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The involvement of Type II Neuregulin-1 in rat visuospatial learning and memory

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Abstract

The cognitive deficits observed in schizophrenia are considered a core feature of the disease. Neuregulin-1 is a risk gene for schizophrenia that is involved in many neurodevelopmental and synaptic plasticity-related processes relevant to schizophrenia. Here, we have utilized a rat model (*Nrg1^{Tn}*), which is hypomorphic for the neuregulin-1 (*Nrg1*) gene, to test whether reduced Type II NRG1 in the rat brain leads to cognitive deficits relevant to schizophrenia. Wild-type and homozygous *Nrg1^{Tn}* male rats were tested in memory tasks that evaluated spatial memory (Morris water maze) and visuospatial working and reference memory (Can test). *Nrg1^{Tn}* rats were not impaired on the Morris water maze, but did show a deficit in the appetitive visuospatial discrimination test. *Nrg1^{Tn}* rats committed more reference and working memory errors in this test. These results indicate that decreased Type II NRG1 in the brain may lead to deficits in visuospatial learning and memory.

Introduction

Schizophrenia is a chronic, debilitating neuropsychiatric disorder, consisting of positive (hallucinations and delusions), negative (anhedonia and social withdrawal) and cognitive symptoms, that afflicts approximately 1% of the population [4]. Historically, the positive and negative symptoms have been considered the key facets of the illness. Recently however, it has become clear that the cognitive deficits suffered by individuals with schizophrenia (such as working memory, attention and problem solving) are a core feature and account for much of the morbidity associated with the disorder [2,15,18]. However, the etiology of the cognitive symptoms remains unclear.

Numerous genetic studies, including genome-wide association studies, have identified several potential schizophrenia susceptibility genes [6]. One gene that has been repeatedly

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associated with schizophrenia is the neuregulin-1 gene (*NRG1*) [28,29]. *NRG1* codes for a family of growth factors (NRG1 types I - VI) which are involved in neuronal migration, axon guidance, glial development, myelination, and synapse formation during development [5,23]. NRG1 is also involved in synaptic plasticity via involvement with both glutamatergic and GABAergic neurotransmission [23]. Recently, several studies investigating the genetics of cognitive phenotypes in schizophrenia found a highly significant association of *NRG1* polymorphisms with several of the cognitive features of the illness [11,12], suggesting that a better understanding of the role of NRG1 in cognition is needed.

Mouse models of decreased NRG1 function have yielded evidence that NRG1 is involved in various aspects of behavioral regulation, including cognition. Stefansson et al. [29] showed that mice heterozygous for the NRG1 transmembrane (TM) domain or for the NRG1 receptor, ErbB4, were hyperactive and had impaired prepulse inhibition (PPI) compared to wild-type (WT) mice, though both of these effects were more robust in heterozygous *Nrg1* TM domain knock-out (KO) mice than in *erbB4* KO mice. This hyperactive phenotype in heterozygous *Nrg1* TM domain KO mice has been confirmed [17], in addition to several other behavioral impairments including altered social behaviors [24,25]. However, recent evidence suggests that PPI deficits found in NRG1 mutant animals are highly protocol and location specific [16]. Furthermore, Karl and colleagues have reported that heterozygous *Nrg1* TM domain KO mice also show subtle cognitive alterations in non-spatial memory [7].

Together, the above studies in mice confirm that NRG1 may be involved in schizophrenia-related behaviors. However, the region of the gene deleted in the mouse model mentioned above, i.e. the transmembrane domain, is in the 3' region of the gene, while the majority of schizophrenia gene association studies have found polymorphisms associated with the 5' region of *NRG1*, which codes for Types II and IV NRG1 [14]. In our studies, we utilize a line of mutant rats (*Nrg1^{Tn}*) in which a transposon [20] disrupts the 5' region of the *Nrg1* gene just downstream of the coding sequence for the Type II NRG1 isoform. Using this unique preparation, we have found that *Nrg1^{Tn}* rats exhibit decreased Type II NRG1 mRNA and protein as well as alterations in neuroendocrine and behavioral responses to stress [30,31]. In addition, we previously found that male *Nrg1^{Tn}* rats fail to habituate to an open field despite normal overall levels of locomotor activity and tend to demonstrate increased anxiety-like behavior on the elevated plus maze [31,32]. In another schizophrenia-related assay, PPI, we found that male *Nrg1^{Tn}* rats demonstrate normal PPI, while female *Nrg1^{Tn}* rats exhibited a deficit [30]. However when testing emotional memory using fear conditioning, both male and female *Nrg1^{Tn}* rats display impairment [32]. The present study used the *Nrg1^{Tn}* rats to test whether reduced Type II NRG1 in the brain leads to schizophrenia-related cognitive deficits. Specifically, we examined the performance of the *Nrg1^{Tn}* rats in two cognitive tests, the Morris water maze and an appetitive visuospatial object discrimination test, known as the Can Test [26]. We found that the *Nrg1^{Tn}* rats have deficits in reference and working memory in the visuospatial discrimination task but have no differences in learning or long-term memory in the water maze compared to WT rats.

Material and Methods

Animals

Male WT and homozygous *Nrg1^{Tn}* rats were originally obtained from the PhysGen Program in Genomic Applications (<http://pga.mcw.edu/>) at the Medical College of Wisconsin. *Nrg1* disruption was created by using the Sleeping Beauty transposon system on a Fischer 344 inbred rat strain background (F344-Nrg1^{Tn}(sb-T2/Bart3)2.183 Mcwi) [20]. The transposon inserted randomly into the first intron of the *Nrg1* gene, just downstream of the coding sequence for the Type II NRG1 isoform. (see <http://www.knockoutrat.com/> and http://rgd.mcw.edu/tools/strains/strains_view.cgi?id=2290103). All animals used in these

experiments were derived from our breeding colony at the Maryland Psychiatric Research Center. Genotyping was performed to confirm the presence or absence of the mutation. The rats were housed in a light (lights on at 06:00 hr and off at 20:00 hr) and temperature-controlled AAALAC-approved animal housing facility. With the exception of experimental water manipulations (see below, Can Test) animals were given unlimited access to rat chow (Harlan Teklad, Frederick, MD) and water. All procedures conform to guidelines for animal research established by the National Institutes of Health, and were approved by the University of Maryland School of Medicine Institutional Animal Care and Use Committee.

Can Test

Twelve adult WT male rats and 18 adult *Nrg1^{Tn}* male rats were used in this experiment. The Can Test is an appetitive task that interrogates visual and spatial working and reference memory and was adapted from our previously published protocol [22]. Animals were handled for five days prior to habituation. On habituation day 1, each animal was allowed 20 min to explore the arena: a 100 cm × 100 cm × 46 cm box with black Plexiglas walls. Animals were returned to their home cage without access to water, in order to facilitate motivation for finding the water reward during subsequent testing. On habituation day 2, 7 identical aluminum cans (13 cm tall), filled with cement for weight, were placed in the arena in a fan arrangement so as to be equidistant from a starting point (Figure 1). The cans were upside-down, in order to provide a dish to hold a bolus of water (0.3 ml). Water was placed in each of the cans and each animal explored the arena for 20 min. On the third habituation day, the arena was set up as above, except only 3 of 7 cans were baited with 0.3 ml of water, and each rat was allowed to explore the arena until it found all three water rewards, or until 10 min had elapsed. After finding the third reward, the animals were removed to a holding area while water was placed in 3 different cans. Each animal was then reintroduced to the arena and allowed to explore until it found the 3 rewards again, or until 10 min had elapsed. Following habituation, animals were returned to their home cages and left undisturbed for 2 days. Water was again removed from the rat's cages the day before testing began (see below). After each habituation and testing session, rats were given access to water for a 45-min period.

Visuospatial discrimination test

Seven cans were arranged in the apparatus as above with the exception that 1 can was covered in white tape with three black horizontal lines (Figure 1). Each rat was given 10 trials per day over a 3-day period to learn that the water reward was always to be found in the unique can, the location of which remained stationary. Thus it was possible for animals to use either spatial or visual cues (or a combination) to learn the location of the water. Following consumption of the reward, each animal was removed to a holding area while the can was re-baited. A visit to a can was recorded when an animal stood on its hind paws and looked for the water reward in the dish created by the base of the can. A correct trial was recorded when the animal visited the rewarded can first. A reference memory error was scored the first time each rat visited a non-rewarded can prior to visiting the rewarded can during a given trial. A working memory error was scored each time an animal revisited the *same* non-rewarded can during a given trial. Average correct trials, reference memory errors, and working memory errors were calculated on a per animal basis for each day of training.

Morris Water Maze

Morris water maze training was performed as described in our previously published protocol [22] with 10 adult male WT and 10 adult male *Nrg1^{Tn}* rats. Briefly, rats were habituated to the water maze, a circular tank 1.8 m in diameter with a depth of 0.9 m (0.6 m water depth), for 2 days. The first day, animals swam for 2 min with no escape platform. The second day, each rat was given 4 trials with an escape platform hidden 2 cm beneath the surface of

water, which was made opaque by the addition of non-toxic white tempura paint. Training began the next day and continued for a total of 3 days. Training consisted of 4 trials per day, with a 15 min inter-trial interval. If the rats did not reach the platform within 2 min, they were gently guided to it by an experimenter, and left on the platform for 15 sec before being placed back in a holding cage. After the final day of training, rats were returned to the colony room and not handled for 6 consecutive days, with the exception of normal animal husbandry. On the seventh day, rats were returned to the water maze for a retention test consisting of 2 trials conducted in the same manner as training.

Statistical Methods

Statistical analyses were conducted using Graph Pad Prism (version 4). Repeated measures analysis of variance (ANOVA) was used to analyze genotype differences across training days in both experiments. Grubbs test for outliers was used to determine if there were any outlying data points. A p value of 0.05 or less was considered significant. Data are presented as mean $\pm$ SEM.

Results

Can Test

Performance on the visuospatial discrimination task improved over the 3-day testing period, regardless of genotype (Figure 2). A 2×3 repeated measures ANOVA (Genotype (WT vs *Nrg1^{Tn}*) $\times$ Training Day (1-3)) revealed a main effect of day on all measures, indicating increased correct trials ($F_{2,56} = 12.18$; $p < 0.001$; Figure 2A) and decreased reference errors ($F_{2,56} = 22.31$; $p < 0.001$; Figure 2B) and working errors ($F_{2,56} = 16.08$; $p < 0.001$; Figure 2C) across training days. A main effect of genotype was not identified on correct trials, though *Nrg1^{Tn}* rats tended to achieve fewer correct trials during the three days of training ($F_{1,28} = 3.36$; $p = 0.08$; Figure 2A) compared to WT animals. However, a significant main effect of genotype was identified for both reference memory and working memory errors. ANOVA revealed that *Nrg1^{Tn}* animals made significantly more reference memory errors ($F_{1,28} = 5.79$; $p = 0.02$; Figure 2B) and working memory errors ($F_{1,28} = 4.10$; $p = 0.05$; Figure 2C) than WT rats in this test. An interaction between training day and genotype was not identified in any measure. Further tests of simple visual and simple spatial discrimination were not conducted due to the inadequate performance of both genotypes after the completion of the visuospatial discrimination task.

Morris Water Maze

One animal from each group was determined to be a statistical outlier by Grubbs test and was excluded from further analysis. No difference in the ability to locate the hidden platform was identified between genotypes during habituation (WT: 92.5 ± 11.7 s, *Nrg1^{Tn}*: 106.3 ± 5.0 s). A 2×3 (Genotype (WT vs *Nrg1^{Tn}*) $\times$ Training Day (1-3)) repeated measures ANOVA was used to determine the effect of both genotype and day of training on the latency to find the platform. A main effect of day ($F_{2,32} = 11.33$; $p < 0.001$) revealed that all animals decreased latency to find the platform over the 3 days of training (Figure 3) indicating that they were able to learn the location of the hidden platform. No main effect of genotype was identified on performance during the 3 days of training ($F_{1,16} = 0.23$; $p = 0.64$; Figure 3). To determine the extent to which rats of each genotype retained the memory of the platform location, a 2×2 (Genotype (WT vs *Nrg1^{Tn}*) $\times$ Time (Day 3 vs. Retention)) ANOVA was performed. This analysis revealed a significant main effect of Day ($F_{1,16} = 5.15$; $p = 0.04$; Figure 3) but the effect of genotype did not reach statistical significance ($F_{1,16} = 3.32$; $p = 0.09$; Figure 3).

Discussion

The cognitive impairments in schizophrenia include deficits in spatial, long-term and working memory, executive function and attention [1,13,19]. These cognitive impairments have been shown to be strong predictors of overall outcome in patients with schizophrenia [12] and are core features of the illness [2,8,18]. Recent studies by Greenwood and colleagues [11,12] have shown a strong association between schizophrenia and its cognitive endophenotypes and *NRG1* single nucleotide polymorphisms. Spatial processing, verbal learning and sensorimotor deficits all appear to be profoundly influenced by *NRG1* genotypes. In order to gain insight into possible genetic origins of certain cognitive deficits in schizophrenia, we used rats hypomorphic for Type II NRG1 [31], which is encoded by the 5' region of the gene that has been consistently associated with schizophrenia [28,29].

Nrg1^{Tn} rats exhibited an overall deficit in a visuospatial discrimination test. This impairment is reflected by increased reference and working memory errors, as well as a trend toward fewer correct trials compared to WT rats during training. It is unlikely that this impairment is due to altered visual acuity in the *Nrg1^{Tn}* rats, as they continued to improve their performance across training days as opposed to remaining constant as would be expected in visually impaired rats and they were able to perform the Morris water maze task as well as WT rats. However, the present studies do not rule out the possibility that these impairments on the visuospatial discrimination task are due to altered appetitive motivation. There was no effect of genotype on spatial learning or long-term memory of the platform location in the Morris Water Maze. However, use of additional training days may have revealed a significant effect of genotype such that the *Nrg1^{Tn}* rats might fail to further decrease latency to find the platform.

Previous work has shown that genetic disruption of 3' regions of the *Nrg1* gene also led to subtle changes in cognitive performance. Duffy and colleagues reported that heterozygous *Nrg1* TM domain KO mice had no deficit in hippocampal-dependent memory tasks such as passive avoidance, Y-maze or spatial learning in the radial arm maze [7]. These investigators did find a minor deficit in object recognition memory, however. Other studies revealed that genetic disruption of this same region of the *Nrg1* gene also failed to alter spatial memory in the Barnes maze [24]. Therefore, our results showing an absence of a spatial memory deficit in the Morris water maze are consistent with these previous reports and support the conclusion that NRG1-dependent mechanisms are probably not involved in hippocampal-dependent simple spatial memory, which is consistent with what has been shown for patients with schizophrenia [11]. However, the deficit in both working and reference memory revealed by the Can test implies that the genetic disruption of Type II NRG1 may have a significant impact on brain regions involved in processing visuospatial information. In fact, this is also implied by findings from emotional learning and memory tasks, such as fear conditioning and memory which involve the amygdala-hippocampal-prefrontal cortex circuit [see 21 for review]. We and others have shown that disruption of either the *Nrg1* gene [9,32] or the NRG1 receptor gene, *ErbB4* [27], induce significant deficits in fear learning and recall. Moreover, an impaired ability to process complex sensory information is consistent with our earlier findings in *Nrg1^{Tn}* males of compromised environmental habituation and performance on the elevated plus maze [31,32], though sensorimotor function as measured by PPI remained intact [30]. Therefore the disruption of Type II NRG1 may have more global effects on processing and integrating environmental information than originally proposed. Interestingly, the *Nrg1^{Tn}* rats display many sex-specific behaviors and additional studies on cognitive function in female *Nrg1^{Tn}* are needed.

In the current studies, the Can Test was employed because of its ability to assess both working and reference memory with discrete visual and spatial cues. Furthermore, the use of

a less aversive task precludes the potential confounding effects of stress on the outcomes in the *Nrg1^{Tn}* rats, which are known to be sensitive to stressful situations [31]. While the precise brain regions underlying the ability to perform the Can Test have not been fully elucidated, the known role of the prefrontal cortex in working memory [10] and the dorsal striatum's role in discrimination learning [3], may indicate that the *Nrg1^{Tn}* rats may have a functional defect in these brain regions rather than the hippocampus. Given that others have found deficits in non-spatial hippocampal-mediated behaviors, such as contextual fear conditioning, it is possible that NRG1 influences some hippocampal functions and not others in a task-dependent manner [9]. Thus, future studies examining the role of NRG1 in the molecular correlates of learning and memory, such as long-term potentiation and glutamatergic receptor expression in brain regions beyond the hippocampus are warranted.

Conclusion

The present studies indicate that genetic disruption of Type II NRG, resulting in reduced NRG1 protein expression in the rat brain, may lead to cognitive deficits. While simple spatial learning appears to be intact, *Nrg1^{Tn}* rats make more reference and working memory errors in an appetitive task that encompasses both visuospatial learning and discrimination. These deficits may be analogous to some aspects of memory that are disturbed in patients with schizophrenia and suggest that decreased NRG1 function may play a discrete role in cognitive impairments of schizophrenia and potentially, other psychiatric disorders characterized by cognitive decline.

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References

- [1]. Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am. J. Psychiatry.* 1999; 156:1358–1366. [PubMed: 10484945]
- [2]. Bora E, Yucel M, Pantelis C. Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond. *Schizophr. Bull.* 2010; 36:36–42. [PubMed: 19776206]
- [3]. Broadbent NJ, Squire LR, Clark RE. Rats depend on habit memory for discrimination learning and retention. *Learn. Mem.* 2007; 14:145–151. [PubMed: 17351137]
- [4]. Carpenter WT Jr, Buchanan RW. Schizophrenia. *N. Engl. J. Med.* 1994; 330:681–690. [PubMed: 8107719]
- [5]. Corfas G, Roy K, Buxbaum JD. Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. *Nat. Neurosci.* 2004; 7:575–580. [PubMed: 15162166]
- [6]. Duan J, Sanders AR, Gejman PV. Genome-wide approaches to schizophrenia. *Brain. Res. Bull.* 2010; 83:93–102. [PubMed: 20433910]
- [7]. Duffy L, Cappas E, Lai D, Boucher AA, Karl T. Cognition in transmembrane domain neuregulin 1 mutant mice. *Neuroscience.* 2010; 170:800–807. [PubMed: 20678553]
- [8]. Elvevag B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. *Crit. Rev. Neurobiol.* 2000; 14:1–21. [PubMed: 11253953]
- [9]. Ehrlichman RS, Luminais SN, White SL, Rudnick ND, Ma N, Dow HC, et al. Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. *Brain Res.* 2009; 1294:116–27. [PubMed: 19643092]
- [10]. Goldman-Rakic PS. Cellular basis of working memory. *Neuron.* 1995; 14:477–485. [PubMed: 7695894]

- [11]. Greenwood TA, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am. J. Psychiatry.* 2011; 168:930–46. [PubMed: 21498463]
- [12]. Greenwood TA, Light GA, Swerdlow NR, Radant AD, Braff DL. Association analysis of 94 candidate genes and schizophrenia-related endophenotypes. *PLoS One.* 2012; 7:e29630. [PubMed: 22253750]
- [13]. Hanlon FM, Weisend MP, Hamilton DA, Jones AP, Thoma RJ, Huang M, et al. Impairment on the hippocampal-dependent virtual Morris water task in schizophrenia. *Schizophr. Res.* 2006; 87:67–80. [PubMed: 16844347]
- [14]. Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. *Biol. Psychiatry.* 2006; 60:132–140. [PubMed: 16442083]
- [15]. Harvey PD, Howanitz E, Parrella M, White L, Davidson M, Mohs RC, et al. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. *Am. J. Psychiatry.* 1998; 155:1080–1086. [PubMed: 9699697]
- [16]. Karl T, Burne TH, Van den Buuse M. Do transmembrane domain neuregulin 1 mutant mice exhibit a reliable sensorimotor gating deficit? *Behav Brain Res.* 2011; 223:336–341. [PubMed: 21605597]
- [17]. Karl T, Duffy L, Scimone A, Harvey RP, Schofield PR. Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: implications for understanding schizophrenia. *Genes. Brain. Behav.* 2007; 6:677–687. [PubMed: 17309661]
- [18]. Keefe RS, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophr. Bull.* 2007; 33:912–920. [PubMed: 17567627]
- [19]. Kuperberg G, Heckers S. Schizophrenia and cognitive function. *Curr. Opin. Neurobiol.* 2000; 10:205–210. [PubMed: 10753790]
- [20]. Lu B, Geurts AM, Poirier C, Petit DC, Harrison W, Overbeek PA, et al. Generation of rat mutants using a coat color-tagged Sleeping Beauty transposon system. *Mamm. Genome.* 2007; 18:338–346. [PubMed: 17557177]
- [21]. Maren S, Quirk GJ. Neuronal signaling of fear memory. *Nat. Rev. Neurosci.* 2004; 5:844–852. [PubMed: 15496862]
- [22]. Markham JA, Taylor AR, Taylor SB, Bell DB, Koenig JI. Characterization of the cognitive impairments induced by prenatal exposure to stress in the rat. *Front. Behav. Neurosci.* 2010; 4:173. [PubMed: 21151368]
- [23]. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat. Rev. Neurosci.* 2008; 9:437–452. [PubMed: 18478032]
- [24]. O'Tuathaigh CM, Babovic D, O'Sullivan GJ, Clifford JJ, Tighe O, Croke DT, et al. Phenotypic characterization of spatial cognition and social behavior in mice with 'knockout' of the schizophrenia risk gene neuregulin 1. *Neuroscience.* 2007; 147:18–27. [PubMed: 17512671]
- [25]. O'Tuathaigh CM, O'Connor AM, O'Sullivan GJ, Lai D, Harvey R, Croke DT, et al. Disruption to social dyadic interactions but not emotional/anxiety-related behaviour in mice with heterozygous 'knockout' of the schizophrenia risk gene neuregulin-1. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2008; 32:462–466. [PubMed: 17980471]
- [26]. Popovic M, Biessels GJ, Isaacson RL, Gispen WH. Learning and memory in streptozotocin-induced diabetic rats in a novel spatial/object discrimination task. *Behav Brain Res.* 2001; 122:201–207. [PubMed: 11334650]
- [27]. Shamir A, Kwon OB, Karavanova I, Vullhorst D, Leiva-Salcedo E, Janssen MJ, Buonanno A. The importance of the NRG-1/ErbB4 pathway for synaptic plasticity and behaviors associated with psychiatric disorders. *J Neurosci.* 2012; 32:2988–2997. [PubMed: 22378872]
- [28]. Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E, et al. Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. *Am. J. Hum. Genet.* 2003; 72:83–87. [PubMed: 12478479]
- [29]. Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, et al. Neuregulin 1 and susceptibility to schizophrenia. *Am. J. Hum. Genet.* 2002; 71:877–892. [PubMed: 12145742]

- [30]. Taylor SB, Markham JA, Taylor AR, Kanaskie BZ, Koenig JI. Sex-specific neuroendocrine and behavioral phenotypes in hypomorphic Type II Neuregulin 1 rats. *Behav. Brain. Res.* 2011; 224:223–232. [PubMed: 21620900]
- [31]. Taylor SB, Taylor AR, Markham JA, Geurts AM, Kanaskie BZ, Koenig JI. Disruption of the neuregulin 1 gene in the rat alters HPA axis activity and behavioral responses to environmental stimuli. *Physiol. Behav.* 2011; 104:205–214. [PubMed: 21092742]
- [32]. Taylor SB, Taylor AR, Koenig JI. The interaction of disrupted Type II Neuregulin 1 and chronic adolescent stress on adult anxiety- and fear-related behaviors. *Neuroscience*. 2012 (in press, <http://dx.doi.org/10.1016/j.neuroscience.2012.09.045>).

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Research Highlights

- Type II Neuregulin 1 is involved in visuospatial working and reference memory
- *Nrg1^{Tn}* rats were impaired in a visuospatial discrimination task
- *Nrg1^{Tn}* rats were not impaired on the Morris water maze

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Figure 1. The Can Test Apparatus

Rats were trained to locate the water reward in the visually distinct can which remained in the same spatial location. After extensive habituation, 10 trials a day for 3 days were conducted. A correct trial was recorded when the animal visited the rewarded can first. A reference memory error was scored the first time each rat visited a non-rewarded can prior to visiting the rewarded can during a given trial. A working memory error was scored each time an animal revisited the *same* non-rewarded can during a given trial.

Figure 2. Visuospatial Memory

Nrg1^{Tn} rats tended to achieve fewer correct trials ($p = 0.08$; Panel A) and committed significantly more reference memory (* $p = 0.02$; Panel B) and working memory errors (* $p = 0.05$; Panel C) than WT rats in the Can Test. Data shown are mean trials/errors $\pm$ SEM on each testing day as well as collapsed over all days of testing (average).

Figure 3. Spatial Memory

While both genotypes exhibited decreased latency to find the platform across training days, WT and *Nrg1*^{Tn} rats did not differ in their time to find the platform in the Morris water maze. Data shown are mean latency to find escape platform (s) $\pm$ SEM.