenbaum et al., 2003; Stalnaker et al., 2007; Tait and Brown, 2007, 2008). Therefore, the evaluation of reversal learning and set-shifting within the same task can provide an informative framework for testing multiple areas in the frontostriatal circuitry.

For reversal learning, the mouse must learn to discriminate between two cues. In the touchscreen task, the subject is trained to select between two images, and correct choices are rewarded (Brigman et al., 2005; Bussey et al., 1997a). Once the mouse has reached criterion, usually 85% correct choices, the cues are reversed, such that the previously rewarded image is incorrect, and the previously incorrect image is now rewarded. Perseverative errors, those that are contextually inappropriate or an unintentional repetition of the response, as defined by Crider (Crider, 1997), are used as a measure of cognitive inflexibility. Unlike maze tasks, the touchscreen method requires little movement and can be used to evaluate mice with motor deficits (Morton et al., 2006). Data from multiple mouse strains, genetic mutants and pharmacological manipulations are forming a basis to validate the test as an animal model of prefrontal cognition.

Automated reversal learning using a touchscreen: effects of genetic variation

Common mouse strains have known behavioral differences due their unique genetic alleles and modifiers (Crawley, 2000; Crawley and Davis, 1982). The majority of cognitive testing is performed on the C57BL/6J (B6) line or congenic mice which have been backcrossed to the B6 background for at least 10 generations (Moy et al., 2008; Nadler et al., 2006). This initial touchscreen tests reported successful reversal learning in B6 adult males (Brigman et al., 2005). When compared to the inbred DBA/2J (DBA) strain B6 mice learn more slowly, requiring 10 daily sessions (of 30 trials/session) to reach criterion (85% correct) of the discrimination task, whereas the DBA mice completed the task in 5 sessions (Izquierdo et al., 2006). The reversal task normally poses a challenge for rodents and primates, and the B6 needed about 20sessions (a two-fold increase) to reach criterion. However, the DBA mice completed the task in 5 sessions, the same number as for the discrimination. DBA mice were generally quicker in performing the task, with shorter latency per trial. The total numbers and types of errors were not reported, but the DBA mice did have fewer correction errors. As suggested by the authors, the attributes of each mouse line can be further investigated by using the BxD recombinant inbred mouse lines in which chromosomal segments from either B6 or DBA are selectively expressed in known patterns. The choice of genetic background can greatly influence behavioral outcome and is critical when comparing across studies.

The *REELIN* gene has been implicated in schizophrenia (Guidotti et al., 2000; Torrey et al., 2005). Reelin expressing cells the frontal cerebral cortex are GABAergic interneurons that are hypothesized to be dysfunctional in schizophrenia. Multiple variants of the null alleles are available; however mice with two mutant alleles carry motor deficits that preclude cognitive behavioral testing. Mice harboring a single mutant allele on a mixed B6C3Fe background were assessed in the touchscreen reversal discrimination task. Mice with the mutant *reelin* allele were impaired on the reversal, but had normal acquisition (Brigman et al., 2006). Error analysis did not show evidence of perseveration. The same mouse line was evaluated in an operant task with visual stimuli, and the *reelin* mutant mice were not found to differ from control mice (Krueger et al., 2006). In the operant task, two *reelin* mutant mice were unable to reach criteria, possibly due to visual deficits that accompany the retinal degeneration present in the C3Fe background strain. Disparities in age or difficulty of the task may explain the conflicting results, as may the contributions of each of the background strains.

The majority of the reports with the touchscreen assay was performed with mice on the B6 background and evaluated the effects of individual genes that were associated with cognitive impairments in humans. In addition to the GABA system, the glutamatergic system may be dysfunctional (Clinton and Meador-Woodruff, 2004; Kim et al., 1980). While mice lacking the NMDA receptor 2A subunit (NR2A, gene:*Grin2a*) mice readily learned the instrumental behavior to obtain the reward and had no differences with acquisition or extinction, the mice showed abnormal discrimination performance and impaired reversal learning on the pair discrimination task, regardless of sex (Brigman et al., 2008). Mice missing a single *Grin2a* allele were similar to wildtype (B6) control mice, showing no deficit with the hapolinsufficiency.

Increased synaptic glutamate in a mouse missing GLAST (glial glutamate and aspartate transporter, excitatory amino-acid transporter 1, gene:*Slc1a3*) led to normal learning of the pre-training parts of the touchscreen task but inability to reach the 85% criterion for the pair discrimination, regardless of sex (Karlsson et al., 2009). Wildtype (B6) mice attained criterion within 22 sessions, but *Slc1a3* null mice reached only 80% correct trials after 60 sessions (days of testing). The mGlu2/3 receptor agonist LY379268 (novel putative anti-pyschotic) was not able to rescue the discrimination learning. However, 2/3 of the null mice were able to attain 70% correct performance (trials), an indication that the *Slc1a3* null mice performed above chance levels. Due to inability to reach criterion on the discrimination task, the reversal task was not performed. In summary, the touchscreen task has successfully verified multiple gene candidates and their role in reversal learning.

Touchscreen task: evidence from pharmacological manipulations

In rats, the subchronic treatment of the NMDA receptor antagonist phencyclidine (PCP) mimics multiple behavioral endophenotypes observed in human schizophrenic patients (Jentsch and Taylor, 2001). B6 male mice were subjected to a similar protocol, using the touchscreen method. Mice were trained to learn the discrimination, treated with PCP for 7 days, tested on the discrimination task again, followed by the reversal tasks. Compared to saline treated controls, no differences in either trials to criterion or errors or perseverative errors in either the discrimination or reversal portions of the task were observed (Brigman et al., 2009). These data conflict with some findings in rat using instrumental tasks (Abdul-Monim et al., 2007; Jentsch and Taylor, 2001), but agree with data in rat with the two cup digging task (Egerton et al., 2005; Goetghebeur and Dias, 2009). With respect to other mouse PCP studies, acute administration of PCP induced reversal learning deficits (Laurent and Podhorna, 2004), contrary to chronic administration reported by others. Without replicated experiments among separate groups, the effects of subchronic PCP appear to be dependent upon dosing regimen and chosen task.

Depletion of serotonin selectively disables correct reversal learning in the primate visual task (Clarke et al., 2005). Using the similar touchscreen task in B6 male mice, chronic fluoxetine did not alter the number of trials to criterion or overall errors, but fluoxetine decreased the number of errors in the learning phase of the reversal test (Brigman et al., 2010). These results suggest that fluoxetine may increase mouse sensitivity to negative rewards. In the same study, acute treatment with para-chlorophenylalanine (PCPA), which blocks serotonin synthesis, had no effect on trials to criterion or errors. Mice lacking the serotonin transporter (5-HTT, gene: *Slc6a4*) had normal discrimination performance, but required fewer trials to reach criterion for the reversal (both heterozygous and null mice) and had fewer errors, including fewer perseverative errors (Brigman et al., 2010), supporting a role for 5-HTT in modulating sensitivity to negative feedback. The effect is selective for 5-HT, as depletion of norepinephrine was the same as control performance. Finally, severe loss of 5-HT neurons (70%) and subsequent 89% reduction cortical 5-HT levels in mice

missing the transcription factor Pet-1 (gene:*Fev*) (Hendricks et al., 2003) has no effect on discrimination or reversal testing. In summary, loss of 5-HTT increases sensitivity and may be therapeutic for reversal learning deficits, whereas the overall lack of 5-HT is unclear and in the *Fev* null mouse may be masked due to compensatory changes.

Digging task

An alternative to the touchscreen or maze tasks is the two cup digging task based on naturalistic foraging. Two cups contain scented digging medium and a food reward (Figure 1). The rule is set by one of the dimensions, odor or digging medium, and the rodent chooses the cup with the correct odor (or digging medium). Throughout the discrimination trials, the correct cue (i.e. odor) is randomly paired with the other irrelevant dimension (digging medium). For the reversal task, the correct cue (i.e. odor 1) is incorrect, and the previously incorrect cue (i.e. odor 2) is rewarded. Originally designed for rats, lesions in rat OFC lead to impaired performance (McAlonan and Brown, 2003). Several successful adaptations show robust performance in mice (Colacicco et al., 2002; Garner et al., 2006), with lesions to mouse OFC specifically altering reversal learning, but having no effect on attentional set-shifting (Bissonette et al., 2008). Like the touchscreen task, the two cup digging task has been used to study the genetic and neurotransmitter alterations in human psychiatric disorders.

Pharmacological effects

The effects of altering neurotransmitter levels have been reported with the two cup digging task. Acute administration of subchronic doses of PCP in B6 male mice impaired initial discrimination and reversal tests (Laurent and Podhorna, 2004). On subsequent reversal discriminations tests, all groups performed similarly. However, the number of trials for the reversal tests was not significantly different than the preceding compound discrimination, suggesting that only the initial reversal presentation requires novel learning. Ketamine, the atypical antipsychotic sertindole, and the NR2B specific antagonist Ro 25-6891 had no effect on reversal discriminations (Kos et al., 2010). Again, although four unique discrimination and reversal test pairs were performed, only the first reversal required more trials than the preceding discrimination in order to achieve criterion. The role of serotonin has not yet been evaluated in the digging task. Early life exposure to the acetylcholinesterase inhibitor diisopropylfluorphosphate (DFP) impaired reversal discrimination during the first presentation of the combinations for both male and female B6 adult mice (Levi et al., 2008). Female mice continued to require additional trials to reach criterion even after successfully completing the task previously.

Assessing the roles of candidate genes in reversal learning using the digging task

Several lines of mice harboring candidate genes for human cognitive disorders have been evaluated. Similar to human schizophrenic patients, female B6 mice lacking the dopamine type-2 receptor (gene: *Drd2*) had difficulty acquiring the association between food reward and the odor cue on the compound discrimination and the reversal tests (Kruzich and Grandy, 2004). The *Drd2* null mice committed more perseverative errors, leading the authors to suggest the Drd2 is necessary to disengage associative responding when the previously correct cue is no longer rewarded. B6 mice that were treated with the D1-like receptor agonist, SKF81297, had normal discrimination performance but fewer correct choices and more perseverative errors on the touchscreen task (Izquierdo et al., 2006), confirming a role for dopamine. In contrast, transgenic B6CD1 mice overexpressing the human catechol-O-methyltransferase (gene: *COMT*) Val polymorphismspecifically in

neurons showed no reversal impairment (Papaleo et al., 2008). COMT regulates the catabolism of dopamine (Tunbridge et al., 2004). On the mixed B6CD1 background, only the first reversal discrimination required more trials to complete the reversals, as compared to the compound discriminations. While not significant, the *COMT-Val* transgenic mice required more trials to criterion for the intradimensional shift (change in compound discrimination), indicating difficulty in the association between stimulus and reward, similar to the *Drd2* null mice. The mixed background or compensatory mechanisms may explain the lack of a reversal deficit in the *COMT-Val* mice.

In addition to dopamine, the inhibitory neurotransmitter, GABA, been implicated in schizophrenia (Benes et al., 1991; Lewis et al., 2005; Torrey et al., 2005). The ontogeny of GABAergic interneurons is mediated by the Met receptor tyrosine kinase (gene: *Met*), its ligand hepatocyte growth factor/scatter factor (HGF/SF; gene: *Hgf*) and the associated molecule urokinase plasminogen activator receptor, uPAR (also known as Plaur; gene: *Plaur*) (Bae et al., 2010; Levitt et al., 2004; Martins et al., 2011; Powell et al., 2003; Powell et al., 2001). All three genes have been associated with autism or schizophrenia (Burdick et al., 2010; Campbell et al., 2006). Mice with the null mutation of *Plaur* or targeted loss of functional *Met* in developing GABAergic interneurons display normal discrimination acquisition but impaired reversal learning (Bissonette et al., 2010; Martins et al., 2011). The reversal learning deficits in the *Plaur* mice are attributed to loss of parvalbumin expressing interneurons in the frontal cortical areas and can be rescued by the postnatal addition of HGF, provided a possible avenue for future therapies (Bissonette et al., 2010). In these reports, developmental disorders have been model using transgenic mice and the two cup digging task.

Attentional Set-shifting

Multiple human neuropsychiatric conditions report poor performance on the WCST (Grant and Berg, 1948), which requires the subject to alter the response strategy and use previously irrelevant information to solve the new set of problems. The main measurement of the WCST is the ID/ED (intradimensional/extradimenional) shift, the difference in the number of trials required in changing strategy from using the same type of cues (in the intradimensional (IDS) discrimination) to the other (previously irrelevant) type of cue (termed an extra-dimensional shift, EDS). In control subjects, the ID/ED shift requires more trials to criterion than a shift between two consecutive IDS problems. If the number of trials to solve the EDS problem is not significantly greater than the previous IDS problem, then the data are interpreted as the lack of formation of the attentional set. Hence, the ID/ED shift is the metric to compare strategy shifting in animal models of human disease.

Evidence from lesion studies

Neurotoxic lesions in monkeys using an automated visual discrimination analogue of the WCST revealed the prefrontal cortex was the neural substrate for the attentional set-shift (Dias et al., 1996a, b). The impairments observed in the non-human primates were similar to abnormal responses reported in humans with prefrontal damage. The automated visual discrimination test has been adapted for the rat and mouse to test attention, along with discrimination and reversal learning (Brigman et al., 2005; Bussey et al., 1997b). Testing in the male B6 mouse did not yield the ID/ED shift, leading to the conclusion that mice were not capable of complex learning, such as attentional set shifting (Brigman et al., 2005). However, by including additional discrimination tests, the same group has shown a significant ID/ED shift in mice, the *Reelin* heterozygote on the B6C3Fe background (Brigman et al., 2006). *Reelin* haploinsufficiency did not impair set-shifting. Future studies with the touchscreen task will validate its role in assessing mouse prefrontal function.

A more common version of the WCST for rodents is the two cup digging task (Colacicco et al., 2002; Garner et al., 2006). Originally designed and validated for rats, lesions to the medial wall of either rat or mouse lead to impaired performance (Birrell and Brown, 2000; Bissonette et al., 2008). The mouse version of the task employs multiple days of testing in order to avoid satiety of the reward and to accommodate the ethiological differences between species. The initial adaptation demonstrated an ID/ED shift for males of the B6 strain, but not for 129/SvEv or first generation of the B6x129/SvEv cross (Colacicco et al., 2002); again questioning whether mice are capable of forming the attentional set. Subsequent studies demonstrated that increasing the number of discrimination problems, with additional new problems or with overtraining, led to the formation of the attention al set (Bissonette et al., 2008; Garner et al., 2006). Thus, with either the touchscreen or two cup choice task, mice are able to form an attentional set, as defined by the ID/ED shift, but mice require additional discriminations, as compared to the rat versions of the task.

Effects of pharmacological and genetic manipulations on set-shifting

Several adaptations of the two cup digging tasks with numerous odors, media textures and configurations have been reported to assess the role of pharmacological and genetic manipulations. Acute administration of subchronic doses of PCP altered the ID/ED shift at the highest dose, but the control and low dose B6 males did not show a significant ID/ED shift (Laurent and Podhorna, 2004). A possible explanation for lack of formation of the attentional set in the control mice is that only three discrimination problems were presented, and the high dose of PCP strengthened the association between dimension and reward on the compound discriminations, inadvertently forming the attentional set. A similar disparity in formation of the attentional set in control and treated mice was reported with acetylcholinesterase inhibitor DFP, no ID/ED shift was observed, but there was a significant increases in trials to criterion for the DFP treated group (Levi et al., 2008). In a task including two intradimensional shift and three reversals, attentional set formation was impaired by ketamine, but reversed with the addition of sertindole (Kos et al., 2010). The role of the NR2B receptor is unclear, as treatment with the antagonist Ro 25-6981 did not consistently demonstrate the ID/ED shift (Kos et al., 2010). The success of the pharmacological studies was dependent on the demonstration of the ID/ED, which required multiple discrimination tests.

Loss of the dopamine receptor 3 (Drd3, gene: *Drd3*) or Drd2 did not alter the trials to criterion for the EDS. However, in this study no ID/ED shift was shown for the control B6 male mice after the single IDS. The *Drd3* mice had increased latency to complete all discrimination tasks and *c-fos* activation in the medial prefrontal cortex (Glickstein et al., 2005). In contrast, *COMT- Val* transgenic mice on the B6CD1 background were impaired on the EDS when all mice in the cohort demonstrated the ID/ED shift after two IDS tests and three reversals (Papaleo et al., 2008). Like in the rat and primate, dopamine regulates strategy shifting in the mouse.

Sex differences

Sex also plays a role on the formation of the attentional set. Female mice on the B6 X SJL background did not have an ID/ED shift in an Alzheimer Disease model (Zhuo et al., 2007). The mixed genetic background and female sex may alter the strength of the reward association. Female B6 mice require additional discrimination problems to form the attentional set (Bissonette and Powell, unpublished observation). Supporting the findings of Colacicco et al. (Colacicco et al., 2002), the B6129 control mice (male and female) did not show the ID/ED shift, limiting the interpretation of the in a study of the role of expression of huntingtin protein (gene: *Hdh*) in the $Hdh^{CAG(150)}$ transgenic mouse (Brooks et al., 2006).

The performance disparities with sex are particularly interesting considering that males, which can readily form the attentional set, are disproportionately affected by schizophrenia and autism, disorders in which set-shifting is abnormal.

Future directions and challenges

Multiple factors affect reversal learning and set-shifting. While the OFC appears to be critical for reversal learning, and the MFC for set-shifting, the tasks involved additional subcortical structures, including dorsal striatum and basal lateral amygdala (Clarke et al., 2008; Crofts et al., 2001; Owen et al., 1991; Schoenbaum et al., 1998, 2000). A simplified diagram of the potential neural substrates (Figure 2) shows the anatomical connections between regions and factors reviewed here that affect each task in mice. Many questions still remain. In developmental disorders, multiple brain regions may be compromised, and therefore the final behavioral response may be the sum of affected and unaffected regions. Connectivity between areas may not be the same between control and impaired subjects, either mice or patients. Therefore anatomical and functional connections may need to be verified among multiple structures. Finally, the behavioral response is a property of the entire neural network, and therefore studies with multiple selective perturbations or recordings from several areas will give a better understanding of the how the network integrates information and produces the final decision.

Evaluation of complex frontal cortical cognition in the mouse is in its infancy. We are currently on the verge of understanding cortical function, how local networks work independently and integrally with other networks throughout the brain to produce complex cognitive behaviors. Obviously for a complex disease like schizophrenia, with multiple genetic factors of very low penetrance, using murine approaches will not allow us to entirely model the onset of the disease. Murine models will, however, allow us to comprehend the interaction and importance of developmental insults and the cascade of subsequent effects, leading to measurable cognitive deficits. Future studies using transgenic mouse models of schizophrenia will further reveal the contribution of each gene to the circuitry of the prefrontal cortex.

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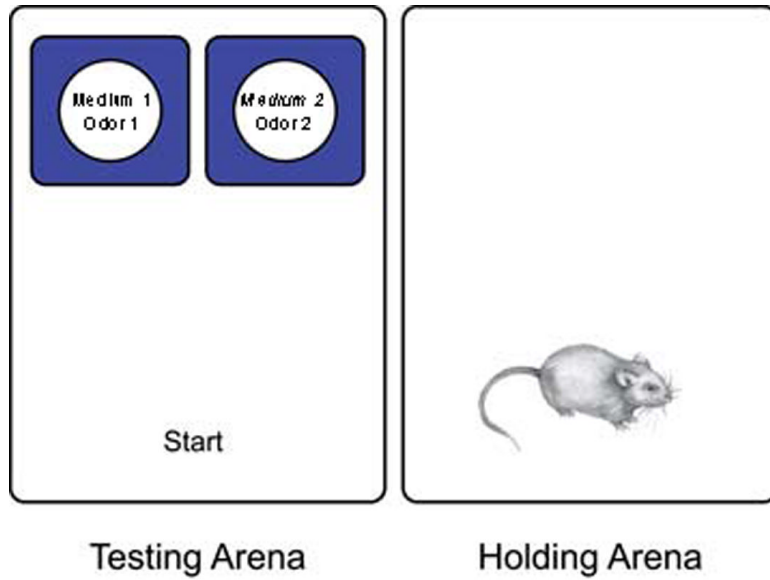
Figure 1.
Schematic of the reversal/set-shifting testing arenas. The mouse was held in the empty plastic cage until cues presentation. The mouse was placed in the back of the testing arena and allowed to explore each bowl until a choice was made. The position of the bowls and the contents of relevant and irrelevant cues were randomly determined. In this example, medium is the relevant dimension and it is paired with irrelevant odor dimension (odor 1 and odor 2). Medium 1 is an incorrect odor choice. If the correct bowl was chosen, the mouse was allowed to eat the reward in the testing arena, and then moved to the holding arena. If the incorrect choice was made, the mouse was immediately removed to the holding arena.
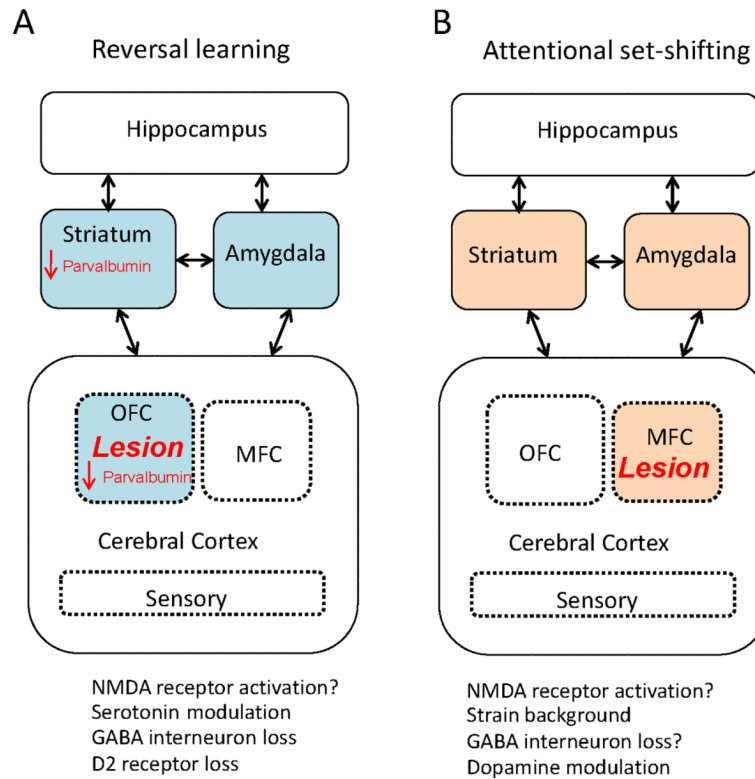
Figure 2.
Summary schematic showing factors that alter reversal learning and attentional set-shifting. The colored structures highlight the main neural substrates of the tasks. A. Lesions to OFC impair reversal learning, as do changes in NMDA receptors, GABAergic interneurons, serotonin and dopamine type 2 receptors. B. In the mouse, lesions to MFC impaired set-shifting. In addition, set-shifting may be altered by NMDA receptor activation or GABAergic interneuron function.