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Neuregulin 1: a prime candidate for research into gene-environment interactions in schizophrenia? Insights from genetic rodent models

Tim Karl[1,2,3]*

[1] Neuroscience Research Australia, Randwick, NSW, Australia
[2] Schizophrenia Research Institute, Darlinghurst, NSW, Australia
[3] School of Medical Sciences, University of New South Wales, NSW, Australia

Edited by:
Jonathon C. Arnold, University of Sydney, Australia

Reviewed by:
Akshay Anand, Post Graduate Institute of Medical Education and Research, India
Sara B. Taylor, Arizona State University, USA

***Correspondence:**
Tim Karl, Neuroscience Research Australia, Barker St., Randwick, NSW 2031, Australia
e-mail: t.karl@neura.edu.au

Schizophrenia is a multi-factorial disease characterized by a high heritability and environmental risk factors. In recent years, an increasing number of researchers worldwide have started investigating the "two-hit hypothesis" of schizophrenia predicting that genetic and environmental risk factors (GxE) interactively cause the development of the disorder. This work is starting to produce valuable new animal models and reveal novel insights into the pathophysiology of schizophrenia. This mini review will focus on recent advancements in the field made by challenging mutant and transgenic rodent models for the schizophrenia candidate gene *neuregulin 1* (*NRG1*) with particular environmental factors. It will outline results obtained from mouse and rat models for various Nrg1 isoforms/isoform types (e.g., transmembrane domain *Nrg1*, Type II *Nrg1*), which have been exposed to different forms of stress (acute *versus* chronic, restraint *versus* social) and housing conditions (standard laboratory *versus* minimally enriched housing). These studies suggest *Nrg1* as a prime candidate for GxE interactions in schizophrenia rodent models and that the use of rodent models will enable a better understanding of GxE interactions and the underlying mechanisms.

Keywords: schizophrenia, *neuregulin 1*, gene-environment interactions, mouse, rat, stress, enrichment, housing

INTRODUCTION

The two-hit hypothesis of schizophrenia states that a combination of genetic and environmental risk factors causes the development of schizophrenia (Bayer et al., 1999; Rapoport et al., 2005; Caspi and Moffitt, 2006). Indeed, twin studies show that nature and nuture are both important in the development of schizophrenia (i.e., concordance rate of monozygotic twins is 50%) (Tsuang et al., 2001) and combined actions of multiple genes of small effect (Owen et al., 2005) and a number of environmental risk factors (McGrath et al., 2004) is likely (Mackay-Sim et al., 2004). Genome wide association studies suggest that it is important to consider the interplay of genes and environment to understand the aetiology of the disorder in more depth (Sanders et al., 2008). In this context, interactions of genetic and environmental risk factors (GxE) occur when an individual's genetic predispositions are expressed dependent on their environment or when environmental influences on a trait differ according to the individual's genome (Tsuang et al., 2004). According to the neurodevelopmental theory of schizophrenia genes and environment together affect brain development negatively during critical periods of neuronal development and thereby induce schizophrenia (Marenco and Weinberger, 2000).

Animal models can incorporate genetic and environmental risk factors at different stages of development, thereby more accurately mimicking the aetiology of schizophrenia, and help elucidate interactions between those factors and underlying mechanism (Burrows et al., 2011). For example, *neuregulin 1* (*NRG1*) is a genetic target for schizophrenia research (Stefansson et al., 2002; Tosato et al., 2005; Munafo et al., 2006) as it influences key neurodevelopmental processes relevant to schizophrenia (e.g., myelination and neuronal migration), and regulates receptors such as N-methyl-D-aspartic acid (NMDA) and γ-aminobutyric acid receptor A ($GABA_A$) (Mei and Xiong, 2008). It has been outlined that there might be genetic subgroups in the population that are more vulnerable to particular environmental risk factors (e.g., cannabis abuse, developmental trauma) (van Os et al., 2010) and *NRG1* might be such a genetic candidate. This review will summarize preclinical data to assess if *Nrg1* might be mediating an increased risk to environmental factors with relevance to schizophrenia (i.e., stress and cannabis) and experimental animal research (i.e., laboratory housing conditions).

Nrg1 X LABORATORY HOUSING

Environmental enrichment (EE) has a significant impact on animal models of neurodegenerative diseases (van Dellen et al., 2000; Spires and Hannan, 2005). Furthermore, enriched cage structures can modify or even rescue knockout-specific abnormalities of genetic mouse models (Rampon et al., 2000; van Dellen et al., 2000). Thus, the behavioral effects of minimally enriched housing (ME) compared to standard laboratory housing were determined in male transmembrane domain *Nrg1* mutant and wild type-like control mice (Karl et al., 2007). This mutant mouse model

has been shown to have compelling construct, face, and predictive validity for schizophrenia (Stefansson et al., 2002; Walss-Bass et al., 2006; Karl et al., 2007, 2011; van den Buuse et al., 2009; Duffy et al., 2010; Chesworth et al., 2012a). Mice were tested at the age of 3–4 and 4–6 months, as the age of patients has a significant impact on the aetiology of schizophrenia (Thompson et al., 2004). Effects of *Nrg1* mutation on locomotion, exploration and anxiety-like behaviors were age-dependent and interacted with the housing condition males were raised in. *Nrg1* mutants kept in ME developed hyper-exploration in the light-dark test and reduced anxiety-like behavior in the open field test at 3–4 months of age whereas *Nrg1* males kept in standard housing displayed these phenotypes only at the age of 4–6 months. Importantly, well-known explorative and anxiolytic-like properties of cage enrichment (Chapillon et al., 1999; Roy et al., 2001; Benaroya-Milshtein et al., 2004) were more pronounced in *Nrg1* mutant mice than control mice suggesting that mutant transmembrane domain *Nrg1* increased the behavioral sensitivity to ME.

Nrg1 mutant mice are characterized by hypo-phosphorylation of the NR2B subunit (Bjarnadottir et al., 2007). This is in line with Nrg1's up-regulation of NMDA subunits expression (Ozaki et al., 1997; Stefansson et al., 2004) and the stimulation of Y1472 phosphorylation on the NR2B subunit of NMDA receptors. As NMDA antagonists induce increased locomotor activity (Wong and Van Tol, 2003; Javitt and Coyle, 2004) and as mouse models for NMDA receptors suggest an involvement of the glutamatergic system in rodent hyperactivity (Smith et al., 1998; Dulawa et al., 1999; Mohn et al., 1999; Zhuang et al., 2001), hypo-phosphorylated NR2 subunits may be responsible for the observed hyperactivity. Nonetheless, it should be noted that Hahn and colleagues found that Nrg1 stimulation suppressed NMDA receptor activation in the human prefrontal cortex (Hahn et al., 2006). EE does not impact the behavioral susceptibility to NMDA receptor antagonists, but mRNA expression of specific NMDA receptor subunits was decreased in mice kept in enriched housing (Grilli et al., 2009). This suggests that combined effects of mutant *Nrg1* and ME (i.e., additive GxE) might be responsible for the earlier onset of hyperactivity.

Importantly, hypo-phosphorylation of NR2B subunits in *Nrg1* mutant mice might also support the activation of dopaminergic pathways (Duncan et al., 1999; Kapur and Seeman, 2002) and thereby contribute to their anxiolytic-like and hyper-locomotive phenotype. Indeed, dopamine transporter deficient mice are not only characterized by hyperactivity but also decreased anxiety-like-like responses (Carpenter et al., 2012). In this context, it is important to note that exposure to enriched housing affects the dopaminergic system as enrichment increased the susceptibility of rats to the behavioral and neurochemical effects of amphetamine (Bowling et al., 1993) although another study found reduced dopamine receptor 1 function as a consequence of enriched housing (Del Arco et al., 2007). Further research is needed to pinpoint the mechanisms underlying the differential potency of ME in *Nrg1* mutant and control mice but an involvement of dopaminergic and glutamatergic circuits is likely.

Other genetic mouse models of schizophrenia have been reported to benefit from more complex enriched housing environments (McOmish et al., 2008). Thus, the disease-related phenotype-strengthening effects of ME in *Nrg1* mice are interesting and opposite to reports by others (van Dellen et al., 2000; Olsson and Dahlborn, 2002; Spires and Hannan, 2005). *Nrg1/NRG1* has been described as being critical for how an organism responds and adapts to the environment (Stefansson et al., 2004). Thus, the biological function of *Nrg1* may dictate this disease phenotype-strengthening response to an enriched housing environment, which is different to the effects normally described for EE (i.e., reversing disease phenotypes).

Nrg1 X STRESS

Stressful life events and changes in HPA axis function are associated with and precipitate the onset of psychiatric disorders (Koenig et al., 2002; Walker et al., 2008). Furthermore, stress plays a role in the development [e.g., behavioral sensitization: (van Os et al., 2010)] and severity of psychotic symptoms (Corcoran et al., 2003) and triggers relapse in schizophrenia patients (Hultman et al., 1997). There appears to be a genetic component to stress vulnerability in schizophrenia: schizophrenia patients are more sensitive to stress (van Winkel et al., 2008), handle negative life events more poorly (Horan et al., 2005), and show impaired cortisol and HPA axis activity in stressful situations (van Venrooij et al., 2010). Importantly, a *NRG1* polymorphism interacts with psychosocial stress thereby affecting reactivity to expressed emotions in schizophrenia patients (Keri et al., 2009) and *NRG1* also interacts with job strain thereby increasing the risk of heart disease (Hintsanen et al., 2007). Furthermore, Nrg1 is expressed in brain regions controlling stress reactivity (Chen, 2007). Thus, a number of research teams have investigated the response of *Nrg1* rodent models to models.

A first study investigated the behavioral and endocrine response of male transmembrane domain *Nrg1* mutant mice to acute restraint stress before and after the onset of the age-dependent hyper-locomotive phenotype (Chesworth et al., 2012b). The suppressive effect of stress on locomotion was evident in all mice regardless of genotype or age. Surprisingly, older *Nrg1* mutants appeared insensitive to anxiety-like-related stress effects in the open field (i.e., center locomotion). All mice displayed robust stress-induced increases in serum corticosterone, although the response was more pronounced in young *Nrg1* mutants compared to WT mice. The study suggested that there is no pronounced effect of mutant transmembrane domain *Nrg1* on the endocrine and behavioral effects of acute restraint stress. Nevertheless, Nrg1 modified corticosterone release in young *Nrg1* mutants and the anxiety-like response of hyper-locomotive older *Nrg1* mice, confirming that the gene plays a role in how an organism responds to environmental manipulations. The phenomenon of a disconnected behavioral and endocrine stress response of older *Nrg1* mice (i.e., no stress-induced anxiety-like response in open field but increased glucocorticoid levels) is consistent with other mouse models (Laarakker et al., 2011; Trainor et al., 2011). Future research should address the impact of chronic stress on *Nrg1* mutant mice and consider additional aspects of HPA functions.

Importantly, recent rat research suggests that *Nrg1* might be involved in stress reactivity downstream from the release of glucocorticoids (Taylor et al., 2011b). More specifically, a rat model for

disrupted Type II *Nrg1* expression was characterized by increased baseline corticosterone levels and improved recovery of corticosterone levels post-acute restraint stress. Importantly, in control rats, Type II *Nrg1* was expressed in the neurocircuitry involved in regulating HPA responses to environmental stimuli. The authors concluded that disruptions to Type II *Nrg1* expression mediated an increased basal HPA axis activity. Elevated levels of glucocorticoid (but not mineralocorticoid) receptors in the hippocampus and pituitary glands of *Nrg1* mutant rats under baseline conditions could then result in a more pronounced negative feedback loop thereby increasing the inhibition of HPA axis activity following acute restraint stress. Interestingly, shifts in the balance of glucocorticoid and mineralocorticoid receptor levels in humans can create a vulnerability to psychiatric disease, especially among genetically predisposed individuals (De Kloet et al., 1998; Zhe et al., 2008). The change in the endocrine stress response of mutant Type II rats was accompanied by altered habituation to an open field environment across test days (Taylor et al., 2011b). Nrg1 is necessary for the establishment of excitatory synapses in GABAergic interneurons and for the development of a balanced excitatory/inhibitory tone in the brain (Ting et al., 2011). As GABAergic mechanisms play a role in controlling HPA axis function (Herman et al., 2004), Nrg1-induced changes to the GABAergic system might present a potential mechanism for the observations in Type II *Nrg1* mutant rats.

In a follow-up study it was found that some of the behavioral and brain characteristics of *Nrg1* hypomorphic rats were highly sex-specific (Taylor et al., 2011a). It should be noted that sex-specificity in rodent models for *Nrg1* is a common phenomenon (O'Tuathaigh et al., 2006; Duffy et al., 2010; Chesworth et al., 2012a) and is in line with gender effects reported for schizophrenia patients (Canuso and Pandina, 2007). Inconsistencies between the stress response of the two investigated *Nrg1* rodent models are most likely due to (1) species differences (Asan et al., 2005), (2) differences in the restraint stress models used (rats were habituated to the general stress procedure whereas mice were naïve), and (3) the particular characteristics of the *Nrg1* mutation [(Harrison and Law, 2006; Mei and Xiong, 2008); for overview on *Nrg1* rodent models see: (Duffy et al., 2008; Karl et al., 2011)]. Adding to the complexity of potential *Nrg1*-stress interactions is a study reporting that Type III *Nrg1* mutant mice display a blunted increase in corticosterone release after mild acute stress (Chen, 2007).

Adolescence is a period of heightened risk to develop schizophrenia (Walker and Bollini, 2002; Costello et al., 2003; Paus et al., 2008) as abnormal adolescent brain development contributes to the aetiology of schizophrenia (Paus et al., 2008; Walker et al., 2008). Furthermore, stress response-relevant neuronal pathways develop during adolescence (Andersen et al., 2000; Spear, 2000; Casey et al., 2008) and HPA axis plasticity appears sensitive to adolescent stress exposure as well (Romeo et al., 2006). Thus, it is important to assess interactions between Nrg1 and stress also during adolescence.

Indeed, Taylor and co-workers investigated the effects of chronic variable stress during adolescence on endocrine and behavioral measures in adult Type II *Nrg1* mutant rats (Taylor et al., 2012). Sex-specific interactions between *Nrg1* genotype and adolescent stress were found. Stress during adolescence reduced baseline corticosterone levels in female control but not mutant rats. Furthermore, stress increased extinction of cued fear conditioning but only in *Nrg1* females. The authors concluded that the findings represent a true *Nrg1* x stress interaction and are consistent with a reduction in sensitivity to environmental stimuli and novelty as described earlier (Taylor et al., 2011a,b). However, *Nrg1* females were the only group susceptible to the effects of adolescent stress on fear extinction. In addition, most earlier findings had been evident in male rats (Taylor et al., 2011b), which failed to be affected by the adolescent stress model chosen.

Social defeat stress models aspect of psychosocial stress in humans, which has been found to interact with a single nucleotide polymorphism of *NRG1* to affect the reactivity of schizophrenia patients to expressed emotion (Keri et al., 2009). Psychosocial stress might also contribute to the development of schizophrenia via sensitization of the pro-inflammatory immune response leading to excessive pro-inflammatory cytokine release. Thus, researchers investigated behavioral and neurophysiological effects of adolescent repeated intermittent social defeat in adult transmembrane domain *Nrg1* mutant males (Desbonnet et al., 2012) and found that *Nrg1* modified the effects of social defeat on several behavioral, immunological and brain measures. For example, psychosocial stress diminished the hyper-locomotive phenotype of *Nrg1* mutant mice without accompanying effects on control littermates. In addition, stress had cognitive-impairing effects in *Nrg1* mice only and decreased sucrose preference (model for anhedonia) in control but not mutant mice. Social defeat also altered the lipopolysaccharide and concanavalin A-stimulated cytokine response of the spleen in a genotype-specific manner (see study for details). In the brain, stress decreased interleukin-beta mRNA levels in the prefrontal cortex of mutant mice only, whereas striatal interleukin-beta was down-regulated in controls and up-regulated in *Nrg1* mice. Finally, hippocampal BDNF mRNA levels were elevated in control mice and reduced in mutant mice whereas tumor necrosis factor-alpha was up-regulated in *Nrg1* mice only. Reduced striatal BDNF levels might have been involved in the disrupting effects of social defeat stress on the spatial memory of *Nrg1* mutant mice (Almli et al., 2000). Importantly, Nrg1 can interact with BDNF in regulating neuronal processes (Mei and Xiong, 2008; Balu and Coyle, 2011), BDNF down-regulation has been reported in schizophrenia (Weickert et al., 2003; Favalli et al., 2012), and BDNF expression changes impact on the sensitivity to social defeat stress (Berton et al., 2006; Krishnan et al., 2007). The authors concluded that the experience of psychosocial stress during adolescence may trigger further pathophysiological features that contribute to the development of schizophrenia in individuals underlying *NRG1* gene abnormalities. The interactive nature of the effects of stress and mutant *Nrg1* resulted in cognitive deficits and an imbalance in BDNF and immunological parameters. On the other side, stress impacted positively on the hyper-locomotive phenotype of *Nrg1* mutant mice, outlining the complexity of GxE interactions in schizophrenia and the need to look at specific disease endophenotypes.

In summary, research teams have started evaluating the role of *Nrg1* in the neuro-endocrine, behavioral, and immunological response of mice to stress. Results so far are inconclusive demanding that future research should focus on schizophrenia-relevant stress models [similar to (Desbonnet et al., 2012)], consider sex and age in experimental designs, and focus on schizophrenia-like behaviors and disease-relevant brain markers.

Nrg1 X CANNABIS

A review on the role of *Nrg1* in GxE in schizophrenia would be incomplete without mentioning the extensive mouse work on

Table 1 | Effects of environmental factors on rodent models for the schizophrenia candidate gene *neuregulin 1.*

***Nrg1* × Laboratory housing (i.e., minimal enrichment)**	
Transmembrane domain *Nrg1* mutant male mice (Karl et al., 2007)	Minimal enrichment shifted the onset of the hyper-explorative and anxiogenic phenotype of *Nrg1* mice to 3–4 months of age compared to mutant mice kept in standard laboratory housing (onset at 4–6 months of age).
***Nrg1* × Stress**	
Acute restraint stress Transmembrane domain *Nrg1* mutant male mice (Chesworth et al., 2012b)	No pronounced effect of *Nrg1* on the endocrine and behavioral effects of acute restraint stress—only subtle, age-dependent modification of stress-induced corticosterone release and anxiety-like behaviors.
Acute restraint stress Adult Type II *Nrg1* mutant rats (Taylor et al., 2011a,b)	Altered habituation to an open field environment in *Nrg1* mutant rats. Mutant *Nrg1* resulted in increased baseline corticosterone levels and improved recovery of those levels post stress. Elevated baseline levels of glucocorticoid receptors in hippocampus and pituitary glands. Results are highly sex-specific.
Chronic variable stress Adolescent Type II *Nrg1* mutant rats (Taylor et al., 2012)	Female *Nrg1* rats displayed no stress-induced reduction in corticosterone levels and showed increased extinction of cued fear conditioning (no such effects in male *Nrg1* mutants).
Social defeat stress Transmembrane domain *Nrg1* mutant mice (Desbonnet et al., 2012)	Stress diminished hyper-locomotion and induced cognitive deficits in *Nrg1* mutant mice without accompanying effects in control mice. *Nrg1* mutant mice were protected against anhedonic properties of social defeat. The effects of stress on the cytokine response of mice were genotype-dependent (for details see study). Stress decreased interleukin-beta mRNA levels in the prefrontal cortex of *Nrg1* mice. Striatal interleukin-beta levels were reduced in control mice and increased in *Nrg1* mice. Hippocampal BDNF mRNA levels were elevated in control mice and reduced in mutant mice whereas tumor necrosis factor-alpha was up-regulated in *Nrg1* mice only.
***Nrg1* × Cannabis reviewed in (Arnold et al., 2012; Karl and Arnold, 2013; Ng et al., 2013)**	
Acute treatment with Δ^9-tetrahydrocannabinol (THC) Adult transmembrane domain *Nrg1* mutant mice (Boucher et al., 2007a,b; Long et al., 2010)	*Nrg1* mutants displayed a sex-dependent increased susceptibility to the locomotion-suppressive effects of THC and showed improved prepulse inhibition post THC treatment. THC induced increased neuronal activity in the ventral part of the lateral septum and greater activity in central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus in *Nrg1* mutant mice.
Chronic treatment with CP55,940 (CP) Adult transmembrane domain *Nrg1* mutant male mice (Boucher et al., 2011)	*Nrg1* mutants developed a behavioral tolerance to CP-induced hypothermia and hypolocomotion more rapidly, whereas the same mice did not develop a tolerance to CPs anxiogenic effects. Mutant mice showed a selectively increase in CP-induced FosB/ΔFosB expression in the ventral part of lateral septum.
Chronic THC treatment Adolescent transmembrane domain *Nrg1* mutant male mice (Long et al., 2013)	THC exacerbated hyperlocomotion 48 h after THC withdrawal. *Nrg1* mutant mice were more resistant to social withdrawal effects of THC. THC promoted genotype-dependent effects on CB1, 5-HT2A and NMDA receptor expression (see study for details).

Nrg1 x cannabis interactions. As those studies have been reviewed elsewhere (Arnold et al., 2012; Karl and Arnold, 2013; Ng et al., 2013), this section will only provide a brief summary. It has long been established that cannabis is a component/cumulative cause for the development of schizophrenia (Arseneault et al., 2002, 2004) suggesting interactions with other risk factors (D'Souza et al., 2009). Until recently, Catechol-O-methyltransferase (*COMT*) was the only candidate for a possible interaction between a genetic predisposition for schizophrenia and heavy cannabis abuse [(Caspi et al., 2005; O'Tuathaigh et al., 2010) but see also (Zammit et al., 2011)]. Comprehensive analyses on *Nrg1* x cannabis interactions in transmembrane domain *Nrg1* mutant mice suggest that *Nrg1* increases the susceptibility of an organism to the neuro-behavioral effects of cannabis as well (Boucher et al., 2007a,b, 2011; Long et al., 2010, 2012, 2010). The clinical relevance of this research has recently been highlighted by a genetic study in African Americans, which discovered *NRG1* as a major candidate for the development of cannabis dependence (Han et al., 2012).

CONCLUSIONS

Recent research utilizing genetic rodent models has revealed an interactive relationship between *Nrg1* and a variety of environmental factors. These interactions appear to be complex and sensitive to a number of subtle variables, but do exist and justify the need for future research in this area (van Os et al., 2010). Researchers should focus on models with significant relevance to schizophrenia including, for example, cannabis abuse (discussed above) and maternal immunization (Ibi et al., 2010; Giovanoli et al., 2013) and consider not only *Nrg1* but also other genetic candidates for GxE interactions. Importantly, the research into *Nrg1*xE outlined above suggests that valid GxE mouse models will be very sensitive to the laboratory environment and other potential test confounders (e.g., age and sex) so that a high level of transparency and standardization of test conditions across research sites will be crucial.

Although the exact nature of *Nrg1*xE and their consequences for schizophrenia have to be evaluated further, an involvement of the GABAergic, glutamatergic and BDNF systems seems likely. Importantly, environmental (risk) factors not always induced adverse (i.e., disease phenotype-strengthening) effects in *Nrg1* mutants, which should be taken into account when looking into GxE interactions [for genotype-specific effects of environmental factors see also (Tucci et al., 2006; Valdar et al., 2006)]. The findings on *Nrg1*xE summarized in **Table 1** are in line with the GxE theory, contribute to the understanding of the pathogenesis of schizophrenia, and might eventually help with possible early intervention programs. Importantly, recent discussions on the appropriate statistical modeling of GxE interactions (van Winkel et al., 2008; Zammit et al., 2010) as well as the limitations of animal model research into schizophrenia (Ayhan et al., 2009) should be considered for future work.

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