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Altered neuregulin 1–erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia

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Recent molecular genetics studies implicate neuregulin 1 (NRG1) and its receptor erbB in the pathophysiology of schizophrenia[1–3]. Among NRG1 receptors, erbB4 is of particular interest because of its crucial roles in neurodevelopment and in the modulation of *N*-methyl-D-aspartate (NMDA) receptor signaling[4–6]. Here, using a new postmortem tissue–stimulation approach, we show a marked increase in NRG1-induced activation of erbB4 in the prefrontal cortex in schizophrenia. Levels of NRG1 and erbB4, however, did not differ between schizophrenia and control groups. To evaluate possible causes for this hyperactivation of erbB4 signaling, we examined the association of erbB4 with PSD-95 (postsynaptic density protein of 95 kDa), as this association has been shown to facilitate activation of erbB4. Schizophrenia subjects showed substantial increases in erbB4–PSD-95 interactions. We found that NRG1 stimulation suppresses NMDA receptor activation in the human prefrontal cortex, as previously reported in the rodent cortex. NRG1-induced suppression of NMDA receptor activation was more pronounced in schizophrenia subjects than in controls, consistent with enhanced NRG1-erbB4 signaling seen in this illness. Therefore, these findings suggest that enhanced NRG1 signaling may contribute to NMDA hypofunction in schizophrenia.

Recent genetic studies in Icelandic and other populations point to neuregulin 1 (*NRG1*) as a susceptibility gene for schizophrenia[2,3,7]. The NRG1 family consists of a family of structurally related proteins containing an epidermal growth factor (EGF)-like domain that specifically activate receptor tyrosine kinases of the erbB family: erbB2, erbB3 and erbB4 (refs. 8,9). NRG1-mediated erbB signaling has important roles in neural and glial development[10], as well as in the regulation of neurotransmitter receptors thought to be involved in the pathophysiology of schizophrenia[11,12]. ErbB4 is of particular interest in relation to the pathophysiology of schizophrenia because erbB4 signaling can modulate neurobiological processes often disturbed in the disorder: neuronal migration[4,13], the biology of GABAergic interneurons[5,14] and NMDA receptor (NMDAR) transmission[6,15,16].

Several groups have examined the expression of *NRG1* mRNAs in postmortem prefrontal cortex of schizophrenic subjects, with somewhat variable results: an overall increase, an increase in type I mRNA or subtle changes in the ratio of type II/type I or type II/type III mRNA (R. Navon *et al.*, *Abstr. XIIth World Congr. Psychiatr. Genet.* P8.20, 2004; J. Law *et al.*, *Soc. Neurosci. Abstr.* 109.7, 2004; and ref. 17, respectively). To date, however, no specific role for NRG1 has been established in schizophrenia. We show that schizophrenia is marked by increased NRG1-erbB4 signaling, which may lead to further suppression of NMDA receptor function.

We used a matched-pairs design to compare postmortem tissues from 14 nonpsychiatric controls and 14 schizophrenia individuals in a prospective, longitudinal study of schizophrenia (see **Supplementary Table 1** online). We first quantified NRG1 and erbB4 proteins in postmortem brains using immunoblotting with a polyclonal antiserum (SC-348) that specifically recognizes the 'a' type cytoplasmic tail of NRG1 (ref. 18). By this method, we first quantified NRG1 proteins in cytosolic and membranous fractions prepared from the dorsolateral prefrontal cortex (PFC). The NRG1-specific antibody identified four major bands, at 65 kDa, 95 kDa, 110 kDa and 140 kDa, in both fractions, all of which were eliminated by preadsorption with antigen peptides (**Fig. 1a**). Normalized levels of the four bands in the PFC of the schizophrenic subjects were not significantly different from those in the controls ($P < 0.30$; **Fig. 1b**). Both fractions of PFC were also probed with antibody to erbB4, a polyclonal antiserum specific to the carboxy terminus of human erbB4. Two major bands were identified: a 185-kDa intact molecule and an 80-kDa product of proteolytic cleavage (**Fig. 1c**). As in the case of NRG1, levels of both erbB4 bands in schizophrenia were not significantly different from control values ($P < 0.80$; **Fig. 1d**).

We then investigated the functional integrity of erbB4 signaling in schizophrenia. We used an experimental protocol in which postmortem brain slices were stimulated with NRG1. The activation of erbB4 signaling was measured in protein extracts of the tissues

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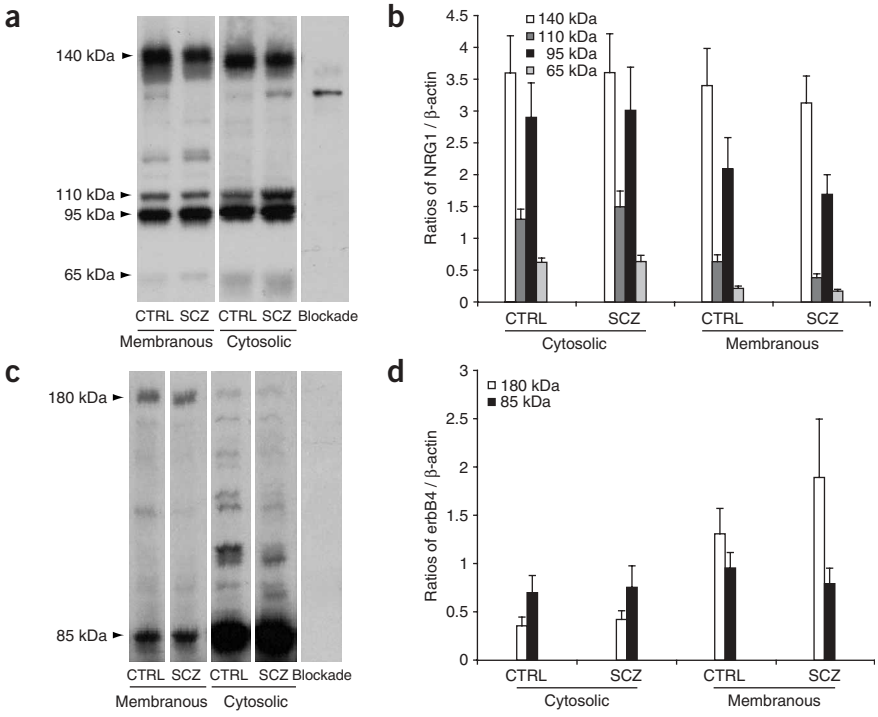

Figure 1 The expression of NRG1 or erbB4 proteins is not altered in the PFC of subjects with schizophrenia (SCZ). PFC tissues of control (CTRL) and SCZ subjects were separated for cytosolic and membranous fractions, to assess the expression of NRG1 and erbB4 proteins. (**a**) NRG1 immunoblotting of slices from control and SCZ subjects. NRG1-specific antibody identified four main bands (at 140 kDa, 110 kDa, 95 kDa and 65 kDa). (**b**) The main bands were quantified individually and normalized with respect to the signals for β-actin. Between-group differences were not statistically significant. (**c**) Immunoblotting with erbB4 in slices from control and SCZ subjects. erbB4-specific antibody identified two main bands (at 180 kDa and 85 kDa) that were blocked by the blocking peptide. (**d**) Quantification of erbB4 proteins in control and SCZ groups showed no significant differences for either the 185-kDa or the 80-kDa bands. Data are presented as mean ± s.e.m. $n = 14$ for each group.

prepared under conditions in which protein-protein interactions are maintained. This protocol has been used extensively in live culture cells and fresh tissues in animals but not in postmortem human brain tissues. We extensively tested the validity of this protocol in postmortem brains (**Supplementary Figs. 1** and **2** online) and have successfully used it to study other intracellular signaling mechanisms[19,20]. At present, the degree to which the results of this protocol correspond to *in vivo* measurements is unclear. However, this postmortem brain–stimulation protocol, in conjunction with a careful study design, can provide valuable information on intracellular events in diseased brains.

Here, NRG1 stimulation enhanced tyrosine phosphorylation of erbB4 in postmortem brains from an almost undetectable basal level. These enhancements were accompanied by parallel increases in the activation of ERK and AKT, downstream signaling molecules, as well as in the formation of erbB4 and erbB2 heterodimers (**Supplementary Fig. 1**). In control experiments, we verified the specificity of the NRG1 stimulation protocol for erbB4 signaling by incubating tissues with the control glutathione *S*-transferase (GST) fusion protein (used for NRG1) alone or with brain-derived neurotrophic factor (BDNF), another trophic factor for a different tyrosine kinase receptor. Neither enhanced the tyrosine phosphorylation of erbB4 (data not shown).

We then assessed erbB4 signaling in the PFC of schizophrenic subjects and matched controls (**Fig. 2a**). NRG1-induced tyrosine phosphorylation of erbB4 was markedly enhanced in schizophrenic subjects compared to controls ($t(13) = 8.52$, $P < 0.001$; **Fig. 2b**). Activation of downstream signaling by NRG1 was also enhanced in the schizophrenia group, as indicated by elevated activation of ERK2 ($t(13) = 6.61$, $P < 0.001$) and AKT ($t(13) = 9.18$, $P = 0.002$) in these cases (**Fig. 2c,d**). This suggests that enhanced erbB4 signaling in schizophrenia results in downstream cellular effects.

To assess potential confounding effects of demographic or clinical variables, we assessed the levels of NRG1 and erbB4 isoforms, as

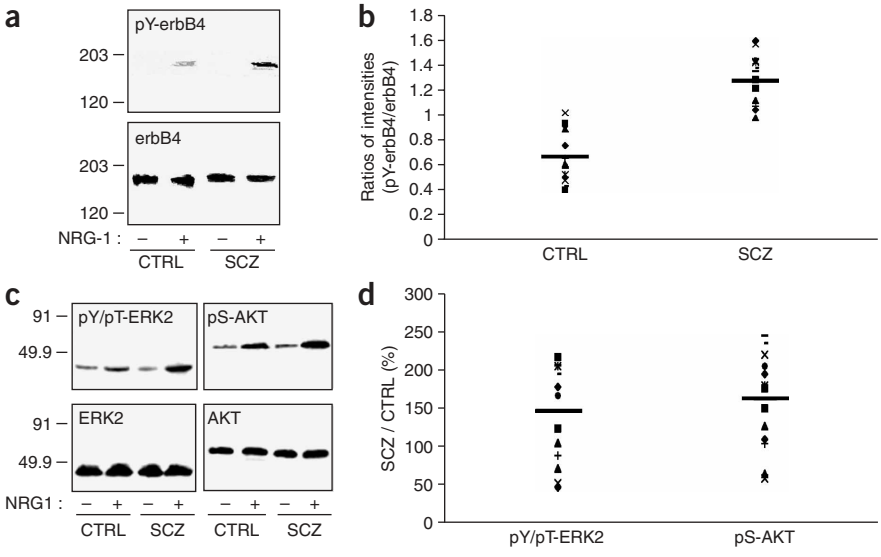

Figure 2 NRG1-induced erbB4 activation is increased in the PFC of SCZ subjects. (**a**) PFC slices from control (CTRL) and schizophrenic (SCZ) subjects were stimulated with or without NRG1. Tissue lysates were immunoprecipitated for erbB4 and then immunoblotted with an antibody to phosphotyrosine or erbB4. (**b**) Scatter plot of pY-erbB4/erbB4 ratios. (**c**) Immunoblot showing enhanced ERK-2 and AKT activation in PFC of SCZ group after NRG1 stimulation. Tissue lysates were immunoprecipitated for ERK-2 or AKT and then immunoblotted with antibodies to the indicated molecules. (**d**) Scatterplot showing percent increase in ERK2 and AKT activation in SCZ group with respect to matched controls. pY-ErbB4, phosphotyrosine erbB4; pY/pT-ERK2, phosphotyrosine/threonine ERK2; pS-AKT, phosphoserine AKT.

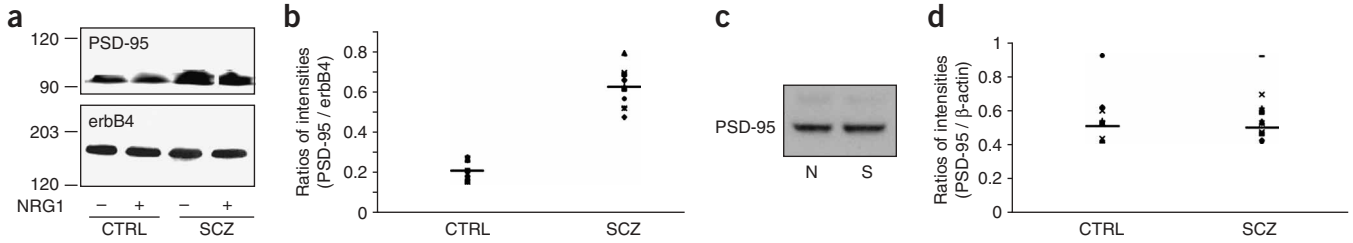

Figure 3 Association of erbB4 with PSD-95 is enhanced in the PFC of schizophrenic subjects. (**a**) PFC slices were incubated with or without NRG1 for 30 min. Tissue lysates were immunoprecipitated for erbB4 and then probed with PSD-95–specific antibody or erbB4-specific antibody. (**b**) The ratios of PSD-95 to erbB4 densitometric signals were plotted for the control and schizophrenic groups. (**c**) A representative immunoblot analysis of PSD-95 in the PFC gray matter. (**d**) Densitometric analysis of PSD-95 in the slices from 14 matched pairs of schizophrenic and control subjects. CTRL, control; SCZ, schizophrenic.

well as the activation of erbB4, ERK and AKT, for correlations with sex, age, brain pH, postmortem interval and, for the schizophrenia group, exposure to an antipsychotic drug 1 month before death. No significant correlations were found. To further test whether antipsychotic medication alters erbB4 signaling, we examined the effects of chronic haloperidol treatment in mice at a serum concentration of 3.1 ng/ml for 12 weeks, a level known to induce dopamine D2 receptor upregulation and typical behavioral and physiological changes in mice. NRG1-induced erbB4 activation was significantly reduced in the mice treated with haloperidol compared to those treated with vehicle ($t(6) = 4.00$, $P = 0.006$; **Supplementary Fig. 3** online).

To evaluate the molecular mechanisms of enhanced erbB4 signaling in schizophrenia, we considered erbB4's association with PSD-95, because this protein-protein interaction has a crucial role in the activation of erbB4 (refs. 15,21). PFC tissue lysates were immunoprecipitated for erbB4 and probed with an antibody to PSD-95 (05494). ErbB4 immunoprecipitates contained substantial amounts of PSD-95, indicating a robust association of erbB4 with PSD-95 in postmortem brains (**Fig. 3a**). Compared to matched controls, the association of erbB4 with PSD-95 was significantly higher in the brains of schizophrenia subjects ($t(13) = 14.27$, $P < 0.001$; **Fig. 3b**). In addition, the association of erbB4 with NMDAR1 was also increased (**Supplementary Fig. 4** online). NRG1 stimulation, however, did not increase erbB4–PSD-95 coupling, either in schizophrenia or control subjects, indicating that the enhancement of the erbB4–PSD-95 association in schizophrenia is independent of erbB4 stimulation (**Fig. 3a**). To determine whether the increased erbB4–PSD-95 association was a result of an increased availability of PSD-95 in schizophrenia, we measured PSD-95 protein expression by immunoblotting. There was no difference between the schizophrenia and control groups (**Fig. 3c,d**). This suggests that enhanced erbB4–PSD-95 association is not due to an increased amount of PSD-95, but to an enhanced interaction between the two molecules.

Several groups have examined postmortem brains of schizophrenia subjects and have reported that PSD-95 levels are either decreased or not significantly altered in these tissues[22,23]. Our observation that the erbB4–PSD-95 association was distinctly increased in schizophrenia, with PSD-95 protein levels unaltered (**Fig. 3**), highlights the protein-protein interactions of PSD-95 as a potentially important mode of dysregulation in this disorder.

NMDAR hypofunction is a leading hypothesis for explaining the pathophysiology of schizophrenia[24,25]. Because erbB4 associates with NMDAR via PSD-95 (refs. 15,21), increased coupling of erbB4 with PSD-95 could result in more pronounced effects of NRG1 on NMDAR activation in schizophrenia. To test this, we examined PFC extracts to measure the coupling of erbB4 with NMDAR1, the obligatory subunit of NMDAR. As with PSD-95, the association of erbB4 with NMDAR1 was significantly enhanced in schizophrenia ($t(13) = 10.19$, $P < 0.001$; **Supplementary Fig. 5** online), suggesting increases in the modulation of NMDAR function by NRG1 stimulation in this disorder.

Evidence is accumulating that in rodent brain cells, NRG1 stimulation decreases NMDA-mediated ionic currents within minutes[15,16,26]. If this is also the case in human PFC, then the enhanced NRG1-erbB4 signaling observed in schizophrenia could result in a further decrease in NMDAR function. To test this, we examined the effects of NMDA stimulation in slices of PFC from ten matched subject pairs using (i) vehicle only, (ii) NMDA (100 μM) + glycine (1 μM),

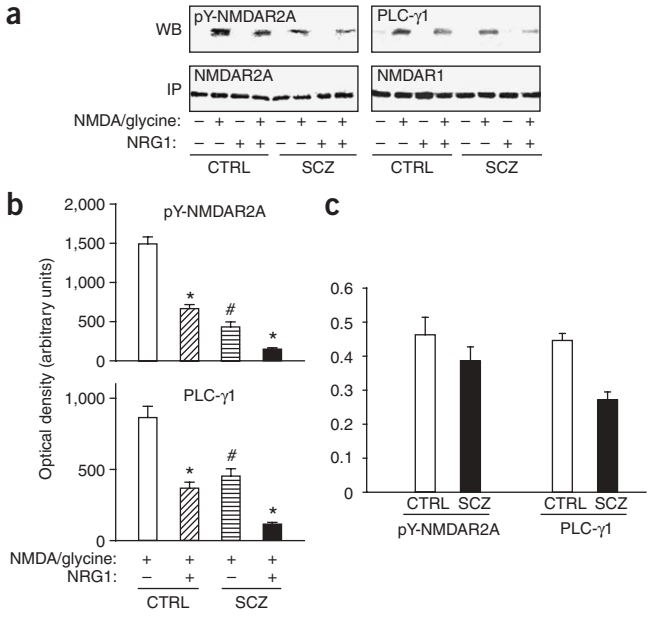

Figure 4 NRG1 attenuation of NMDAR activation is greater in the schizophrenic subjects than in controls. (**a**) NRG1 treatment attenuated the NMDA-induced enhancement of NMDAR2A tyrosine phosphorylation as well as the recruitment of PIPLC-γ1 by NMDAR1. (**b**) Densitometric quantification showing that NMDAR activation induced by NMDA + glycine was decreased in the schizophrenic group. (**c**) NRG1 suppressed NMDAR activation in the schizophrenic group more than it did in the controls. The *y*-axis represents the ratio of NMDAR activation in the presence of NRG1 to that in the absence of NRG1. NR, NMDAR; pY-NR2A, phosphotyrosine NR2A; PLC-γ1, PIPLC-γ1; WB, western blot; IP, immunoprecipitation. CTRL, control; SCZ, schizophrenic. $*P < 0.05$, $\#P < 0.01$.

(iii) NRG1 (200 ng/ml) or (iv) NMDA + glycine + NRG1. We measured the changes from baseline in the tyrosine phosphorylation of NMDAR2A and the recruitment of phosphotidyl inositol phospholipase C-γ1 (PIPLC-γ1), using the coimmunoprecipitation protocol (**Fig. 4**).

Tyrosine phosphorylation of NMDAR2A and recruitment of PIPLC-γ1 significantly increased when the slices were stimulated with NMDA and glycine (**Fig. 4a**) in all cases, as expected. However, the increase in tyrosine phosphorylation of NMDAR2A ($t(9) = 9.08$, $P < 0.001$) and recruitment of PIPLC-γ1 by NMDAR1 ($t(9) = 6.05$, $P < 0.001$) were significantly less in the schizophrenia group (**Fig. 4**). To our knowledge, this is the first evidence of decreased NMDA receptor function in postmortem brains from schizophrenia individuals.

To test whether there were differences in the effects of NRG1-erbB4 signaling on NMDA activation in the schizophrenia group, we conducted the NMDA stimulation experiments while costimulating the tissues with NRG1. NRG1 attenuated NMDA-induced receptor activation in both control and schizophrenia subjects ($P < 0.001$ for tyrosine phosphorylation and PIPLC-γ1 recruitment; **Fig. 4**). This effect was greater in the schizophrenia group than in matched controls. Even with the relatively small sample size, NRG1 stimulation significantly attenuated PIPLC-γ1 recruitment by NMDAR1 in the schizophrenia group ($t(9) = 5.64$, $P < 0.001$), whereas NMDAR tyrosine phosphorylation was more modestly reduced ($t(9) = 1.05$, $P = 0.16$).

There is evidence that schizophrenia is associated with NMDAR hypofunction[7,12,24]. Molecular and genetic studies have implicated cross-talk between NRG1-erbB4 signaling and NMDAR function in schizophrenia[1,27]. Our study shows that erbB4 signaling is enhanced in schizophrenia and that as one of its effects, NRG1 stimulation can further mediate NMDAR hypofunction. We propose that erbB4-mediated suppression of NMDAR signaling should be considered an important mechanism underlying the susceptibility to NMDAR hypofunction in schizophrenia.

METHODS

Research design and subjects studied. Psychiatric subjects met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnostic criteria for schizophrenia. Diagnosis was determined by consensus of at least two board-certified research psychiatrists after comprehensive review of medical records, direct clinical assessments and interviews with caregivers. Autopsy consent was obtained from the next of kin or a legal guardian in all cases, based on a protocol approved by the Institutional Review Board at the University of Pennsylvania. Control and psychiatric subjects were matched for sex, age (within 10 years) and postmortem interval (PMI, within 7 h). Additional details are in **Supplementary Note** online.

Mice. Adult CH3 mice were implanted with a Medisorb bioabsorbable polymer disc (Alkermes Inc.), fabricated with haloperidol ($n = 7$) or polymer vehicle only ($n = 7$). These implants were previously shown to release haloperidol for at least 5 months with a calculated release rate of approximately 2 mg/kg per day. After 12 weeks of treatment, mice were killed and the pooled serum haloperidol concentration was measured. Animal experiments were approved by the Institutional and Animal Care and Use Committee of the University of Pennsylvania.

Tissue dissection and fractionation. We dissected 1-g blocks of PFC tissue from fresh frozen coronal brain sections maintained at –80°C. These blocks were derived from Brodmann areas 9, 10 and/or 46. We isolated cytosolic and membranous fractions as described previously[20].

Tissue extracts. We homogenized tissue slices in 10 volumes of ice-cold homogenization buffer (25 mM Tris-HCl (pH 7.5), 200 mM NaCl, 2 mM EDTA, 0.5 mM EGTA, 50 μg/ml leupeptin, 0.2 mM phenylmethylsulfonyl fluoride (PMSF), 25 μg/ml pepstatin A, 0.01 U/ml soybean trypsin inhibitor, 5 mM NaF, 1 mM sodium vanadate, 0.5 mM β-glycerophosphate and 0.1% 2-mercaptoethanol) and centrifuged the homogenates at 800*g* for 10 min. We solubilized the supernatant with 0.5% digitonin, 0.2% sodium cholate and 0.5% NP-40 for 60 min. We analyzed cleared extracts for immunoblotting.

Stimulation-induced erbB4 signaling in postmortem brain tissues. We gradually thawed postmortem PFC tissues and sliced them using a McIlwain tissue chopper (200 μm × 200 μm × 3 mm). We suspended tissue slices (50 μm thick) in ice-cold Krebs-Ringer solution containing 118 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 10 mM glucose, 100 μM ascorbic acid, 50 μg/ml leupeptin, 0.2 mM PMSF, 25 μg/ml pepstatin A and 0.01 U/ml soybean trypsin inhibitor (pH 7.4). We incubated ~20 mg of tissue with Krebs-Ringer solution containing either 200 ng/ml GST fusion protein or a mixture of neuregulin-1α–GST and neuregulin-1β–GST (200 ng/ml each), at 37 °C for 30 min. During stimulation, we aerated the incubation mixture with 95% O_2, 5% CO_2 every 10 min for 1 min. We terminated ligand stimulation by adding of 1 ml ice-cold Ca^{2+}-free Krebs-Ringer solution containing 0.5 mM EGTA. We harvested tissue slices by a brief centrifugation and homogenized them in 0.25 ml ice-cold immunoprecipitation buffer (same make-up as homogenization buffer described above). We centrifuged the homogenates at 800*g* for 10 min and sonicated the supernatant for 10 s. We solubilized the proteins in 0.5% digitonin, 0.2% sodium cholate and 0.5% NP-40 for 60 min. We cleared lysates by centrifugation at 50,000*g* for 5 min and diluted them with 0.75 ml of immunoprecipitation buffer. We determined protein concentrations using the Bradford method (Bio-Rad).

Immunoprecipitation and immunoblotting. Using 2 μg of anti-erbB4 (SC-283; **Supplementary Fig. 6** online), we immunoprecipitated 200 μg tissue lysates overnight and then reacted them with 50 μl agarose-conjugated protein A or protein G beads (Santa Cruz). We boiled erbB4 immunoprecipitates for 5 min in 100 μl PAGE sample buffer and size-fractionated them in 7.5% SDS-PAGE. Immunoblotting was conducted with antibodies for phosphotyrosine (SC-508), erbB2 (SC-7301), NR1 (SC-9058; all from Santa Cruz) and PSD-95 (Upstate, 05494). We stripped and reprobed blots with erbB4-specific antibody (SC-8050; Santa Cruz). To assess the activation of ERK2 and AKT, brain lysates were immunoprecipitated with antibody to ERK2 (SC-154; Santa Cruz) and antibody to AKT (SC-8312; Santa Cruz), respectively. ERK2 and AKT immunoprecipitates were immunoblotted with antibody to phosophotyrosine ERK (SC-7383; Santa Cruz) and antibody to phosphoserine AKT (SC-7985R; Santa Cruz). We stripped the blots and reprobed them with ERK-specific antibody (SC-1647; Santa Cruz) or AKT-specific antibody (Transduction Laboratories, P65920-150) to assess the levels of ERK2 and AKT, respectively.

Data analysis. We quantified immunoblotting signals by densitometric scanning, and normalized signals for each molecule with respect to β-actin for the analysis of NRG1 or erbB4 expression, or as indicated above. Between-group comparisons were conducted for all parameters using linear mixed effects models (MEM) as the general framework to account for the cluster structure due to pair matching and to include the impact of covariates (age, race, sex and PMI). For multiple comparisons, we implemented Bonferroni adjustment ($P = 0.0019$ when adjusted for 26 parameters) and set our alpha level to 0.001. The MEM models were implemented through SAS PROC MIXED. With no covariates, the MEM produces exactly the same results as a paired *t*-test.

Note: Supplementary information is available on the Nature Medicine website.

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COMPETING INTERESTS STATEMENT
The authors declare that they have no competing financial interests.

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