Published in final edited form as:

Physiol Behav. 2012 December 5; 107(5): 666–669. doi:10.1016/j.physbeh.2011.12.024.

Examining the genetic and neural components of cognitive flexibility using mice

Jonathan L. Brigman¹, Elizabeth M Powell², Guy Mittleman³, and Jared W. Young^{4,*}

¹Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM

²Departments of Anatomy and Neurobiology, Psychiatry, and Bioengineering, University of Maryland School of Medicine, Baltimore, MD

³Department of Psychology, University of Memphis, Memphis, TN

⁴Department of Psychiatry, University of California San Diego, La Jolla, CA

Abstract

This commentary summarizes the research presented during the symposium “Examining the genetic and neural components of cognitive flexibility using mice” at the annual meeting of the International Behavioral Neuroscience Society 2011. Research presented includes examining: 1) Corticostriatal networks underlying reversal learning using GluN2B knockout mice, cFos expression, and in vivo electrophysiological recording; 2) Cerebellar contribution to reversal learning using mutants with Purkinje cell loss and in vivo electrochemical recording; 3) Parvalbumin contribution to reversal learning and set-shifting using PLAU mutants and in vitro recording to examine fast-spiking interneurons; and 4) Alpha 7 nAChR contribution to reversal learning, set-shifting, motivation, and the ‘eureka moment’ of rule acquisition. It is proposed that these studies revealed more about the neurobiology underlying these behaviors than could be discovered using pharmacological techniques alone. Together, the research presented stressed the importance of exploring the genetic contribution to neuropsychiatric disease and the important role that the mouse, coupled with robust behavioral measures, can play in understanding neurobiology underlying cognitive flexibility.

Keywords

executive functioning; reversal learning; mouse; in vivo electrophysiology; learning

1. Introduction

Impairment in cognitive functioning has received increasing research focus in Psychiatry and Neuroscience over the past 10 years. This focus on cognitive research has stemmed in part from the recognition that improving functional outcome in patients with psychiatric disorders is likely to require improving their cognitive capabilities [1–3]. Behavioral flexibility is one cognitive domain that is adversely affected in numerous disorders including

© 2011 Elsevier Inc. All rights reserved.

*Corresponding author: Jared W. Young, Ph.D., Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA, 92093-0804, Tel: +01 619 543 3582, Fax: +01 619 735 9205, jaredyoung@ucsd.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

schizophrenia, bipolar disorder, Huntington's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder. This domain refers to a subjects' ability to alter behavior in response to changing environmental contingencies [4]. Examples of cognitive flexibility include reversal learning, set-shifting, and dynamic adjustment of control [5].

In order to improve cognitive flexibility in patients, an early step is to assess the efficacy of putative treatments in animals [6]. Moreover, because some disorders require the development of entirely novel treatments (i.e. no approved positive controls with which to compare against novel compounds), we must also be able to examine the genetic and neurobiological underpinnings of cognitive flexibility [7]. With the advent of sequencing of the human genome and the ability to precisely manipulate the mouse genome, the mouse has rapidly become the model species of choice for researchers investigating the genetic underpinnings of cognition. Given the strong genetic contributions to multiple neuropsychiatric diseases, assessing the behavior of genetic variants has become imperative. The development of paradigms to assess cognitive functioning in mice has only begun to catch up with rat cognitive paradigms [4, 8]. Publications investigating pharmacological-induced alterations in cognitive behavior using mice are dwarfed by the number of corresponding studies performed in rats [9]. This in part is due to mouse cognitive testing being a relatively young field largely based on rat protocols that have been developed over the past 50–60 years while cognitive testing in mice has a more recent history. In fact it is rare for a cognitive paradigm to be developed first in mice and not in rats, but such events are occurring [8].

This disparity between the numbers of pharmacological studies performed in rats compared to mice should be addressed given the interactions that are known to occur between genetic and pharmacological manipulations. The concern that mice cannot readily perform such cognitive tasks may have contributed to this disparity. We gathered experts in the field of assessing cognitive flexibility testing in mice to demonstrate that mice do perform complex tasks using neural circuitry analogous to the rat and primate. The power of assessing multiple genetic variants was highlighted within the contexts of several anatomical substrates, including examining corticostriatal networks and flexibility, cerebellar modulation of executive function, and fast spiking interneurons assist cortical tuning. The use of a battery of cognitive tests including flexibility has also been used to characterize the contribution of specific genes to cognitive performance (details of each talk are provided below).

2.1 Dr. Brigman: Corticostriatal networks underlying cognitive flexibility

In order for an organism to behave optimally in its environment it must automatize behaviors that consistently lead to positive outcomes while retaining the ability to shift its behavior in response to changing demands. Across species, corticostriatal networks are thought to underlie this balance of flexible and habitual behavior that is impaired in a wide range of neuropsychiatric disorders [10, 11]. In order to take advantage of the genetic, behavioral and pharmacological tools mouse models provide to investigate these impairments, it is essential to firmly establish the circuits underlying these behaviors in the species. We conducted a series of experiments using a touch-screen-based visual discrimination and reversal task [12] to explore cortical and striatal contributions to flexible and habitual action in the mouse. We first examined the activation patterns of cortical and striatal subregions during task performance via the immediate early gene c-Fos and then confirmed the functional role of these regions via targeted lesion. Patterns of cortical and striatal activation during discrimination and reversal learning in the mouse were consistent

with the established role of these areas in flexible and well-learned behavior respectively and selective loss of function in these areas impaired task performance [13, 14].

Given its role in the plasticity underlying learning and memory [15, 16], the N-methyl-D-aspartate receptor (NMDAR) may be a potential molecular mechanism underlying these behaviors. To test this hypothesis we utilized both genetic and pharmacological techniques to deplete or inactivate GluN2B-containing NMDAR in either cortical, striatal or corticostriatal subregions. Loss of GluN2B in cortex was sufficient to impair reversal, while GluN2B in cortex and striatum impaired discrimination. Results from GluN2B antagonism were consistent with these findings.

Finally, in order to directly measure the organization of neuronal firing in the striatum during flexible and habitual learning, *in vivo* electrophysiological recordings [17] were combined with the touch-screen task. Striatal firing patterns showed robust learning related changes in association with changes in task behavior. Taken together, these findings demonstrate the utility of the mouse for examining cognitive dysfunction that accompanies neuropsychiatric disease as well as establish a role for GluN2B in regulating corticostriatal control of flexibility and habit.

2.2 Dr. Mittleman: Cerebellar modulation of executive function

Neuroimaging studies showing cerebellar activation during cognitive tasks as well as research demonstrating cerebellar pathophysiology coupled with deficits in executive functions (e.g., autism) provide mounting evidence for a cerebellar role in cognition. We investigated the relationship between developmental loss of cerebellar Purkinje cells (the sole outflow of cerebellar cortex) and cognitive dysfunction through a series of studies utilizing aggregation chimeras made from wildtype and *lurcher* mouse embryos. *Lurcher* mice lose 100% of their cerebellar Purkinje cells due to a gain-of-function mutation in the *Grin2b* glutamate receptor (GRID2) gene while individual wildtype↔*lurcher* chimeras have between 0 and 100% of normal Purkinje cell numbers depending on the incorporation of each lineage.

Using operant techniques we assessed the performance of these chimeras on tasks designed to measure spatial working memory, sustained attention, perseverative lever pressing, and serial reversal learning of a conditional visual discrimination. The strategy in all experiments was to determine if Purkinje cell numbers correlated with behavioral measures in order to determine what cognitive abilities were, or were not affected by Purkinje cell loss. We found that Purkinje cell numbers were significantly correlated with serial reversal learning and perseverative lever pressing in that lower numbers were associated with more learning errors and enhanced perseveration [18, 19]. Interestingly, lower numbers of Purkinje cells were also associated with facilitated working memory performance [20]. We found no relationship between sustained attention and Purkinje cell numbers [21].

As behavioural deficits in serial reversal learning, working memory, and perseveration have been found to be related to frontal cortical function (e.g. Dalley, Cardinal, et al. 2004) we used *in vivo* electrochemistry to explore the hypothesis that disruption of cerebellar-prefrontal cortex (PFC) projections could lead to a dysregulation of dopaminergic-mediated activity in medial PFC. Dopamine (DA) efflux evoked by cerebellar or dentate nucleus electrical stimulation was recorded in the PFC of *lurcher* mice and wildtype controls. DA efflux following stimulation at either site was markedly attenuated in *lurcher* mice in comparison to controls [22]. Considered together, these experiments suggested that the cerebellum is involved in multiple cognitive functions, given Purkinje cell number was highly negatively correlated with serial reversal deficits and perseverative behaviour but was unrelated to sustained attention. These results also suggest that a loss of cerebellar

modulation of PFC dopamine efflux may account for some of these behavioural deficits. These findings may explain why cerebellar and frontal cortical pathologies co-occur, and may provide a mechanism that accounts for the diversity of symptoms common to multiple neurological and psychiatric disorders.

2.3 Dr. Powell: Cortical tuning assisted by fast spiking interneurons

Research suggests there may be common underlying alterations to common neural circuits for the similar cognitive etiologies which are observed in multiple psychiatric disorders. One of these common anatomical manifestations involves deficits to the GABAergic system in the cerebral cortex, specifically to the fast spiking parvalbumin-expressing interneurons. The forebrain GABAergic interneurons originate embryonically from subcortical sources, in the precursor to the dorsal striatum [23]. The specification of phenotypically different interneuron subpopulations is an active area of research in developmental neurobiology. The migration paths and signalling mechanisms which govern the final location and function is largely unknown. Yet, perturbations in the number and location of the GABAergic interneurons, in particular the parvalbumin-expressing subpopulation, have been reported in human schizophrenia, autism and epilepsy. Therefore, abnormal interneuron ontogeny is hypothesized to lead to neuropsychiatric disorders.

One gene that is associated with interneuron development and human diseases of schizophrenia and autism is urokinase plasminogen activator receptor (*PLAUR*, also known as uPAR or CD87)[24]. Mice lacking *Plaur* have specific loss of parvalbumin expressing interneurons in frontal and parietal cortical areas [25]. To better understand the functional changes elicited by the interneuron deficit, we developed a mouse task to assess reversal learning and attentional set-shifting in which we could record *in vivo* electrophysiological activity. In the *Plaur* null mutant mouse, behavioral deficits in the ability to optimally modify learned associations and update decision making behaviors become apparent. The *Plaur* null mouse was impaired in reversal learning and unable to form the attentional set [26]. *In vitro* research with slice recordings indicated that parvalbumin-expressing interneurons are essential for the generation of high frequency oscillations, coordinating large ensembles of neurons. Local field potentials in the *Plaur* null mouse demonstrated decreased activity in the beta and gamma frequencies during reversal learning. Our research works to illuminate a common neural substrate for learning and prefrontal decision related processes between mouse circuitry and behavior and human cortical function in psychiatric disease states.

2.4 Dr. Young: Alpha 7 nicotinic acetylcholine receptor contribution to learning

There are numerous psychiatric disorders for which impaired cognitive functioning is being given increasing relevance. The primary neuropathologies for some diseases are clear, such as dopaminergic neuronal loss in the caudate/putamen in Parkinson's disease [27] or repeat of the CAG allele in Huntington's disease [28]. Schizophrenia, on the other hand, has a wide ranging pathology affecting > 20 brain regions and numerous genetic abnormalities contributing to the heterogeneity of the disease [29]. It is perhaps for this reason that no drug has been approved for treating cognitive dysfunction in this disorder despite many attempts and increasing research. The field has turned in part toward understanding the impact of psychosocial (cognitive remediation) techniques which assist patients learning to cognate at a higher level. Not all cognitive remediation studies have been positive however, which may in part be due to poor learning in patients with schizophrenia [30, 31]. Thus, improving learning in patients with schizophrenia may be useful to maximize the effects of cognitive remediation and may lead to improved functional outcome for these patients.

Identifying the mechanisms underlying learning may provide a target for pro-learning treatments to be developed and used in conjunction with cognitive remediation. Nicotine enhances learning across species but its mechanism of action remains unclear. Earlier studies characterizing the cognitive performance of alpha 7 nicotinic acetylcholine receptor (nAChR) knockout (KO) mice identified impaired attention and working memory of these mice [32, 33]. One commonality of these studies were the ad hoc references to learning deficits in these mice compared to their wildtype (WT) littermates [34–36]. Thus, we began to systematically assess the learning capabilities of these mice using an operant-based holepoking task, a foraging task, and the ethologically relevant attentional set-shifting task to assess simple and reversal learning as well as set-shifting behavior [37]. We also examined the motivation of these mice using the progressive ratio breakpoint paradigm [38, 39]. It became apparent that null mutation of the alpha 7 nAChR resulted in impaired initial learning in each paradigm across all modalities despite normal motivation. Assessing the cognitive flexibility of these mice provided the most compelling evidence that the learning deficit of these mice was limited to initial learning of an operant acquired rule. Despite impaired simple learning in the initial stages of the attentional set-shifting task, KO mice exhibited normal reversal learning and set-shifting performance. When subjected to repeated reversals, the WT mice ‘learned to reverse’, while the KO also did so but took longer to acquire this rule. Thus, it became clear that the alpha 7 nAChR is involved in learning the concept of a rule and that removing this receptor delays this ‘eureka’ moment whereby the rule becomes clear and can be followed irrespective of changing contingencies [40]. It is possible therefore, that by administering an agonist at the alpha 7 nAChR might improve this reward-related learning, providing a viable target for pharmacological augmentation to cognitive remediation.

2.5 Dr. Feldon: Discussant

Dr. Feldon summarized each of the talks, describing where similarities between studies and findings were observed, as well as where discrepancies existed. He also emphasized the strength of an integrated approach to investigating cognitive flexibility, combining not only genetic, behavioral and pharmacological approaches, but also intracellebellar recording in cognitive task performing animals. Dr. Feldon also noted that each of the presentations described reversal learning performance of mice during each of these manipulations and stressed that going forward a major goal should be to standardize both procedures for assessment and just as importantly, methods for analyzing and presenting results from reversal learning tasks. In particular, he recommended that in future analyses of data, the speakers could learn as much from an in-depth analysis of error types (regressive, perseverative) made as was observed from total errors.

3. Conclusion

The research described here highlighted the ability of modern researchers to assess cognitive flexibility in mice. Moreover, these studies can be performed across different testing environments – visual, olfactory, lever, and nose-poking – as well as using *in vivo* EEG recording. Combining these techniques with genetic manipulations available in mouse research offers an opportunity to examine the genetic contribution to cognitive flexibility. The effects of such genetic manipulations on basic cognitive functioning and neuronal activity may reveal more about the neurobiology underlying these behaviors than could be discovered using pharmacological techniques alone [41]. In addition, genetic animal models of disease can be created and the similarity of their behavioral profile to the disease in question can be tested. In an age where it is being recommended that pharmacological interventions be tailored to genetic background, such capabilities will prove invaluable.

Highlights

- A commentary on the application of genetic and pharmacological manipulation effects on cognitive flexibility in mice.
- Striatal, cortical, and cerebellar in vivo recording of animals performing reversal learning tasks.
- Utilizing a battery of tasks to determine the contribution of receptors to specific behavioral aspects of cognition.
- Utilizing genetic animal models of disease in order to develop treatments to be tailored to specific genotypes.

Acknowledgments

Research supported by the National Institute for Mental Health funding R21MH091571 and R01MH73991 (JWY), the National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1K22AA020303-01) (JB), the National Institute of Neurological Disorders and Stroke 1R01NS063009 (GM), the National Institutes on Drug Abuse R01DA018826 (EMP), and National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award (EMP) and the NIAAA intramural research program.

References

1. Barch DM, Carter CS, Arnsten A, Buchanan RW, Cohen JD, Geyer M, et al. Selecting paradigms from cognitive neuroscience for translation into use in clinical trials: proceedings of the third CNTRICS meeting. *Schizophr Bull.* 2009; 35:109–114. [PubMed: 19023126]
2. Buchanan RW, Freedman R, Javitt DC, Abi-Dargham A, Lieberman JA. Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. *Schizophr Bull.* 2007; 33:1120–1130. [PubMed: 17641146]
3. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *The Journal of clinical psychiatry.* 2006; 67(Suppl 9):3–8. discussion 36–42. [PubMed: 16965182]
4. Brigman JL, Graybeal C, Holmes A. Predictably irrational: assaying cognitive inflexibility in mouse models of schizophrenia. *Front Neurosci.* 2010;4. [PubMed: 20582258]
5. Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW. CNTRICS final task selection: executive control. *Schizophr Bull.* 2009; 35:115–135. [PubMed: 19011235]
6. Floresco SB, Jentsch JD. Pharmacological enhancement of memory and executive functioning in laboratory animals. *Neuropsychopharmacology.* 2011; 36:227–250. [PubMed: 20844477]
7. Floresco SB, Geyer MA, Gold LH, Grace AA. Developing predictive animal models and establishing a preclinical trials network for assessing treatment effects on cognition in schizophrenia. *Schizophr Bull.* 2005; 31:888–894. [PubMed: 16079387]
8. Young JW, Light GA, Marston HM, Sharp R, Geyer MA. The 5-choice continuous performance test: evidence for a translational test of vigilance for mice. *PLoS One.* 2009; 4:e4227. [PubMed: 19156216]
9. Young JW, Powell SB, Geyer MA. Mouse pharmacological models of cognitive disruption relevant to schizophrenia. *Neuropharmacology.* 2011
10. Chudasama Y, Baunez C, Robbins TW. Functional disconnection of the medial prefrontal cortex and subthalamic nucleus in attentional performance: evidence for corticostriatal interaction. *J Neurosci.* 2003; 23:5477–5485. [PubMed: 12843247]
11. Featherstone RE, McDonald RJ. Dorsal striatum and stimulus-response learning: lesions of the dorsolateral, but not dorsomedial, striatum impair acquisition of a simple discrimination task. *Behav Brain Res.* 2004; 150:15–23. [PubMed: 15033275]
12. Brigman JL, Mathur P, Harvey-White J, Izquierdo A, Saksida LM, Bussey TJ, et al. Pharmacological or Genetic Inactivation of the Serotonin Transporter Improves Reversal Learning in Mice. *Cereb Cortex.* 2010

13. Schoenbaum G, Nugent SL, Saddoris MP, Setlow B. Orbitofrontal lesions in rats impair reversal but not acquisition of go, no-go odor discriminations. *Neuroreport*. 2002; 13:885–890. [PubMed: 11997707]
14. Yin HH, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci*. 2004; 19:181–189. [PubMed: 14750976]
15. Brigman JL, Wright T, Talani G, Prasad-Mulcare S, Jinde S, Seabold GK, et al. Loss of GluN2B-containing NMDA receptors in CA1 hippocampus and cortex impairs long-term depression, reduces dendritic spine density, and disrupts learning. *J Neurosci*. 2010; 30:4590–4600. [PubMed: 20357110]
16. Partridge JG, Tang KC, Lovinger DM. Regional and postnatal heterogeneity of activity-dependent long-term changes in synaptic efficacy in the dorsal striatum. *J Neurophysiol*. 2000; 84:1422–1429. [PubMed: 10980015]
17. Yin HH, Mulcare SP, Hilario MR, Clouse E, Holloway T, Davis MI, et al. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nat Neurosci*. 2009; 12:333–341. [PubMed: 19198605]
18. Dickson PE, Rogers TD, Del Mar N, Martin LA, Heck D, Blaha CD, et al. Behavioral flexibility in a mouse model of developmental cerebellar Purkinje cell loss. *Neurobiology of learning and memory*. 2010; 94:220–228. [PubMed: 20566377]
19. Martin LA, Goldowitz D, Mittleman G. Repetitive behavior and increased activity in mice with Purkinje cell loss: a model for understanding the role of cerebellar pathology in autism. *The European journal of neuroscience*. 2010; 31:544–555. [PubMed: 20105240]
20. Martin LA, Goldowitz D, Mittleman G. The cerebellum and spatial ability: dissection of motor and cognitive components with a mouse model system. *The European journal of neuroscience*. 2003; 18:2002–2010. [PubMed: 14622233]
21. Martin LA, Goldowitz D, Mittleman G. Sustained attention in the mouse: a study of the relationship with the cerebellum. *Behav Neurosci*. 2006; 120:477–481. [PubMed: 16719710]
22. Mittleman G, Goldowitz D, Heck DH, Blaha CD. Cerebellar modulation of frontal cortex dopamine efflux in mice: relevance to autism and schizophrenia. *Synapse*. 2008; 62:544–550. [PubMed: 18435424]
23. Wonders CP, Anderson SA. The origin and specification of cortical interneurons. *Nature Reviews Neuroscience*. 2006; 7:687–696.
24. Campbell DB, D'Oronzio R, Garbett K, Ebert PJ, Mirnics K, Levitt P, et al. Disruption of cerebral cortex MET signaling in autism spectrum disorder. *Ann Neurol*. 2007; 62:243–250. [PubMed: 17696172]
25. Powell EM, Campbell DB, Stanwood GD, C D, Noebels JL, Levitt P. Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. *Journal of Neuroscience*. 2003; 23:622–631. [PubMed: 12533622]
26. Bissonette GB, Bae MH, Suresh T, Jaffe DE, Powell EM. Astrocyte-mediated hepatocyte growth factor/scatter factor supplementation restores GABAergic interneurons and corrects reversal learning deficits in mice. *J Neurosci*. 2010; 30:2918–2923. [PubMed: 20181589]
27. Schapira AH, Jenner P. Etiology and pathogenesis of Parkinson's disease. *Mov Disord*. 2011; 26:1049–1055. [PubMed: 21626550]
28. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2011; 10:83–98. [PubMed: 21163446]
29. Levitt JJ, Bobrow L, Lucia D, Srinivasan P. A selective review of volumetric and morphometric imaging in schizophrenia. *Curr Top Behav Neurosci*. 2010; 4:243–281. [PubMed: 21312403]
30. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 2007; 62:756–764. [PubMed: 17300757]
31. Waltz JA, Frank MJ, Wiecki TV, Gold JM. Altered probabilistic learning and response biases in schizophrenia: behavioral evidence and neurocomputational modeling. *Neuropsychology*. 2011; 25:86–97. [PubMed: 21090899]

32. Hoyle E, Genn RF, Fernandes C, Stolerman IP. Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. *Psychopharmacology (Berl)*. 2006; 189:211–223. [PubMed: 17019565]
33. Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, et al. Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. *Eur Neuropsychopharmacol*. 2007; 17:145–155. [PubMed: 16650968]
34. Keller JJ, Keller AB, Bowers BJ, Wehner JM. Performance of alpha7 nicotinic receptor null mutants is impaired in appetitive learning measured in a signaled nose poke task. *Behav Brain Res*. 2005; 162:143–152. [PubMed: 15922075]
35. Levin ED, Petro A, Rezvani AH, Pollard N, Christopher NC, Strauss M, et al. Nicotinic alpha7- or beta2-containing receptor knockout: effects on radial-arm maze learning and long-term nicotine consumption in mice. *Behav Brain Res*. 2009; 196:207–213. [PubMed: 18831991]
36. Young JW, Finlayson K, Spratt C, Marston HM, Crawford N, Kelly JS, et al. Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. *Neuropsychopharmacology*. 2004; 29:891–900. [PubMed: 14970827]
37. Young JW, Powell SB, Geyer MA, Jeste DV, Risbrough VB. The mouse attentional set-shifting task: A method for assaying successful cognitive aging? *Cognitive, Affective & Behavioral Neuroscience*. 2010; 10:243–251.
38. Eagle DM, Humby T, Dunnett SB, Robbins TW. Effects of regional striatal lesions on motor, motivational, and executive aspects of progressive-ratio performance in rats. *Behav Neurosci*. 1999; 113:718–731. [PubMed: 10495080]
39. Young JW, Geyer MA. Action of Modafinil-Increased Motivation Via the Dopamine Transporter Inhibition and D1 Receptors? *Biol Psychiatry*. 2010; 67:784–787. [PubMed: 20132929]
40. Young JW, Meves JM, Tarantino IS, Caldwell S, Geyer MA. Delayed procedural learning in alpha7-nicotinic acetylcholine receptor knockout mice. *Genes Brain Behav*. 2011
41. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol*. 2006; 2:267–290. [PubMed: 17716071]