Role of the Neuregulin Signaling Pathway in Nicotine Dependence and Co-morbid Disorders

Fisher, Miranda L.

ACADEMIC PRESS INC ELSEVIER SCIENCE
2015

Fisher , M L , Loukola , A , Kaprio , J & Turner , J R 2015 , Role of the Neuregulin Signaling Pathway in Nicotine Dependence and Co-morbid Disorders . in M DeBiasi (ed.) , NICOTINE USE IN MENTAL ILLNESS AND NEUROLOGICAL DISORDERS . 1. p. edn , International Review of Neurobiology , vol. 124 , ACADEMIC PRESS INC ELSEVIER SCIENCE , pp. 113-131 . https://doi.org/10.1016/bs.irn.2015.07.006

http://hdl.handle.net/10138/224172
https://doi.org/10.1016/bs.irn.2015.07.006

publishedVersion

CHAPTER FOUR

Role of the Neuregulin Signaling Pathway in Nicotine Dependence and Co-morbid Disorders

Miranda L. Fisher*, Anu Loukola†, Jaakko Kaprio†,‡,§, Jill R. Turner*,1

*Department of Drug Discovery and Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, South Carolina, USA
†Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland
‡National Institute for Health and Welfare, Helsinki, Finland
§Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland
1Corresponding author: e-mail address: jiturner@sccp.sc.edu

Contents

Abstract

Smoking is currently the leading cause of preventable death in the United States and is responsible for over four million deaths annually worldwide. Therefore, there is a vast clinical unmet need with regards to therapeutics targeting smoking cessation. This is even more apparent when examining smokers co-morbid with psychiatric illness, as rates of smoking in this population are ~4× higher than in the general population.

International Review of Neurobiology, Volume 124
ISSN 0074-7742
http://dx.doi.org/10.1016/bs.irn.2015.07.006

Examining common genetic and molecular signaling pathways impinging upon both smoking behavior and psychiatric illness will lead to a better understanding of co-morbid disorders and potential development of novel therapeutics. Studies have implicated the Neuregulin Signaling Pathway in the pathophysiology of a number of psychiatric illnesses. Additionally, recent studies have also shown an association between the Neuregulin Signaling Pathway and smoking behaviors. This review outlines basic mechanisms of the Neuregulin Signaling Pathway and how it may be exploited for precision medicine approaches in treating nicotine dependence and mental illness.

1. INTRODUCTION

Tobacco smoking is still the leading cause of preventable death in the United States even years after the discovery of multiple smoking cessation therapies. The main addictive component in cigarette smoke is nicotine (United States. Department of the Army. Office of the Surgeon General, 1988), which drives the reinforcement behind smoking behavior. With global smoking-related mortality reaching nearly six million deaths annually ("WHO urges more countries to require large, graphic health warnings on tobacco packaging: the WHO report on the global tobacco epidemic, 2011 examines antitobacco mass-media campaigns," WHO, 2011), there is a high demand for targeted therapeutics that successfully aid smokers to quit. Several smoking cessation pharmacotherapies are available, including nicotine replacement therapy, prescription medication such as bupropion (originally designed as an antidepressant) and the nicotinic acetylcholine receptor (nAChR) partial agonist varenicline (Cummings & Mahoney, 2006; Jorenby et al., 2006); however, the success rate of such therapies after 1 year is at best only 20–25% (Gonzales et al., 2006). In comparison, approximately 3% of individuals trying to quit without any pharmacotherapies are still abstinent after 6 months (Hughes et al., 1992). The majority of smokers would like to quit and are aware of the risks of smoking, but are unable to do so. The positive reinforcing effect of nicotine is an important determinant of cessation failure; however, it is not the only factor that should be taken into account. The significant aversive withdrawal symptoms that occur during abstinence are also considered a major determinant of high relapse rates (Le Foll & Goldberg, 2009).

Withdrawal symptoms are relatively well-characterized and include both cognitive and affective symptoms. These symptoms primarily include

depressed mood states, anxiety, irritability, concentration difficulties, and craving (Hughes, 2007). It is suggested that withdrawal symptom severity is a more valid indicator of smoking cessation outcome than nicotine intake or dependence (West, Hajek, & Belcher, 1989). Of these aversive withdrawal symptoms, a common affective symptom is depression. Interestingly, depressed mood is also associated with nicotine dependence, but it is not known whether depression predisposes an individual to begin smoking or whether depression develops during the course of nicotine dependence.

Broadly, nicotine dependence is highly co-morbid with several psychiatric illnesses and other substance use disorders, which further complicates smoking cessation. However, the relationship between nicotine use and mental disorders is still elusive and debatable (Moylan, Jacka, Pasco, & Berk, 2012). It has been suggested that nicotine is used in an effort to self-medicate symptoms occurring in psychiatric illnesses such as schizophrenia (Royal College of Physicians of London & Royal College of Psychiatrists, 2013), i.e., smoking would primarily be a consequence of the psychiatric disease. The second possible explanation for the co-morbidity is that smoking is itself a cause of psychiatric illness; the evidence for this is variable and depends on conditions being examined. For example, growing evidence supports the causal role of smoking in the etiology of depression (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Kendler et al., 1993; Pasco et al., 2008). However, evidence must come from well-conducted prospective epidemiological studies, within-family studies, or Mendelian randomization studies using genetic markers to test causality, as randomized clinical trials cannot be used to test this hypothesis. The third potential reason for the co-morbidity may be that there are underlying genetic factors in common to specific mental disorders and smoking-related phenotypes, including nicotine dependence and withdrawal. A prime candidate for this third explanation is the co-morbidity observed between nicotine dependence and schizophrenia.

Within the co-morbid population, overall prevalence of smoking in schizophrenia patients is higher than in patients with other psychiatric conditions (Dickerson et al., 2013). Strikingly, high smoking prevalences, 60–90%, have been reported in schizophrenia patients (Dickerson et al., 2013; Matthews, Wilson, & Mitchell, 2011; Zabala et al., 2009), compared to the approximately 18% prevalence rate in the general U.S. population (Jamal et al., 2014). In addition to being more frequently current smokers, schizophrenia patients typically smoke more, are more likely nicotine dependent, and are less likely to succeed in quitting (Addington &

el-Guebaly, 1998; George et al., 2002; Ziedonis & George, 1997). However, the association of smoking with schizophrenia is not universal. For example, among Chinese women with schizophrenia, the prevalence of smoking was only slightly higher than in the general Chinese population (Hou et al., 2011; Xu et al., 2014). However, this finding could reasonably be due to a greater percentage of smokers in the Chinese population (28.1%) (Li, Hsia, & Yang, 2011) as compared to the ~20% of Americans. Nonetheless, the strength and consistency of the association over the Western world suggests that there may also be an underlying biological basis for it. Furthermore, given the differences in genetic architecture between major human ancestry groups, the findings in Chinese patients do not exclude a genetic contribution in European ancestry populations.

The neurodevelopmental theory of schizophrenia suggests that genetic and/or environmental factors negatively affect brain development during critical neural development milestones (Rapoport, Addington, Frangou, & Psych, 2005). These in turn are responsible for the biochemical alterations observed in people diagnosed with the disease (Marenco, Weinberger, & Schreurs, 2003). Breaking down the symptom profile of schizophrenia into several disease-relevant endophenotypes has enabled investigation of the role of specific risk genes that impact behavioral and biological components of this disease phenotype (Braff, Freedman, Schork, & Gottesman, 2007; Waddington et al., 2007; Walters & Owen, 2007). For example, linkage and association studies have resulted in several candidate genes such as *DTNBP1*, *DISC1*, *NRG1,* and *NRG3*. One of the most promising susceptibility genes for schizophrenia is *NRG3* due to the observation that structural and polymorphic variations of this gene are associated with a wide spectrum of neurodevelopmental disorders with phenotypes encompassing developmental delay, impairment of cognition, and autism (Balciuniene et al., 2007). This genetic variation is due to recurrent microdeletions of chromosome 10q22-q23 that involve the *NRG3* gene and also shows linkage to schizophrenia in Ashkenazi Jewish and Han Chinese populations (Fallin et al., 2003; Faraone et al., 2006). A noncoding genetic variation in *NRG3* has also been observed as a putative risk factor for schizophrenia (Chen et al., 2009; Morar et al., 2011; Sonuga-Barke et al., 2008; Wang et al., 2008). Additionally, genetic association studies show multiple genes and epistatic locus interactions (Benzel et al., 2007) within the NRG–ErbB signaling pathway that increases the risk for schizophrenia. These multiple genes encode for NRG3, NRG1, ERBB4, and AKT1, suggesting this signaling cascade may represent a pathogenic network occurring in schizophrenia.

While it is difficult to evaluate the possible therapeutic effects of nicotine in mental disorders, it may be more approachable to view these co-morbidities through the lens of genetics. For example, genes encoding for the Neuregulin Signaling Pathway have been consistently implicated in the etiology of schizophrenia (Li, Collier, & He, 2006; Munafo, Attwood, & Flint, 2008; Munafo, Thiselton, Clark, & Flint, 2006) and these same genes have recently also been implicated in smoking behavior (Loukola et al., 2014; Turner et al., 2014). Therefore, examining this pathway for possible alterations both in psychiatric illness and in nicotine dependence and cessation outcomes may aid in identifying a common link for these co-morbid disorders.

2. KNOWN MECHANISMS OF NEUREGULIN–ErbB SIGNALING

2.1 Overview

Recently, neuregulins (NRGs) have been studied as molecular links between several co-morbid disorders such as nicotine dependence, schizophrenia, attention deficit hyperactivity disorder (ADHD), and depression. This family of epidermal growth factor (EGF)-like proteins is widely expressed within the central nervous system (CNS) and has been implicated in a variety of processes, including neural development and brain activity homeostasis (for review, see Mei & Nave, 2014). While this review focuses on their effects in the CNS, NRGs signal through receptor tyrosine kinases of the ErbB family to achieve cell-to-cell interactions throughout the body, including breast and heart tissue (Yarden & Sliwkowski, 2001), where they have broad impact on cellular function and signaling. The *NRG* gene family encodes for NRG1-6, and each gene gives rise to multiple splice variants. NRG1 was the first ligand to be discovered in the brain for its function in biological processes such as activation of ErbB receptors, stimulation of Schwann cell growth, and induction of acetylcholine receptor expression (Falls, 2003; Mei & Xiong, 2008). NRG1 was also found to be a key regulator in neurotransmitter function, myelination, and synaptic plasticity related to drugs of abuse and schizophrenia (Law, 2014). However, since then, other members of the NRG family have been identified for various functions in the CNS (Carraway et al., 1997; Chang, Riese, Gilbert, Stern, & McMahan, 1997; Harari et al., 1999; Howard, Panchal, McCarthy, & Ashworth, 2005; Kanemoto et al., 2001; Kinugasa et al., 2004; Uchida et al., 1999; Watanabe et al., 1995; Zhang et al., 1997).

2.2 Neuregulin Binding and ErbB Dimerization

Neuregulins are produced as transmembrane bound precursors (Massague & Pandiella, 1993; Fig. 1(1)). The intracellular domain of NRG1 is released after proteolytic cleavage and is translocated to the nucleus of the presynaptic neuron, where it influences processes such as apoptosis (Bao, Wolpowitz, Role, & Talmage, 2003); this cascade of events is called *back signaling*. NRGs also interact with and activate ErbB receptors (ErbB1–4), resulting in

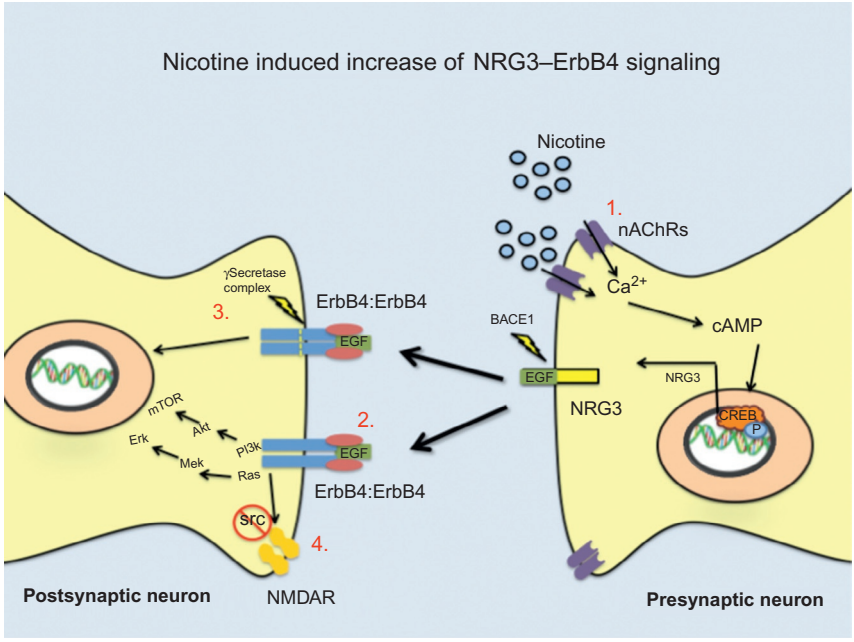

Figure 1 (1) Nicotine binds to the nicotinic acetylcholine receptor, causing a conformational change that opens the receptor's ion channel and allowing entry of Ca^{2+} and Na^{+}. The influx of these cations further activates voltage-dependent calcium channels, allowing more Ca^{2+} to enter, increasing the production of second messenger cyclic AMP (cAMP). These increases in cAMP lead to the activation of the transcription factor CREB, inducing increased expression of *NRG3*. (2) The *NRG3* EGF-like domain is then proteolytically cleaved by BACE1 and binds to the ErbB4 receptor. Upon binding of NRG3, conformational changes increase the affinity for another ErbB molecule, thus leading to homo- or heterodimerization. This dimerization results in activation of ErbB receptor tyrosine kinases and other intracellular signaling pathways referred to as *canonical forward signaling*. (3) An alternative pathway results from the cleavage of the intracellular domain of ErbB4 by a gamma-secretase complex and subsequent translocation to the nucleus to regulate gene transcription, also known as *noncanonical forward signaling*. (4) NRG–ErbB4 signaling can also directly suppress Src-mediated enhancement of synaptic NMDAR function.

activation of intracellular signaling pathways (such as ERK-, PI3K-, and Akt-mediated signaling) within the postsynaptic cell; this cascade of events is called *canonical forward signaling*, which has been shown to modulate neuronal migration and differentiation (Falls, 2003), as well as to play a role in the stimulation or inhibition of processes such as apoptosis, adhesion, proliferation, differentiation, and migration (Yarden & Sliwkowski, 2001; Fig. 1 (2)). The extracellular EGF domain of NRG binds to the ErbB receptor and initiates conformational changes in the receptor molecule, thereby increasing the affinity for another ErbB molecule and leading to homo- or heterodimerization (i.e., ErbB1–ErbB1 or Erb1–ErbB4) (Olayioye, Neve, Lane, & Hynes, 2000). This recruitment of specific ErbB molecules seems to be driven in part by the activating NRG. For example, NRG3 binds exclusively to ErbB4 receptors, but this can either be ErbB4 homodimers or be ErbB4:ErbB2 heterodimers (Zhang et al., 1997). Unlike recruitment of the dimer, however, the recruited phosphorylated ErbB partner determines the functional nature of signaling, irrespective of the ErbB ligand. The receptor dimerization activates the tyrosine kinase domain and allows it to phosphorylate tyrosine residues in the cytoplasmic region of the ErbB partner. The phosphorylated tyrosine residues then recruit various adaptors/effectors that induce specific intracellular signaling cascades, which appear to be subtype dependent. For example, ErbB4 mainly links to the Ras–MAPK and PI3k–Akt pathways (Muraoka-Cook, Feng, Strunk, & Earp, 2008; Ortega et al., 2012), and this signaling is considered to be important in many neural developmental processes, including circuitry generation, neurotransmission, and synaptic plasticity (Mei & Nave, 2014). A third mechanism of action for ErbB is the *noncanonical forward signaling*, where upon binding of NRG to the ErbB receptor, the C-terminal intracellular domain of ErbB is released by proteolytic cleavage and translocated to the nucleus where it can regulate gene transcription (Lee et al., 2002; Ni, Murphy, Golde, & Carpenter, 2001; Fig. 1(3)).

2.3 Effects of Alternative Splicing of the ErbB4 Receptor

In addition to dimerization of ErbB receptors, alternative splicing of the various ErbB receptors increases the system complexity by selectively shunting activation of intracellular signaling cascades. For example, in the human genome, alternative splicing of the *ERBB4* gene at exon 15/16 and exon 26 produces multiple ERBB4 variants (JM-a/b/c/d and CYT-1/2) (Veikkolainen et al., 2011; Zeng et al., 2009). These splice variants can have

distinct effects. For example, the CYT-1 variant can recruit the p85 regulatory adapter to preferentially activate PI3k signaling. Additionally, this same splice variant is susceptible to proteolytic cleavage by TNF-alpha converting enzyme (TACE) and gamma-secretase (Sundvall et al., 2010; Vidal, Naresh, Marrero, & Jones, 2005), producing an 80-kDa intracellular fragment (ERBB4-ICD), which interacts with the transcription factor STAT4 and migrates to the nucleus, acting as a molecular chaperone (Sundvall et al., 2010; Vidal et al., 2005).

2.4 Neuregulin–ErbB4 Effects on NMDA Receptors

ErbB4 also contains a PDZ-binding motif at the carboxyl terminal and is anchored to the postsynaptic density protein 95 (PSD95) in neurons (Huang et al., 2000). Even when ErbB4 is phosphorylated by another partner, or proteolytically cleaved to produce ErbB4-ICD, the signal is only minimally transported to the soma or translocated to the nucleus (Lee et al., 2002; Ni et al., 2001). Instead, the interaction with the scaffolding protein PSD95 allows ErbB4 receptors to closely interact with ionotropic glutamate receptors (NMDARs), thereby enhancing this signaling within the postsynaptic compartments (Garcia, Vasudevan, & Buonanno, 2000). A recent study from Pitcher and colleagues (2011) demonstrated a new mechanism by which NRG–ErbB4 activation results in NMDA hypofunction (Fig. 1(4)). This constrained activity allowed ErbB4 activation to trigger dephosphorylation of the NMDAR, resulting in reduced function of the NMDAR. Dysregulation of glutamatergic transmission has been implicated in schizophrenia, mainly because of psychotomimetic effects of NMDA receptor antagonists (Coyle & Tsai, 2004). Therefore, these findings represent a new pathway by which NMDAR and ErbB4 interaction could underlie schizophrenic pathophysiology. However, whether and how this mechanism is altered in nicotine dependence is currently unknown.

2.5 Acetylcholine Receptor Inducing Activity: Modulation of nAChR Expression

One potential way that NRG–ErbB signaling and nicotine dependence may overlap is through modulation of nAChR expression. Some members of the NRG family are shown to stimulate nAChR synthesis and clustering in cultured chick and rat myotubes (Falls, Rosen, Corfas, Lane, & Fischbach, 1993), and thus are called "acetylcholine receptor inducing activity" (ARIA) proteins. This observation has now been extended to the CNS, where studies have demonstrated that NRG1 activity results in an increase

in synaptic expression of α7-containing nAChRs (Hancock, Canetta, Role, & Talmage, 2008; Yang, Kuo, Devay, Yu, & Role, 1998). Thus, a direct association between NRG and cholinergic signaling exists at the level of nAChR expression. These studies are particularly intriguing in light of reported deficits in α7-homopentameric nAChRs in schizophrenia patients (Leonard et al., 1996, 2002). However, these phenomena have only been recently evaluated in nicotine dependence and cessation phenotypes.

3. NRG3: RELEVANCE IN SMOKING BEHAVIOR AND CO-MORBID DISORDERS

3.1 Potential Role of NRG3 in Nicotine Withdrawal and Smoking Cessation Outcome

Recent research showcasing the translational utility of cross-species models identified potential mechanisms and functional outcomes associated with NRG3–ErbB4 signaling during nicotine withdrawal (Loukola et al., 2014; Turner et al., 2014). Turner and colleagues (2014) evaluated molecular adaptations to nicotine withdrawal in discrete brain regions implicated in both cognitive and affective withdrawal symptoms. These studies investigated chromatin alterations and transcriptional control of CREB target genes following chronic nicotine exposure and 24-h withdrawal using next-generation sequencing. This coupling of CREB chromatin immunoprecipitation and high-throughput sequencing (ChIP-seq) resulted in the identification of a novel molecular target for nicotine dependence, NRG3, with increased expression detected in response to chronic nicotine exposure and withdrawal. To directly evaluate whether NRG3–ErbB4 signaling could impact smoking cessation behaviors, the authors utilized both genetic and pharmacological tools to block NRG3–ErbB4 signaling during chronic nicotine treatment and withdrawal. They observed that a co-occurring induction of NRG3 during early withdrawal is associated with increased anxiety-like behavior in mice. However, if this increased NRG3 signaling is blunted, either in NRG3 hypomorphic mice ($NRG3^{ska}$) or in wild-type mice treated with an ErbB4 inhibitor (afatinib), the anxiety behaviors observed during withdrawal were also blunted, suggesting a relationship between changes in NRG3 signaling and behavior. While the precise mechanism by which NRG3 impacts these withdrawal behaviors is unknown, these studies encouraged further scrutiny of NRG3's role in smoking cessation outcomes. Therefore, in order to evaluate the clinical relevance of this finding in human smokers, Turner and colleagues (2014)

examined genetic polymorphisms in *NRG3* and identified single nucleotide polymorphisms (SNPs) that significantly associated with reduced smoking cessation rates at both 6 weeks and 6 months.

3.2 NRG3 in Schizophrenia

Structural and polymorphic variation of *NRG3* is associated with not only schizophrenia but also a broad spectrum of neurodevelopmental disorders. Previous fine mapping of the 10q22-23 schizophrenia locus identified significant association between delusion severity and polymorphisms on intron 1 of *NRG3* (Morar et al., 2011). Following these findings, Kao and colleagues (2010) examined *NRG3* in 400 postmortem prefrontal cortical tissue samples from schizophrenia patients and controls, evaluating the association between disease state, genetic risk variants, and *NRG3* expression levels. Alternative splicing enables one gene to encode multiple proteins and is often regulated in a tissue-specific and developmental manner (Cotton et al., 2008; Kampa et al., 2004). Using RNA expression profiling, Kao and colleagues revealed that *NRG3* expression is developmentally regulated and increased in schizophrenia (Kao et al., 2010). Furthermore, *NRG3* undergoes complex splicing, leading to many distinct isoforms, all of which have an EGF-like bioactive domain, a transmembrane domain, and a complete cytoplasmic tail (Kao et al., 2010). Hatzimanolis and colleagues (2013) hypothesized that more than one damaging variant in the NRG signaling pathway genes may be needed to cause schizophrenia. They scrutinized all known genes within the NRG signaling pathway and detected an aggregation of predicted damaging variants in a subset of individuals showing unique phenotypic properties. Further, their data supports the notion that damaging variants in the NRG signaling pathway may underlie the heterogeneity of schizophrenia, which is observed in both as phenotypic variability and as genetic complexity.

3.3 NRG3: Possible Mechanisms Underlying Co-morbidity

While evaluation of SNPs common to both nicotine dependence and schizophrenia is unfortunately lacking to date, one potential way NRG3 may be contributing to smoking behavior as well as to co-morbid disorders, such as schizophrenia, is via its role in impulsivity. One shared distinct deficit among co-morbid disorders such as addiction, ADHD, and schizophrenia is impulse control. Impulsivity is suggested to be a prominent, heritable symptom among psychiatric disorders (American Psychiatric Association &

American Psychiatric Association. Task Force on DSM-IV, 1994) and can manifest in a variety of impulsive behaviors, which can be observed for example in computerized response tasks (Loos et al., 2014). A facet of impulsivity is impulsive action, which can be broadly defined as the inability to withhold from making a response. Genetic mapping of impulsive action in mice has revealed a locus on chromosome 14, which is homologous to the human 10q22-q23 schizophrenia-susceptibility locus encompassing *NRG3* (Loos et al., 2014). To confirm its influence on impulsive action, congenic mice carrying the impulsivity locus (Impu1) showed that increased impulsivity was associated with increased *Nrg3* expression in the medial prefrontal cortex (mPFC), a region known for its role in drug abuse-related behaviors. Loos and colleagues (2014) also showed that viral overexpression of *Nrg3* in the mPFC increased impulsivity, whereas loss-of-function mutant mice showed decreased impulsivity (Loos et al., 2014). Although the level of *NRG3* expression appears to influence levels of inhibitory control, the specific mechanism how NRG3 signaling impacts impulsivity and how this relates to nicotine dependence and schizophrenia is unknown.

4. ERBB4: RELEVANCE IN SMOKING BEHAVIOR AND CO-MORBID DISORDERS

4.1 Association Between ERBB4 and Nicotine Dependence

Recently, *ERBB4* was shown to be associated with nicotine dependence. Loukola and colleagues (2014) performed a genome-wide association study on 1114 adult twins ascertained for heavy smoking from a population-based Finnish Twin Cohort study. With 17 smoking-related phenotypes available, the authors were able to comprehensively portray the multiple dimensions of smoking behavior, such as smoking initiation, amount smoked, and nicotine dependence. By employing a convergent approach, the authors gathered multiple independent lines of evidence supporting the association between *ERBB4* and nicotine dependence defined by DSM-IV (American Psychiatric Association, 1994). The initial association detected in the Finnish twin sample was replicated in an independent Australian twin family sample of 4425 individuals. Further, *ERBB4* is located within a regular smoking linkage locus previously identified in the Finnish twin families (Loukola et al., 2008) and within a smoking quantity locus highlighted in a linkage meta-analysis (Han, Gelernter, Luo, & Yang, 2010). These results provided novel evidence for the involvement of ErbB4 in nicotine dependence (Loukola et al., 2014).

4.2 ErbB4–NMDA Receptor Interactions in Schizophrenia and Possible Relevance for Co-morbidity with Nicotine Dependence

While a valid animal model of schizophrenia has been difficult to construct due to the polygenetic nature of the disease, genetic mouse models resulting in increased activation of NRG–ErbB4 signaling have aided understanding of the disease. For example, Paterson and Law (2014) recently investigated the effects of *Nrg3* overexpression with regards to activation of the ErbB4–Akt signaling pathway. They found that excessive ErbB4 activation during development had life-long consequences on discrete behavioral phenotypes and posited that this enhanced signaling impacts early neonatal brain development and influences circuitry that is involved in behaviors related to anxiety and sociability (Paterson & Law, 2014). Further studies by Del Pino and colleagues (2013) examined schizophrenia-like phenotypes in ErbB4-floxed mutant mice. They found that deletion of *ErbB4* from two main types of fast-spiking neurons (chandelier and basket cells) caused disruption in the synchrony of cortical regions. This functional deficit was found to be associated with increased locomotor activity, abnormal emotional and social responses, and impaired cognitive function, thus leading to the conclusion that dysfunction of cortical fast-spiking interneurons might be central to the etiology of schizophrenia (Del Pino et al., 2013). However, these dual observations may be due to the close proximity of and interaction between NMDA and ErbB4 receptors (Garcia et al., 2000). As discussed earlier, ErbB4 activation can result in reduced NMDA receptor function. However, the effects of chronic ErbB4 inhibition on NMDA receptors are unknown, especially during development, but NMDA receptor hypofunction has been suggested to underlie some schizophrenic traits. In line with this, phencyclidine and ketamine, two anesthetics that induce schizophrenia-like symptoms, are in fact NMDAR channel blockers (Anis, Berry, Burton, & Lodge, 1983; Javitt & Zukin, 1991). Additionally, current animal models of NMDAR hypofunction via genetic down-regulation of NMDARs result in traits resembling schizophrenia (Belforte et al., 2010; Mohn, Gainetdinov, Caron, & Koller, 1999). Therefore, these findings represent a new pathway by which NMDAR and ErbB4 receptor interaction could underlie schizophrenic pathophysiology. However, whether and how this mechanism is altered in nicotine dependence is currently unknown, but may hold relevance both for understanding co-morbidity and for developing new treatments.

5. SUMMARY

With continual technological advancements, genetic studies have helped scientists identify common genetic variation within the human population that may underlie nicotine dependence and co-morbid disorders, such as schizophrenia. For example, SNPs on genes encoding the NRG–ErbB signaling pathway have been shown to influence nicotine dependence and withdrawal (Turner et al., 2014), as well as the pathophysiology of schizophrenia (Badner & Gershon, 2002; Gurling et al., 2001), providing researchers new insight into the potential benefits of examining the NRG–ErbB4 pathway for novel therapeutic targets not only for smoking cessation but also for treating symptoms seen in schizophrenia as well. Furthermore, due to such high demand for novel therapeutics targeted at treating co-morbid disorders such as tobacco smoking and schizophrenia, understanding common cellular processes that link these disorders is worth investigating and the NRG–ErbB pathway may represent a promising place to start.

REFERENCES

Addington, J., & el-Guebaly, N. (1998). Group treatment for substance abuse in schizophrenia. *Canadian Journal of Psychiatry*, *43*(8), 843–845.

American Psychiatric Association. (1994). *Diagnostic criteria from DSM-IV*. Washington, DC: The Association.

American Psychiatric Association & American Psychiatric Association. Task Force on DSM-IV. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

Anis, N. A., Berry, S. C., Burton, N. R., & Lodge, D. (1983). The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology*, *79*(2), 565–575.

Badner, J. A., & Gershon, E. S. (2002). Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Molecular Psychiatry*, 7(4), 405–411. http://dx.doi.org/10.1038/sj.mp.4001012.

Balciuniene, J., Feng, N., Iyadurai, K., Hirsch, B., Charnas, L., Bill, B. R., et al. (2007). Recurrent 10q22-q23 deletions: A genomic disorder on 10q associated with cognitive and behavioral abnormalities. *American Journal of Human Genetics*, *80*(5), 938–947. http://dx.doi.org/10.1086/513607.

Bao, J., Wolpowitz, D., Role, L. W., & Talmage, D. A. (2003). Back signaling by the Nrg-1 intracellular domain. *The Journal of Cell Biology*, *161*(6), 1133–1141. http://dx.doi.org/10.1083/jcb.200212085.

Belforte, J. E., Zsiros, V., Sklar, E. R., Jiang, Z., Yu, G., Li, Y., et al. (2010). Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nature Neuroscience*, *13*(1), 76–83. http://dx.doi.org/10.1038/nn.2447.

Benzel, I., Bansal, A., Browning, B. L., Galwey, N. W., Maycox, P. R., McGinnis, R., et al. (2007). Interactions among genes in the ErbB-Neuregulin signalling network are associated with increased susceptibility to schizophrenia. *Behavioral and Brain Functions*, *3*, 31. http://dx.doi.org/10.1186/1744-9081-3-31.

Braff, D. L., Freedman, R., Schork, N. J., & Gottesman, I. I. (2007). Deconstructing schizophrenia: An overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin*, *33*(1), 21–32. http://dx.doi.org/10.1093/schbul/sbl049.

Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking. A longitudinal investigation. *Archives of General Psychiatry*, *55*(2), 161–166.

Carraway, K. L., 3rd, Weber, J. L., Unger, M. J., Ledesma, J., Yu, N., Gassmann, M., et al. (1997). Neuregulin-2, a new ligand of ErbB3/ErbB4-receptor tyrosine kinases. *Nature*, *387*(6632), 512–516. http://dx.doi.org/10.1038/387512a0.

Chang, H., Riese, D. J., 2nd, Gilbert, W., Stern, D. F., & McMahan, U. J. (1997). Ligands for ErbB-family receptors encoded by a neuregulin-like gene. *Nature*, *387*(6632), 509–512. http://dx.doi.org/10.1038/387509a0.

Chen, P. L., Avramopoulos, D., Lasseter, V. K., McGrath, J. A., Fallin, M. D., Liang, K. Y., et al. (2009). Fine mapping on chromosome 10q22-q23 implicates Neuregulin 3 in schizophrenia. *American Journal of Human Genetics*, *84*(1), 21–34. http://dx.doi.org/10.1016/j.ajhg.2008.12.005.

Cotton, R. G., Auerbach, A. D., Axton, M., Barash, C. I., Berkovic, S. F., Brookes, A. J., et al. (2008). Genetics. The Human Variome Project. *Science*, *322*(5903), 861–862. http://dx.doi.org/10.1126/science.1167363.

Coyle, J. T., & Tsai, G. (2004). NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. *International Review of Neurobiology*, *59*, 491–515. http://dx.doi.org/10.1016/S0074-7742(04)59019-0.

Cummings, K. M., & Mahoney, M. (2006). Current and emerging treatment approaches for tobacco dependence. *Current Oncology Reports*, *8*(6), 475–483.

Del Pino, I., Garcia-Frigola, C., Dehorter, N., Brotons-Mas, J. R., Alvarez-Salvado, E., Martinez de Lagran, M., et al. (2013). Erbb4 deletion from fast-spiking interneurons causes schizophrenia-like phenotypes. *Neuron*, *79*(6), 1152–1168. http://dx.doi.org/10.1016/j.neuron.2013.07.010.

Dickerson, F., Stallings, C. R., Origoni, A. E., Vaughan, C., Khushalani, S., Schroeder, J., et al. (2013). Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999–2011. *Psychiatric Services*, *64*(1), 44–50. http://dx.doi.org/10.1176/appi.ps.201200143.

Fallin, M. D., Lasseter, V. K., Wolyniec, P. S., McGrath, J. A., Nestadt, G., Valle, D., et al. (2003). Genomewide linkage scan for schizophrenia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 10q22. *American Journal of Human Genetics*, *73*(3), 601–611. http://dx.doi.org/10.1086/378158.

Falls, D. L. (2003). Neuregulins: Functions, forms, and signaling strategies. *Experimental Cell Research*, *284*(1), 14–30.

Falls, D. L., Rosen, K. M., Corfas, G., Lane, W. S., & Fischbach, G. D. (1993). ARIA, a protein that stimulates acetylcholine receptor synthesis, is a member of the neu ligand family. *Cell*, *72*(5), 801–815.

Faraone, S. V., Hwu, H. G., Liu, C. M., Chen, W. J., Tsuang, M. M., Liu, S. K., et al. (2006). Genome scan of Han Chinese schizophrenia families from Taiwan: Confirmation of linkage to 10q22.3. *The American Journal of Psychiatry*, *163*(10), 1760–1766. http://dx.doi.org/10.1176/appi.ajp.163.10.1760.

Garcia, R. A., Vasudevan, K., & Buonanno, A. (2000). The neuregulin receptor ErbB-4 interacts with PDZ-containing proteins at neuronal synapses. *Proceedings of the National*

Academy of Sciences of the United States of America, *97*(7), 3596–3601. http://dx.doi.org/10.1073/pnas.070042497.

George, T. P., Vessicchio, J. C., Termine, A., Bregartner, T. A., Feingold, A., Rounsaville, B. J., et al. (2002). A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*, *52*(1), 53–61.

Gonzales, D., Rennard, S. I., Nides, M., Oncken, C., Azoulay, S., Billing, C. B., et al. (2006). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *JAMA*, *296*(1), 47–55. http://dx.doi.org/10.1001/jama.296.1.47.

Gurling, H. M. D., Kalsi, G., Brynjolfson, J., Sigmundsson, T., Sherrington, R., Mankoo, B. S., et al. (2001). Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23. *American Journal of Human Genetics*, *68*(3), 661–673. http://dx.doi.org/10.1086/318788.

Han, S., Gelernter, J., Luo, X., & Yang, B. Z. (2010). Meta-analysis of 15 genome-wide linkage scans of smoking behavior. *Biological Psychiatry*, *67*(1), 12–19. http://dx.doi.org/10.1016/j.biopsych.2009.08.028.

Hancock, M. L., Canetta, S. E., Role, L. W., & Talmage, D. A. (2008). Presynaptic type III neuregulin1-ErbB signaling targets alpha7 nicotinic acetylcholine receptors to axons. *The Journal of General Physiology*, *131*(6), i4. http://dx.doi.org/10.1085/JGP1316OIA4.

Harari, D., Tzahar, E., Romano, J., Shelly, M., Pierce, J. H., Andrews, G. C., et al. (1999). Neuregulin-4: A novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. *Oncogene*, *18*(17), 2681–2689. http://dx.doi.org/10.1038/sj.onc.1202631.

Hatzimanolis, A., McGrath, J. A., Wang, R., Li, T., Wong, P. C., Nestadt, G., et al. (2013). Multiple variants aggregate in the neuregulin signaling pathway in a subset of schizophrenia patients. *Translational Psychiatry*, *3*. http://dx.doi.org/10.1038/tp.2013.33. e264.

Hou, Y. Z., Xiang, Y. T., Yan, F., Ungvari, G. S., Dickerson, F., Chiu, H. F., et al. (2011). Cigarette smoking in community-dwelling patients with schizophrenia in China. *Journal of Psychiatric Research*, *45*(12), 1551–1556. http://dx.doi.org/10.1016/j.jpsychires.2011.07.011.

Howard, B., Panchal, H., McCarthy, A., & Ashworth, A. (2005). Identification of the scaramanga gene implicates Neuregulin3 in mammary gland specification. *Genes & Development*, *19*(17), 2078–2090. http://dx.doi.org/10.1101/gad.338505.

Huang, Y. Z., Won, S., Ali, D. W., Wang, Q., Tanowitz, M., Du, Q. S., et al. (2000). Regulation of neuregulin signaling by PSD-95 interacting with ErbB4 at CNS synapses. *Neuron*, *26*(2), 443–455.

Hughes, J. R. (2007). Effects of abstinence from tobacco: Valid symptoms and time course. *Nicotine & Tobacco Research*, *9*(3), 315–327. http://dx.doi.org/10.1080/14622200701188919.

Hughes, J. R., Gulliver, S. B., Fenwick, J. W., Valliere, W. A., Cruser, K., Pepper, S., et al. (1992). Smoking cessation among self-quitters. *Health Psychology*, *11*(5), 331–334.

Jamal, A., Agaku, I. T., O'Connor, E., King, B. A., Kenemer, J. B., & Neff, L. (2014). Current cigarette smoking among adults—United States, 2005–2013. *Morbidity And Mortality Weekly Report*, *63*(47), 1108–1112.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *The American Journal of Psychiatry*, *148*(10), 1301–1308.

Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E., et al. (2006). Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *JAMA*, *296*(1), 56–63. http://dx.doi.org/10.1001/jama.296.1.56.

Kampa, D., Cheng, J., Kapranov, P., Yamanaka, M., Brubaker, S., Cawley, S., et al. (2004). Novel RNAs identified from an in-depth analysis of the transcriptome of human chromosomes 21 and 22. *Genome Research*, *14*(3), 331–342. http://dx.doi.org/10.1101/gr.2094104.

Kanemoto, N., Horie, M., Omori, K., Nishino, N., Kondo, M., Noguchi, K., et al. (2001). Expression of TMEFF1 mRNA in the mouse central nervous system: Precise examination and comparative studies of TMEFF1 and TMEFF2. *Brain Research. Molecular Brain Research*, *86*(1–2), 48–55.

Kao, W. T., Wang, Y., Kleinman, J. E., Lipska, B. K., Hyde, T. M., Weinberger, D. R., et al. (2010). Common genetic variation in Neuregulin 3 (NRG3) influences risk for schizophrenia and impacts NRG3 expression in human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(35), 15619–15624. http://dx.doi.org/10.1073/pnas.1005410107.

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J., & Kessler, R. C. (1993). Smoking and major depression. A causal analysis. *Archives of General Psychiatry*, *50*(1), 36–43.

Kinugasa, Y., Ishiguro, H., Tokita, Y., Oohira, A., Ohmoto, H., & Higashiyama, S. (2004). Neuroglycan C, a novel member of the neuregulin family. *Biochemical and Biophysical Research Communications*, *321*(4), 1045–1049. http://dx.doi.org/10.1016/j.bbrc.2004.07.066.

Law, A. J. (2014). Genetic mouse models of neuregulin 1: Gene dosage effects, isoform-specific functions, and relevance to schizophrenia. *Biological Psychiatry*, *76*(2), 89–90. http://dx.doi.org/10.1016/j.biopsych.2014.05.016.

Le Foll, B., & Goldberg, S. R. (2009). Effects of nicotine in experimental animals and humans: An update on addictive properties. *Handbook of Experimental Pharmacology*, *192*, 335–367. http://dx.doi.org/10.1007/978-3-540-69248-5_12.

Lee, H. J., Jung, K. M., Huang, Y. Z., Bennett, L. B., Lee, J. S., Mei, L., et al. (2002). Presenilin-dependent gamma-secretase-like intramembrane cleavage of ErbB4. *The Journal of Biological Chemistry*, *277*(8), 6318–6323. http://dx.doi.org/10.1074/jbc.M110371200.

Leonard, S., Adams, C., Breese, C. R., Adler, L. E., Bickford, P., Byerley, W., et al. (1996). Nicotinic receptor function in schizophrenia. *Schizophrenia Bulletin*, *22*(3), 431–445.

Leonard, S., Gault, J., Hopkins, J., Logel, J., Vianzon, R., Short, M., et al. (2002). Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. *Archives of General Psychiatry*, *59*(12), 1085–1096.

Li, D., Collier, D. A., & He, L. (2006). Meta-analysis shows strong positive association of the neuregulin 1 (NRG1) gene with schizophrenia. *Human Molecular Genetics*, *15*(12), 1995–2002. http://dx.doi.org/10.1093/hmg/ddl122.

Li, Q., Hsia, J., & Yang, G. (2011). Prevalence of smoking in China in 2010. *The New England Journal of Medicine*, *364*(25), 2469–2470. http://dx.doi.org/10.1056/NEJMc1102459.

Loos, M., Mueller, T., Gouwenberg, Y., Wijnands, R., van der Loo, R. J., Neuro Bsik Mouse Phenomics Consortium, et al. (2014). Neuregulin-3 in the mouse medial prefrontal cortex regulates impulsive action. *Biological Psychiatry*, *76*(8), 648–655. http://dx.doi.org/10.1016/j.biopsych.2014.02.011.

Loukola, A., Broms, U., Maunu, H., Widen, E., Heikkila, K., Siivola, M., et al. (2008). Linkage of nicotine dependence and smoking behavior on 10q, 7q and 11p in twins with homogeneous genetic background. *The Pharmacogenomics Journal*, *8*(3), 209–219. http://dx.doi.org/10.1038/sj.tpj.6500464.

Loukola, A., Wedenoja, J., Keskitalo-Vuokko, K., Broms, U., Korhonen, T., Ripatti, S., et al. (2014). Genome-wide association study on detailed profiles of smoking behavior

and nicotine dependence in a twin sample. *Molecular Psychiatry*, *19*(5), 615–624. http://dx.doi.org/10.1038/mp.2013.72.

Marenco, S., Weinberger, D. R., & Schreurs, B. G. (2003). Single-cue delay and trace classical conditioning in schizophrenia. *Biological Psychiatry*, *53*(5), 390–402.

Massague, J., & Pandiella, A. (1993). Membrane-anchored growth factors. *Annual Review of Biochemistry*, *62*, 515–541. http://dx.doi.org/10.1146/annurev.bi.62.070193.002503.

Matthews, A. M., Wilson, V. B., & Mitchell, S. H. (2011). The role of antipsychotics in smoking and smoking cessation. *CNS Drugs*, *25*(4), 299–315. http://dx.doi.org/10.2165/11588170-000000000-00000.

Mei, L., & Nave, K. A. (2014). Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron*, *83*(1), 27–49. http://dx.doi.org/10.1016/j.neuron.2014.06.007.

Mei, L., & Xiong, W. C. (2008). Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nature Reviews. Neuroscience*, *9*(6), 437–452. http://dx.doi.org/10.1038/nrn2392.

Mohn, A. R., Gainetdinov, R. R., Caron, M. G., & Koller, B. H. (1999). Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell*, *98*(4), 427–436.

Morar, B., Dragovic, M., Waters, F. A., Chandler, D., Kalaydjieva, L., & Jablensky, A. (2011). Neuregulin 3 (NRG3) as a susceptibility gene in a schizophrenia subtype with florid delusions and relatively spared cognition. *Molecular Psychiatry*, *16*(8), 860–866. http://dx.doi.org/10.1038/mp.2010.70.

Moylan, S., Jacka, F. N., Pasco, J. A., & Berk, M. (2012). Cigarette smoking, nicotine dependence and anxiety disorders: A systematic review of population-based, epidemiological studies. *BMC Medicine*, *10*, 123. http://dx.doi.org/10.1186/1741-7015-10-123.

Munafo, M. R., Attwood, A. S., & Flint, J. (2008). Neuregulin 1 genotype and schizophrenia. *Schizophrenia Bulletin*, *34*(1), 9–12. http://dx.doi.org/10.1093/schbul/sbm129.

Munafo, M. R., Thiselton, D. L., Clark, T. G., & Flint, J. (2006). Association of the NRG1 gene and schizophrenia: A meta-analysis. *Molecular Psychiatry*, *11*(6), 539–546. http://dx.doi.org/10.1038/sj.mp.4001817.

Muraoka-Cook, R. S., Feng, S. M., Strunk, K. E., & Earp, H. S., 3rd. (2008). ErbB4/HER4: Role in mammary gland development, differentiation and growth inhibition. *Journal of Mammary Gland Biology and Neoplasia*, *13*(2), 235–246. http://dx.doi.org/10.1007/s10911-008-9080-x.

Ni, C. Y., Murphy, M. P., Golde, T. E., & Carpenter, G. (2001). Gamma-secretase cleavage and nuclear localization of ErbB-4 receptor tyrosine kinase. *Science*, *294*(5549), 2179–2181. http://dx.doi.org/10.1126/science.1065412.

Olayioye, M. A., Neve, R. M., Lane, H. A., & Hynes, N. E. (2000). The ErbB signaling network: Receptor heterodimerization in development and cancer. *The EMBO Journal*, *19*(13), 3159–3167. http://dx.doi.org/10.1093/emboj/19.13.3159.

Ortega, M. C., Bribian, A., Peregrin, S., Gil, M. T., Marin, O., & de Castro, F. (2012). Neuregulin-1/ErbB4 signaling controls the migration of oligodendrocyte precursor cells during development. *Experimental Neurology*, *235*(2), 610–620. http://dx.doi.org/10.1016/j.expneurol.2012.03.015.

Pasco, J. A., Williams, L. J., Jacka, F. N., Ng, F., Henry, M. J., Nicholson, G. C., et al. (2008). Tobacco smoking as a risk factor for major depressive disorder: Population-based study. *The British Journal of Psychiatry*, *193*(4), 322–326. http://dx.doi.org/10.1192/bjp.bp.107.046706.

Paterson, C., & Law, A. J. (2014). Transient overexposure of neuregulin 3 during early postnatal development impacts selective behaviors in adulthood. *PLoS One*, *9*(8). http://dx.doi.org/10.1371/journal.pone.0104172, e104172.

Pitcher, G. M., Kalia, L. V., Ng, D., Goodfellow, N. M., Yee, K. T., Lambe, E. K., et al. (2011). Schizophrenia susceptibility pathway neuregulin 1-ErbB4 suppresses Src upregulation of NMDA receptors. *Nature Medicine*, *17*(4), 470–478. http://dx.doi.org/10.1038/nm.2315.

Rapoport, J. L., Addington, A. M., Frangou, S., & Psych, M. R. (2005). The neurodevelopmental model of schizophrenia: Update 2005. *Molecular Psychiatry*, *10*(5), 434–449. http://dx.doi.org/10.1038/sj.mp.4001642.

Royal College of Physicians of London and Royal College of Psychiatrists. (2013). *Smoking and mental health: A joint report*. London: Royal College of Physicians: Royal College of Psychiatrists.

Sonuga-Barke, E. J. S., Lasky-Su, J., Neale, B. M., Oades, R., Chen, W., Franke, B., et al. (2008). Does parental expressed emotion moderate genetic effects in ADHD? An exploration using a genome wide association scan. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *147B*(8), 1359–1368. http://dx.doi.org/10.1002/Ajmg.B.30860.

Sundvall, M., Veikkolainen, V., Kurppa, K., Salah, Z., Tvorogov, D., van Zoelen, E. J., et al. (2010). Cell death or survival promoted by alternative isoforms of ErbB4. *Molecular Biology of the Cell*, *21*(23), 4275–4286. http://dx.doi.org/10.1091/mbc.E10-04-0332.

Turner, J. R., Ray, R., Lee, B., Everett, L., Xiang, J., Jepson, C., et al. (2014). Evidence from mouse and man for a role of neuregulin 3 in nicotine dependence. *Molecular Psychiatry*, *19*(7), 801–810. http://dx.doi.org/10.1038/mp.2013.104.

Uchida, T., Wada, K., Akamatsu, T., Yonezawa, M., Noguchi, H., Mizoguchi, A., et al. (1999). A novel epidermal growth factor-like molecule containing two follistatin modules stimulates tyrosine phosphorylation of erbB-4 in MKN28 gastric cancer cells. *Biochemical and Biophysical Research Communications*, *266*(2), 593–602. http://dx.doi.org/10.1006/bbrc.1999.1873.

U.S. Department of Health and Human Services (1988). The Health Consequences of Smoking. Nikotine addiction. A report of the Surgeon General. Washington, D.C.

Veikkolainen, V., Vaparanta, K., Halkilahti, K., Iljin, K., Sundvall, M., & Elenius, K. (2011). Function of ERBB4 is determined by alternative splicing. *Cell Cycle*, *10*(16), 2647–2657.

Vidal, G. A., Naresh, A., Marrero, L., & Jones, F. E. (2005). Presenilin-dependent gamma-secretase processing regulates multiple ERBB4/HER4 activities. *The Journal of Biological Chemistry*, *280*(20), 19777–19783. http://dx.doi.org/10.1074/jbc.M412457200.

Waddington, J. L., Corvin, A. P., Donohoe, G., O'Tuathaigh, C. M., Mitchell, K. J., & Gill, M. (2007). Functional genomics and schizophrenia: Endophenotypes and mutant models. *The Psychiatric Clinics of North America*, *30*(3), 365–399. http://dx.doi.org/10.1016/j.psc.2007.04.011.

Walters, J. T., & Owen, M. J. (2007). Endophenotypes in psychiatric genetics. *Molecular Psychiatry*, *12*(10), 886–890. http://dx.doi.org/10.1038/sj.mp.4002068.

Wang, Y. C., Chen, J. Y., Chen, M. L., Chen, C. H., Lai, I. C., Chen, T. T., et al. (2008). Neuregulin 3 genetic variations and susceptibility to schizophrenia in a Chinese population. *Biological Psychiatry*, *64*(12), 1093–1096. http://dx.doi.org/10.1016/j.biopsych.2008.07.012.

Watanabe, E., Maeda, N., Matsui, F., Kushima, Y., Noda, M., & Oohira, A. (1995). Neuroglycan C, a novel membrane-spanning chondroitin sulfate proteoglycan that is restricted to the brain. *The Journal of Biological Chemistry*, *270*(45), 26876–26882.

West, R. J., Hajek, P., & Belcher, M. (1989). Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. *Psychological Medicine*, *19*(4), 981–985.

WHO. (2011). WHO urges more countries to require large, graphic health warnings on tobacco packaging: The WHO report on the global tobacco epidemic, 2011 examines anti-tobacco mass-media campaigns. *Central European Journal of Public Health*, *19*(3), 133, 151.

Xu, Y. M., Chen, H. H., Li, F., Deng, F., Liu, X. B., Yang, H. C., et al. (2014). Prevalence and correlates of cigarette smoking among Chinese schizophrenia inpatients receiving antipsychotic mono-therapy. *PLoS One*, *9*(2). http://dx.doi.org/10.1371/journal.pone.0088478. e88478.

Yang, X., Kuo, Y., Devay, P., Yu, C., & Role, L. (1998). A cysteine-rich isoform of neuregulin controls the level of expression of neuronal nicotinic receptor channels during synaptogenesis. *Neuron*, *20*(2), 255–270.

Yarden, Y., & Sliwkowski, M. X. (2001). Untangling the ErbB signalling network. *Nature Reviews. Molecular Cell Biology*, *2*(2), 127–137. http://dx.doi.org/10.1038/35052073.

Zabala, A., Eguiluz, J. I., Segarra, R., Enjuto, S., Ezcurra, J., Gonzalez Pinto, A., et al. (2009). Cognitive performance and cigarette smoking in first-episode psychosis. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(2), 65–71. http://dx.doi.org/10.1007/s00406-008-0835-6.

Zeng, N., Liu, L., McCabe, M. G., Jones, D. T., Ichimura, K., & Collins, V. P. (2009). Real-time quantitative polymerase chain reaction (qPCR) analysis with fluorescence resonance energy transfer (FRET) probes reveals differential expression of the four ERBB4 juxtamembrane region variants between medulloblastoma and pilocytic astrocytoma. *Neuropathology and Applied Neurobiology*, *35*(4), 353–366. http://dx.doi.org/10.1111/j.1365-2990.2008.01001.x.

Zhang, D. X., Sliwkowski, M. X., Mark, M., Frantz, G., Akita, R., Sun, Y., et al. (1997). Neuregulin-3 (NRG3): A novel neural tissue-enriched protein that binds and activates ErbB4. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(18), 9562–9567. http://dx.doi.org/10.1073/Pnas.94.18.9562.

Ziedonis, D. M., & George, T. P. (1997). Schizophrenia and nicotine use: Report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophrenia Bulletin*, *23*(2), 247–254.