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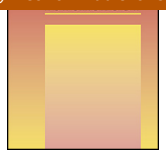

A quantitative review of the postmortem evidence for decreased cortical *N*-methyl-D-aspartate receptor expression levels in schizophrenia: How can we link molecular abnormalities to mismatch negativity deficits?

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ABSTRACT

Evidence suggests that anomalous mismatch negativity (MMN) in schizophrenia is related to glutamatergic abnormalities, possibly involving *N*-methyl-D-aspartate (NMDA) receptors. Decreased cortical expressions of NMDA receptor subunits have been observed in schizophrenia, though not consistently. To aid with integration and interpretation of previous work, we performed a meta-analysis of effect sizes of mRNA or protein levels of the obligatory NR1 subunit in prefrontal cortex from people with schizophrenia. In schizophrenia compared to unaffected controls the pooled effect size was −0.64 (95% confidence interval: −1.08 to −0.20) for NR1 mRNA reduction and −0.44 (95% confidence interval: −0.80 to −0.07) for NR1 protein reduction. These results represent the first step to a deeper understanding of the region-specific, cell-specific, and stage-specific NMDA receptor hypofunction in schizophrenia, which could be linked to mismatch negativity deficits via transgenic and pharmacological animal models.

Introduction

Mismatch negativity (MMN), an electrophysiological response, is elicited when a regularly repeated invariant sequence of sounds is occasionally interrupted by an infrequent sound deviating in a simple physical dimension such as pitch (frequency) or length (duration) (Naatanen, Kujala, & Winkler, 2011b). MMN signals that the deviant sound was not what was expected and is based on the brain detecting a difference between the deviant sound and the sensory or echoic memory trace encoding the preceding regular sounds—that is MMN indexes an "error" in the implicitly learned or encoded "prediction model" (Naatanen, Jacobsen, & Winkler, 2005). MMN reflects automatic or pre-attentive sensory processing and is elicited regardless of whether the subject is paying attention to the sounds. The generation (sources) of MMN include activation within primary auditory cortex (Heschl's gyrus) and non-primary auditory cortex (superior temporal gyrus [STG] or auditory association areas): it is regarded as a sensitive index of central auditory system plasticity (Naatanen, 2008). Hence, the discovery of MMN deficits (particularly reduced amplitude) in schizophrenia reinforced the notion that the pathophysiology of this disease specifically affects multiple aspects of cortical plasticity (Baldeweg & Hirsch, 2015)

Deficits in MMN are evident at all stages of schizophrenia: prodromally (Bodatsch, Brockhaus-Dumke, Klosterkotter, & Ruhrmann, 2015), at first episode (Atkinson, Michie, & Schall, 2012; Nagai et al., 2013; Todd et al., 2008) and in late stage disease (Umbricht & Krljes, 2005) irrespective of whether patients are taking antipsychotic medication or not (Catts et al., 1995; Korostenskaja et al., 2005; Umbricht et al., 1999). In early-stage schizophrenia, duration-deviant MMN deficits are more apparent than frequency-deviant MMN deficits (Atkinson et al., 2012; Nagai

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et al., 2013; Todd et al., 2008) whereas patients with late-stage schizophrenia consistently show deficits in frequency-deviant MMN as well as duration-deviant MMN (Atkinson et al., 2012; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Todd et al., 2008; Umbricht & Krljes, 2005), though the relationship between stage-of-illness and deviant type needed to elicit MMN deficits has recently been challenged (Hay et al., 2015). Support for MMN as "a breakthrough biomarker" for psychotic disorders (Light & Naatanen, 2013) are findings of robust relationships between MMN deficits and the most consistent features of schizophrenia including psychosocial deterioration (Light & Braff, 2005; Rasser et al., 2011; Rissling et al., 2014; Wynn, Sugar, Horan, Kern, & Green, 2010), cognitive deficits (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Kaur, Battisti, Ward, Ahmed, Hickie, & Hermens, 2011; Kawakubo et al., 2006; Kiang et al., 2007; Miyanishi, Sumiyoshi, Higuchi, Seo, & Suzuki, 2013; Naatanen et al., 2011a), and reduced gray matter volumes affecting mainly superior temporal and prefrontal cortex (PFC) (Rasser et al., 2011). Longitudinally progressive increases in MMN deficits correlate with progressive reduction of auditory cortical volumes (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007). Strengthening the evidence that MMN deficits reflect schizophrenia-specific pathophysiology are studies showing MMN deficits have predictive value in identifying individuals with prodromal symptoms who in fact transition to psychosis (reviewed by Naatanen, Shiga, Asano, & Yabe, 2015). Therefore, understanding the neural basis of MMN could shed light on disease processes.

The major cortical sources for MMN are located bilaterally in primary and secondary auditory cortex (Alho, 1995), though extending to a broader frontal, temporal, and parietal network (Fulham et al., 2014). Intra-cortical recordings in the macaque suggest that deviant-related negativity in the MMN response is generated in lamina II/III of the auditory cortex (Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994). Dynamic causal modeling has provided evidence that MMN deficits in schizophrenia relate primarily to impaired connectivity within primary auditory cortex, and secondarily to impaired connectivity between prefrontal and auditory areas (Dima, Frangou, Burge, Braeutigam, & James, 2012). MMN deficits appear to reflect problems in encoding rather than retention of the sensory trace (Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; March et al., 1999). Deficits in schizophrenia can best be explained by the MMN amplitude reaching asymptote at an earlier potential (or lower ceiling) thereby reducing the dynamic range with which the brain can represent the environment (reviewed in Todd, Michie, Schall, Ward, & Catts, 2012).

Pharmacological studies using phencyclidine (PCP) and its analogues in both animals and humans show that the memory-based comparison process underlying MMN is critically dependent on the activity of *N*-methyl-D-aspartate (NMDA) receptors (Ehrlichman, Maxwell, Majumdar, & Siegel, 2008; Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Kreitschmann-Andermahr et al., 2001; Tikhonravov et al., 2008; Umbricht et al., 2000). PCP and its analogues, ketamine and dizocilpine (MK-801), bind at the intra-channel site of the NMDA receptor to prevent calcium ion influx into the cell. Both pyramidal cells and interneurons express functional NMDA receptors (Monyer, Burnashev, Laurie, Sakmann, & Seeburg, 1994). Animals administered non-competitive NMDA receptor antagonists show homologous behavior and cognitive deficits to the PCP-induced psychotomimetic effects observed in healthy human volunteers and individuals with schizophrenia (reviewed in Catts & Catts, 2010). Insights into the neuronal mechanisms underlying PCP-induced psychotomimetic effects have been obtained from in vivo electrophysiological studies, which demonstrate that single dose administration of NMDA receptor antagonists induces sustained large increases in prefrontal excitatory firing and release of glutamate by blocking the activity of inhibitory interneurons (Homayoun & Moghaddam, 2007; Moghaddam & Javitt, 2012). It is thought that blockade of NMDA receptors preferentially acts on fast spiking GABAergic interneurons because these neurons have a more depolarized membrane potential and consequently more open NMDA receptor channels (Moghaddam & Javitt, 2012). Disinhibition of pyramidal cell firing in turn leads to breakdown of synchronised connectivity between neuronal assemblies intra-cortically and excessive cortical discharge to subcortical centres (Marin, 2012). These observations have been incorporated into the NMDA receptor hypofunction model of schizophrenia, which proposes a functional deficit of NMDA receptor predominantly affecting interneurons and resulting in a loss of GABAergic inhibitory control over glutamatergic pyramidal cells (Gordon, 2010). The PCP model and neuron-specific NMDA receptor subunit expression knock-out animal models suggest that a deficit in either interneurons or pyramidal cells is sufficient to create a hyper-excited cortex (Billingslea et al., 2014; Carlen et al., 2012; Korotkova, Fuchs, Ponomarenko, von Engelhardt, & Monyer, 2010; Tatard-Leitman et al., 2015). The literature also supports a staged glutamatergic pathology in which initial hyper-excitability has downstream compensatory consequences, which may lead to hypo-excitability eventually.

The first study to demonstrate the sensitivity of MMN to NMDA receptor function was conducted in the rhesus macaque, which showed a dose-dependent reduction in MMN following local intra-auditory cortical infusion of PCP (Javitt et al., 1996) and no significant effect of PCP on response to the repetitive sounds (standards). In humans, dose dependent reductions of MMN amplitude after a single injection of ketamine have been consistently reported (reviewed in Todd, Harms, Schall, & Michie, 2013). Dynamic causal modeling applied to data from one acute ketamine challenge study in healthy humans (Schmidt et al., 2013) indicated that ketamine selectively reduced the normal increase in synaptic plasticity in the forward connection between left primary auditory cortex and left STG in response to the deviant tones. This appears to be somewhat in contrast with late-stage schizophrenia which is principally thought to be associated with reduced intrinsic connections within primary auditory cortex and significant alteration in prefrontal STG connections (Dima et al., 2012). Analogous MMN deficits have been found in rodent models of NMDA receptor hypofunction, either genetically- (e.g., Featherstone et al., 2015b) or pharmacologically-induced (e.g., Sivarao, 2015). These studies are reviewed elsewhere (Harms, 2016). Though there are concerns about the translational validity of MMN in the rodent (Harms, Michie, & Naatanen, 2016), the homology of MMN findings across non-human primates and humans is particularly impressive (Gil-Da-Costa, Stoner, Fung, & Albright, 2013; Javitt et al., 1996). In summary, there is now general acceptance that NMDA receptor-related neurotransmission is critical for the generation of MMN and that pre-clinical models of NMDA receptor hypofunction are associated with MMN deficits similar to those observed in schizophrenia. The question this research raises is: "how strong is the evidence that NMDA receptor hypofunction is central to the pathophysiology of schizophrenia?".

Converging evidence from several distinct lines of research suggests that NMDA receptor hypofunction may contribute to the expression of schizophrenia. Firstly, there are clinical studies of the deleterious behavioral effects of non-competitive NMDA receptor antagonists, with evidence of chronic use of PCP inducing psychotic disorder beyond the acute symptoms of intoxication (reviewed in Catts & Catts, 2010). Epidemics of PCP abuse in the U.S.A. during the 1960s and 1970s were regionally and temporally discrete, demonstrating a consistent association between heavy PCP use and epidemics of first admission schizophrenia, with most admissions occurring in young people with neither family history of schizophrenia nor displaying other premorbid risk factors (Fauman & Fauman, 1978; Luisada, 1978; Pearlson,

1981; Peterson and Stillman, 1978). Secondly, further evidence for the involvement of NMDA receptor hypofunction in schizophrenia comes from the recently described NMDA receptor encephalitis (Dalmau et al., 2007), in which individuals with high CSF titers of autoantibodies against NMDA receptor subunits develop psychosis (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). In vitro studies suggest that antibodies against the NMDA receptor cause receptor endocytosis indiscriminately of neuronal type (Moscato et al., 2014). Thirdly, enhancing NMDAR function via increasing availability of co-agonists has efficacy in at least a subgroup of patients in clinical trials in schizophrenia (Kinon, Millen, Zhang, & McKinzie, 2015; Tuominen, Tiihonen, & Wahlbeck, 2005) though not all studies show this effect (Carpenter et al., 2005). Fourthly, the serine racemase knock-out mouse (a model of NMDA hypofunction) has a schizophrenia-related phenotype with impaired long-term potentiation, reduced hippocampal volume, and impaired memory (Balu et al., 2013). Finally, NMDA receptor involvement in schizophrenia is suggested by genetic studies, which implicate not only NMDA receptor subunits directly, but also multiple other molecules involved in glutamatergic signaling (Fromer et al., 2014; Purcell et al., 2014). The largest genome wide association study in schizophrenia to date identified genetic linkage to an intronic single nucleotide polymorphism within the GRIN2A gene (Ripke et al., 2014) encoding the NR2A NMDA receptor subunit. Analyses of de novo copy number variations also implicate NMDA receptors, with enrichment of nonsynonymous polymorphisms and loss of function mutations in the GRIN2A gene in individuals with schizophrenia (Fromer et al., 2014; Kirov et al., 2012). That is, there is clinical, experimental, and genetic evidence that NMDA receptor hypofunction is sufficient to induce a phenotype resembling schizophrenia. However, this evidence does not indicate whether NMDA receptor hypofunction is a necessary component of the pathophysiology nor does it clarify the specific brain mechanism causing NMDA hypofunction at a cellular, network, or systems level. In particular, this evidence does not clarify whether NMDA receptor hypofunction is due to an endogenous abnormality of the receptor itself.

The NMDA receptor consists of four subunits, two of which must be the obligatory NR1 subunit for the receptor to be functional, whereas the other two subunits can be any of four NR2 or two NR3 subunits. The NR1 subunit binds glycine and D-serine (Mothet, Le Bail, & Billard, 2015). Expression of the obligatory NR1 subunit is mainly restricted to neurons, due to a consensus neuron restrictive silencer element (NSRE) in exon 1 of the GRIN1 gene (Bai, Norton, Prenger, & Kusiak, 1998; Okamoto, Sherman, & Lipton, 1999). In human cortex, NR1 expression increases from low prenatal levels to a peak at 11–15 years of age and remains relatively stable into adulthood (Catts et al., 2013; Henson et al., 2008). The NR2 subunits (NR2A, NR2B, NR2C and NR2D) bind glutamate. NR2A and NR2B subunits predominate in the adult cortex and are expressed in both interneurons and pyramidal cells (Monyer et al., 1994). In human brain, NR2B expression peaks around birth and decreases in parallel with an increase in NR2A expression (Catts et al., 2013; Law et al., 2003). The resulting decrease in NR2B/NR2A ratio across the lifespan is thought to be responsible for decreased plasticity associated with maturation and aging (Crair & Malenka, 1995). Cortical NR2C and NR2D expressions appear to be mainly restricted to different subsets of interneurons (Monyer et al., 1994; Standaert, Landwehrmeyer, Kerner, Penney, & Young, 1996) and these subunits confer low sensitivity to magnesium blockade of the receptor, resulting in a rapid response to depolarisations (Clarke & Johnson, 2006) and heightened susceptibility to channel blockers, such as PCP analogues (Kotermanski & Johnson, 2009). Human cortical NR2D expression is highest at birth (Catts et al., 2013; Choi, Zepp, Higgs, Weickert, & Webster, 2009), whereas human cortical NR2C expression over the lifespan remains to be fully characterised, perhaps owing to its relatively low expression in cortex relative to the cerebellum (Karavanova, Vasudevan, Cheng, & Buonanno, 2007). The NR3 (NR3A and NR3B) subunits bind glycine, and therefore are unique in forming excitatory glycine receptors when co-expressed with NR1 (Chatterton et al., 2002). In the human PFC, NR3A expression is highest at birth and decreases steadily into adulthood (Catts et al., 2013). NR3B is less well characterised in humans, but studies of rodent brain indicate that there is ubiquitous expression of this subunit in multiple neuron subtypes in the forebrain, and that the expression gradually increases with age (Low & Wee, 2010). Thus, not only do the various NMDA receptor subunits confer unique properties to the NMDA receptor complex, they are differentially expressed according to the age of the organism, brain region, and neuronal type. It is important to consider the many possible permutations and location of expression of the NMDA receptor, as each may uniquely contribute to the development of schizophrenia and to generation of MMN amplitude.

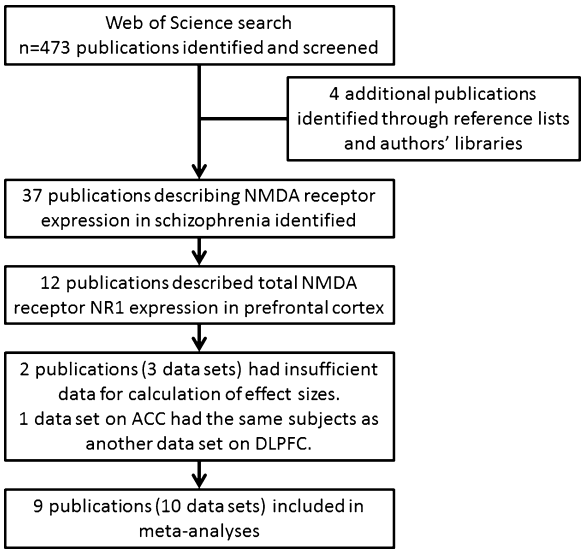

Fig. 1. Identification of literature for qualitative review and meta-analysis. Data collections that quantified the total expression of the obligatory NMDA receptor subunit NR1 in the prefrontal cortex of people with schizophrenia were used to determine effect sizes, which were entered into meta-analyses, with two exceptions. One data collection on NR1 mRNA and two on NR1 protein were excluded from meta-analyses because insufficient data were available for calculation of effect sizes (Dracheva et al., 2001; Emamian et al., 2004). A data collection (Kristiansen et al., 2006) on protein expression in the anterior cingulate cortex (ACC) was excluded because the subjects overlapped with another dataset on the dorsolateral prefrontal cortex (DLPFC) presented in the same publication.

Without knowing which cell types are implicated in generating MMN amplitude and a detailed description of region-specific, cell-specific, and stage-specific changes in NMDA receptor function in schizophrenia, it is difficult to link MMN abnormalities to the glutamatergic pathology in schizophrenia. Even basic information on whether there are expression deficits of the NMDA receptor subunits themselves in brains of individuals with schizophrenia, and if so, which receptor subtypes are the most affected, remains controversial despite recent major narrative reviews of the morphological and molecular evidence in support of a cortical glutamatergic dysfunction in schizophrenia (Featherstone et al., 2015a; Gonzalez-Burgos & Lewis, 2008; Hu, MacDonald, Elswick, & Sweet, 2015; Javitt & Sweet, 2015; Moghaddam & Javitt, 2012). As an important step in addressing this knowledge gap, here we present the first published quantitative review by meta-analysis of NMDA receptor subunit expression in postmortem brain from individuals with schizophrenia, with the hypothesis of reduced cortical NMDA receptor expression in schizophrenia.

1. Materials and methods

1.1. Study selection

Primary studies on the expression of NMDA receptor subunits in patients with schizophrenia were identified from electronic bibliographic searches of Web of Science throughout the period of 1 January 1990–29 April 2015 using the search string '(schizophrenia OR schizophrenic) AND (NMDA* OR ionotropic OR GRIN*) AND (human OR patient OR postmortem OR post-mortem) AND expression'. Studies were also sourced from reference lists of published articles and from the authors' personal libraries. Authors were contacted for further details when published data did not allow study inclusion in the meta-analysis. All identified studies describing cortical NMDA receptor subunit mRNA or protein expression in people with schizophrenia are tabulated in Table 1.

1.2. Meta-analysis

To achieve sufficient study homogeneity and number, we restricted meta-analysis to studies quantifying total NR1 mRNA or protein expression in the PFC of people with schizophrenia (Fig. 1). There were too few studies assessing tissue from the auditory cortex to subject them to meta-analysis. Data were tabulated according to whether the measurement target was mRNA or protein expression. Where mRNA or protein expression was measured in more than one region in the PFC in the same study sample (Kristiansen, Beneyto, Haroutunian, & Meador-Woodruff, 2006), data from the dorsolateral prefrontal cortex (DLPFC) was used in the meta-analysis because this was the region most frequently assessed in other studies that were included. Effect size and confidence intervals were calculated based on the available data, i.e. sample sizes, means and standard deviations. Meta-analysis were carried out using RevMan 5.3.5 (The Cochrane Collaboration, 2014) using random effects model to protect against heterogeneity of sampling. Pooled effect sizes and 95 percent confidence intervals are reported.

2. Results

Our Web of Science search identified 473 unique publications, of which 33 reported on the expression of NMDA receptor subunits in individuals with schizophrenia. An additional four publications were identified from reference lists of the identified papers and from the authors' libraries. Twelve of these 37 publications focused on total NMDA receptor NR1 subunit expression in PFC from people with schizophrenia (Table 1; Fig. 1).

The final meta-analyses of NR1 mRNA and of NR1 protein expressions are displayed in Fig. 2. The five studies of NR1 mRNA included in the meta-analysis consisted of 94 subjects with schizophrenia and 82 control subjects (Table 2). The pooled effect size for these studies was −0.64 (CI −1.08 to −0.20, $p = 0.004$), indicating that the significant decrease in expression of NR1 mRNA in schizophrenia subjects relative to controls is of medium to large effect. The meta-analysis of the five studies of NR1 protein (Table 2), consisting of 95 subjects with schizophrenia and 95 controls, yielded an effect size of −0.44 (CI −0.80 to −0.07, $p = 0.02$),), indicating that the significant decrease in expression of NR1 protein in schizophrenia subjects relative to controls is of medium effect. Inputting these effect sizes into power analyses indicate that more than 30 subjects per group are required to reliably detect statistically significant differences in NR1 expression when using homogenised postmortem brain tissue from medicated chronically ill patients with schizophrenia compared to controls.

Our qualitative review of the NR2 (A, B and D) and NR3A subunits (Table 1) studies suggested there are no consistent statistically significant changes in cortical mRNA expression or protein levels of these subunits. This is not surprising given the small effect sizes detected in our own study (Weickert et al., 2013) for changes in NR2A, 2B and 3A mRNA (0.15–0.24) in schizophrenia subjects compared to controls, which indicates that a much larger sample size ($n \geq 200$/group) is required to reliably detect diagnostic differences in these mRNA expressions if they existed. A notable exception is the diagnostic changes in NR2C, which reached the relatively large effect size of $d = 0.52$ (Weickert et al., 2013). The NR2C subunit mRNA expression decrease in the PFC was statistically significant in all three published studies that examined this subunit (Akbarian et al., 1996; Beneyto & Meador-Woodruff, 2008; Weickert et al., 2013). However, reductions in NR2C mRNA were not evident in studies of temporal lobe regions (see Table 1) (Akbarian et al., 1996; Beneyto, Kristiansen, Oni-Orisan, McCullumsmith, & Meador-Woodruff, 2007). Reductions in NR2C protein were also not observed in DLPFC or anterior cingulate cortex in a study using an elderly cohort (see Table 1) (Kristiansen et al., 2006). In summary, studies of PFC show a fairly robust group-wise decrease in NR1 and NR2C expression in schizophrenia compared to controls with no clear evidence for changes in the other NR2 subunits. However, there is limited investigation of NR3 subunit expression in schizophrenia.

3. Discussion

We show by meta-analysis that expression of NR1 mRNA in the PFC is significantly decreased in subjects with schizophrenia compared to controls, with the decrease being of medium to large effect size. One study that assayed NR1 mRNA expression in the DLPFC (BA46; Dracheva et al., 2001) had to be excluded from the meta-analysis because an effect size could not be calculated. This study of 26 elderly subjects with schizophrenia and 13 elderly controls found an increase in NR1 mRNA in schizophrenia, contrary to the results of our meta-analysis. A comparable study (Sokolov, 1998) that measured NR1 mRNA expression in DLPFC tissue in a similar sized cohort of elderly subjects, from the same Schizophrenia Brain Bank at Mount Sinai School of Medicine, found decreased NR1 mRNA expression. As both studies used quantitative PCR to measure NR1 and may have assayed tissue from overlapping cohort of brains, it is unclear why their results vary from each other.

Our meta-analysis also found that expression of NR1 protein in the PFC is significantly decreased in subjects with schizophrenia compared to controls. Though a similar number of studies were entered into the protein meta-analysis as the NR1 mRNA meta-analysis, the decrease in NR1 protein was of medium effect size, rather than of medium to large effect size as we found for NR1 mRNA. It was necessary to exclude three datasets from our PFC NR1 protein meta-analysis. Two of these datasets were in one publication (Emamian, Karayiorgou, & Gogos, 2004) but had to be excluded because an effect size could not be calculated based on the published data (one dataset yielded no difference in total NR1 protein, and the other a non-significant increase, in subjects with schizophrenia). The third protein study was excluded because of overlap in the brain cohort with a study of DLPFC reported in the same publication (Kristiansen et al., 2006), the latter is included in our current meta-analysis. The excluded study of anterior cingulate cortex found no change in the levels of NR1 2C isoform levels and a significant increase in NR1 2C′ isoform levels in subjects with schizophrenia (Kristiansen et al., 2006).

NR2C mRNA was consistently found to be decreased in the three studies that examined its expression in PFC in subjects with schizophrenia. However NR2C protein was not decreased in the anterior cingulate cortex or DLPFC in an elderly cohort (Kristiansen et al., 2006). Reasons for the inability to replicate the decreased mRNA transcript levels at a protein level include the possibility that NR2C protein, like NR2A and NR2B protein (Henson et al., 2008) is unstable postmortem and therefore diagnostic differences may be more difficult to detect. Also, the molecular techniques used to assay these levels quantitatively are quite distinct and have different levels of sensitivity and amount of variability. That is, quantifying protein by Western blotting is a less precise methodology than quantifying mRNA by real-time PCR and in situ hybridization, and Western blotting may be less sensitive in demonstrating diagnostic differences. Additionally, we found that the NR2C mRNA deficit is more apparent in individuals with a rel-

Table 1
Studies of cortical NMDA receptor subunit expression in schizophrenia, ranked by brain lobes, then publication year.

First author	Year	NR1	NR2A	NR2B	NR2C	NR2D	NR3A	NR3B	Brain region	Methodology	Sz N	Con N
mRNA studies—frontal lobe												
Akbarian	1996	•	•	•	↓	•			Frontal pole	*In situ* hybridisation	15	15
Sokolov	1998	↓[a]							Superior frontal gyrus	qRT-PCR	21	9
Le Corre	2000	•							Middle frontal cortex	*In situ* hybridisation	6	6
Dracheva	2001	↑	•	•					Dorsolateral prefrontal cortex	qRT-PCR	26	13
Mueller	2004						↑		Dorsolateral prefrontal cortex	*In situ* hybridisation	15	15
Woo	2004		↓[b]						Anterior cingulate cortex	*In situ* hybridisation	17	17
Martucci	2006			•					Dorsolateral prefrontal cortex	qRT-PCR	35	35
Beneyto	2008	↓	↓	•	↓	•			Prefrontal cortex	*In situ* hybridisation	15	15
Woo	2008		↑[c]						Anterior cingulate cortex	*In situ* hybridisation	20	20
Weickert	2013	↓	•	•	↓		•		Dorsolateral prefrontal cortex	qRT-PCR	37	37
mRNA studies—temporal lobe												
Akbarian	1996	•	•	•	•	•			Temporal cortex	*In situ* hybridisation	15	15
Humphries	1996	↓							Superior temporal cortex	Slot blot	12	7
Le Corre	2000	↑							Superior temporal cortex	*In situ* hybridisation	6	6
Mueller	2004						•		Inferior temporal cortex	*In situ* hybridisation	15	15
Beneyto	2007	•	•	•	•	•			Perirhinal	*In situ* hybridisation	15	15
Beneyto	2007	•	•	•	•	•			Entorhinal	*In situ* hybridisation	15	15
mRNA studies—occipital lobe												
Le Corre	2000	•							Occipital cortex	*In situ* hybridisation	6	6
Dracheva	2001	↑	↑	•					Occipital cortex	qRT-PCR	26	13
Protein studies—frontal lobe												
Emamian	2004	•							Frontal cortex	Western blotting	10	10
Emamian	2004	•							Frontal cortex	Western blotting	15	14
Toro	2005	•							Orbitofrontal gyrus	Immuno-autoradiography	15	15
Kristiansen	2006	•[d]	•	•	•	•			Dorsolateral prefrontal cortex	Western blotting	13	8
Kristiansen	2006	•[e]							Dorsolateral prefrontal cortex	Western blotting	13	8
Kristiansen	2006	•[d]	•	•	•	•			Anterior cingulate cortex	Western blotting	24	16
Kristiansen	2006	↑[e]							Anterior cingulate cortex	Western blotting	24	16
Hahn	2006	↑[f]							Dorsolateral prefrontal cortex	Western blotting	10	10
Henson	2008	•					•		Dorsolateral prefrontal cortex	Western blotting	15	20
Kristiansen	2010	•[g]		↓[g] •[h]					Dorsolateral prefrontal cortex	Western blotting	13	8
Kristiansen	2010	•[g]		•[g]					Anterior cingulate cortex	Western blotting	13	8
Errico	2013	↓	↓	↓					Prefrontal cortex	Western blotting	15	15
Weickert	2013	↓							Dorsolateral prefrontal cortex	Western blotting	37	37
Protein studies—temporal lobe												
Nudmamud-Thanoi	2004	•							Superior temporal cortex	Western blotting	15	15

• = no statistically significant change↓ = decreased expression↑ = increased expression.
[a] Including several medication free individuals with schizophrenia.
[b] Decrease in GAD67 positive neurons only.
[c] Increase in calbindin positive neurons only.
[d] Measure of the C2 NR1 splice variant.
[e] Measure of the C2′ NR1 splice variant.
[f] Associated with PSD-95 following isolation of post-synaptic density enriched fractions of tissue homogenates.
[g] In endoplasmic reticulum-enriched fraction.
[h] In total homogenate.

Table 2
Detailed demographic data from studies of NMDA receptor subunit expression in prefrontal cortex from individuals with schizophrenia included in the meta-analyses.

First author	Year	Brain region	Methodology	NR1	Sz Sex (F/M)	Con Sex (F/M)	Sz age (years)	Con age (years)	Sz PMI (hours)	Con PMI (hours)
mRNA studies										
Akbarian	1996	Frontal pole	*In situ* hybridisation	•	3/12	3/12	55.2 ± 5.4	57.4 ± 5.3	16.1 ± 2.2	15.1 ± 2.0
Sokolov	1998	Superior frontal gyrus	qRT-PCR	↓[a]	8/13	4/5	73.4 ± 4.2	77. 4 ± 2.7	37.4 ± 7.6	5.4 ± 0.8
Le Corre	2000	Middle frontal cortex	*In situ* hybridisation	•	1/5	1/5	46.6 ± 6.6	48.3 ± 5.6	22.6 ± 4.9	20.3 ± 3.6
Beneyto	2008	Prefrontal cortex	*In situ* hybridisation	↓	6/9	6/9	44.2 ± 13.1	48.1 ± 10.7	33.7 ± 14.6	23.7 ± 10.0
Weickert	2013	DLPFC	qRT-PCR	↓	13/24	7/30	51.3 ± 2.3	51.1 ± 2.4	28.8 ± 2.3	24.8 ± 1.8
Protein studies										
Toro	2005	Orbitofrontal cortex	Immuno-autoradiography	•	6/9	6/9	44.2 ± 13.1	48.1 ± 10.7	33.7 ± 14.6	23.7 ± 10
Kristiansen	2006	DLPFC	Western blotting	•[b]	5/8	5/3	71.8 ± 2.8	79.8 ± 4.7	9.2 ± 1.6	5.1 ± 0.9
Henson	2008	DLPFC	Western blotting	•	5/10	5/15	54.3 ± 4.4	56.7 ± 4.1	21.7 ± 1.3	21.2 ± 1.3
Errico	2013	Prefrontal cortex	Western blotting	↓	7/8	7/8	61.7 ± 4.8	63.3 ± 4.6	57.2 ± 6.5	36.2 ± 5.8
Weickert	2013	DLPFC	Western blotting	↓	13/24	7/30	51.3 ± 2.3	51.1 ± 2.4	28.8 ± 2.3	24.8 ± 1.8

• = no statistically significant change↓ = decreased expression↑ = increased expression DLPFC = dorsolateral prefrontal cortex ± standard error of the mean.
[a] Including several medication free individuals with schizophrenia.
[b] Measure of the C2 and C2′ NR1 splice variants separately.

atively short duration of illness and is less apparent with increased disease duration (Weickert et al., 2013), so it is possible that a decrease in NR2C protein may not be evident in cohorts of elderly individuals with schizophrenia. Taken together, the studies above suggest a NR2C expression deficit could account for NMDA receptor dysfunction in interneurons in schizophrenia, though again it is

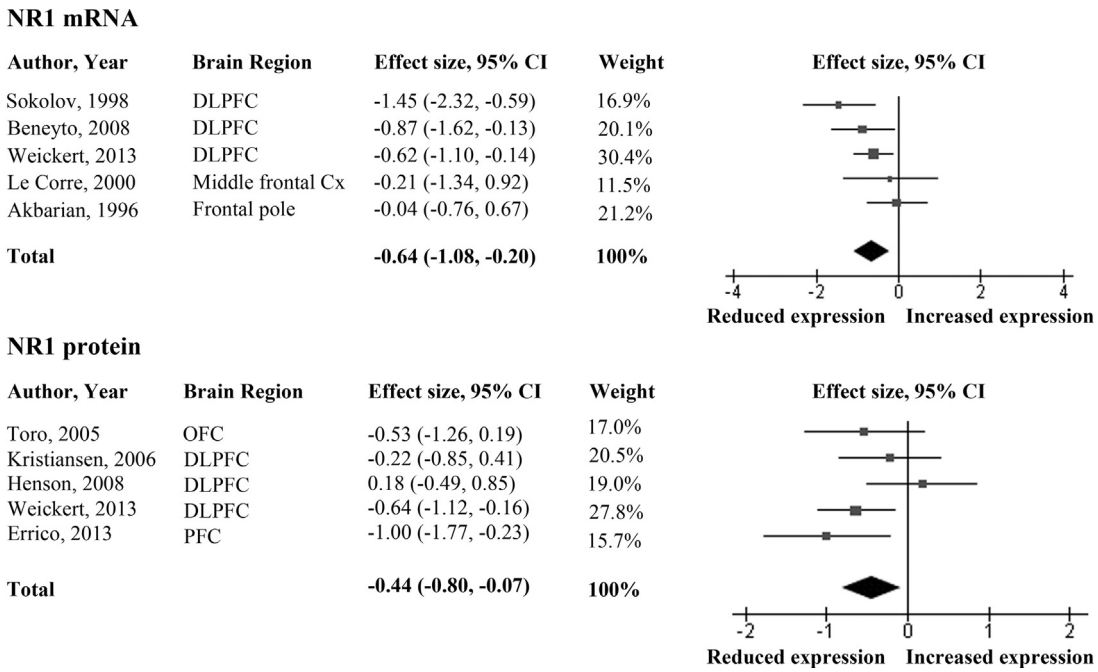

Fig. 2. Meta-analysis of NR1 mRNA and NR1 protein expression levels in prefrontal cortex of individuals with schizophrenia.

unknown what interneuron subtype is most impacted by the NR2C deficit.

While the studies reviewed using total homogenate or film-based in situ hybridization techniques suggest that the NR2A subunit of the NMDA receptor is not greatly altered in people with schizophrenia, two studies of NR2A subunit mRNA in interneurons suggest otherwise. Using double-label in situ hybridization to define interneuron populations, Woo et al. (2004); Woo, Shrestha, Lamb, Minns, and Benes (2008) found a decreased density of NR2A mRNA expressing GAD_{67} positive interneurons, but an increased density in the subset of NR2A and calbindin mRNA-containing neurons in layer II of anterior cingulate cortex. This is noteworthy, as the gene for NR2A has been implicated in the etiology of schizophrenia in large genetics studies (Fromer et al., 2014; Ripke et al., 2014). It also relates to the more general question of which interneuron subtype is specifically affected by NMDA receptor hypofunction in schizophrenia. Several interneuron subtypes have been shown to be impacted in schizophrenia, with somatostatin and parvalbumin having the greatest expression deficits (Beasley & Reynolds, 1997; Cotter et al., 2002; Fung, Fillman, Webster, & Weickert, 2014; Fung et al., 2010; Hashimoto et al., 2008a; Hashimoto et al., 2008b; Lewis, 2000; Morris, Hashimoto, & Lewis, 2008) and calbindin shown to be increased in several studies (Daviss and Lewis, 1995; Fung et al., 2014; Fung et al., 2010; Woo et al., 2008). Our group has recently shown that somatostatin interneuron density is decreased in layer II of the orbitofrontal cortex, and that this is associated with cell death receptor expression (Joshi, Catts, Olaya, & Shannon Weickert, 2015), making somatostatin interneurons a plausible candidate for the NR2A deficit. However, maturation of parvalbumin-positive interneurons, and not somatostatin-positive interneurons, has been shown to be selectively affected by chronic blockade of NR2A (Zhang & Sun, 2011), making parvalbumin-positive interneurons an interesting candidate to link to NMDA receptor dysfunction. Examination of the density of double-labelled NR2A mRNA and somatostatin-positive or parvalbumin-positive interneurons is warranted, in order to localize the putative NR2A deficit to one or more interneuron subtypes.

With expression deficits identified in possibly up to three different NMDA receptor subunits (NR1, NR2A and NR2C), the next question arising is whether different individuals have different NMDA receptor pathologies or whether expression deficits in two or more subunits co-occur in the same individual with schizophrenia. If there is co-occurrence of deficits in two or more subunits, the next questions are whether both deficits arise at once, or could one be a consequence of the other, and do deficits in two or more subunits co-occur in the same cells, or in different cell types? While these questions may be most readily addressed at the mRNA level using dual-label in situ hybridization, there is also a role for protein studies, as these show altered trafficking to (Kristiansen, Patel, Haroutunian, & Meador-Woodruff, 2010), and signaling at (Catts, Derminio, Hahn, & Shannon Weickert, 2015; Hahn et al., 2006), the synapse in cortex from people with schizophrenia, thus demonstrating a deficit in receptor function.

Clinical and preclinical evidence supports stage-specific glutamatergic abnormalities in schizophrenia. Marsman et al. (2013) reported a major meta-analysis of proton magnetic resonance spectroscopy (^{1}H-MRS) studies of brain glutamine concentrations in patients with schizophrenia. Because the majority of physiological active glutamate is derived from glutamine, high levels of glutamine is usually indicative of high glutamate levels and high glutamatergic activity, though theoretically they could be due to decreased catabolism of glutamine to glutamate. The ^{1}H MRS meta-analysis found that overall prefrontal glutamate was decreased and glutamine levels were increased in schizophrenia (Marsman et al., 2013). When studies were divided into those assessing early-stage versus late-stage schizophrenia, the abnormalities in prefrontal glutamine levels were in opposite directions in the two groups. The four studies that assessed early-stage patients revealed a large increase in prefrontal glutamine levels (effect size in the order of 1.0), while the four studies assessing late-stage schizophrenia showed decreases (effect size in the order of 0.5). Thus, early-stage schizophrenia appears to be associated with excessive glutamatergic activity whilst late-stage schizophrenia shows deficient glutamatergic activity.

The results of ketamine challenge studies in humans could be interpreted similarly. When the results from single-dose ketamine

studies (that is, brief NMDA receptor antagonist exposure) are compared with findings in chronic PCP abusers (repeated and long-term NMDA receptor antagonist exposure), single-dose ketamine induces prefrontal hyper-activation (Rowland et al., 2005; Stone et al., 2012) whereas chronic PCP abuse is associated with prefrontal hypo-activation (Hertzman, Reba, & Kotlyarov, 1990; Wu, Buchsbaum, Potkin, Wolf, & Bunney, 1991). A study of PFC connectivity in healthy human volunteers after a single dose of ketamine found hyper-connectivity similar to that observed in individuals at high risk of psychosis and early psychosis patients, but not in those with chronic schizophrenia (Anticevic et al., 2015). In rodent studies, single dosing with NMDA receptor antagonists causes increased activation in frontal regions (Duncan, Leipzig, Mailman, & Lieberman, 1998), whereas repeat dosing causes reduced prefrontal activation (Cochran et al., 2003). Thus, the clinical and pre-clinical research indicates that only brief exposure to NMDA receptor antagonists produces a picture consistent with the NMDA receptor hypofunction model of schizophrenia (with pyramidal cell disinhibition and cortical hyper-activity) whilst prolonged exposure produces a picture inconsistent with the original model (implicating hypo-activation in pyramidal cells). This interpretation is consistent with the ^{1}H MRS data in schizophrenia providing convergent support for disease stage-dependent differences in glutamatergic abnormalities. We propose a revised NMDA receptor hypofunction model of schizophrenia where the early stages of schizophrenia are characterized by an NMDA receptor deficit predominantly in interneurons (NR2A and/or NR2C), which leads to under-activity of the NMDA receptor on interneurons and thus less inhibition and more excitation of pyramidal neurons. This in turn eventually may lead to a compensatory decrease in NMDA receptor expression in pyramidal neurons (NR1) as the disease progresses and may be in response to increased glutamate over time and enduring low level but cumulative excitotoxicity. This proposal requires specification of the cell types affected early and late in the course of schizophrenia to determine primacy and directionality. Further support for the revision of the original NMDA receptor hypofunction model of schizophrenia, especially in terms of the need to also incorporate a deficiency of NMDA receptors in pyramidal cells, is provided by the research using postmortem tissue homogenate (Sokolov, 1998; Weickert et al., 2013) and film-based in situ hybridization (Akbarian et al., 1996; Beneyto & Meador-Woodruff, 2008; Le Corre, Harper, Lopez, Ward, & Catts, 2000). As interneurons account for only about 20% of all neurons in the PFC (Marin, 2012) and have lower abundance of NR1 protein than pyramidal cells (at least at the synapse; Nyiri, Stephenson, Freund, & Somogyi, 2003), then a decrease in cortical NR1 protein expression of up to 36% in schizophrenia (Weickert et al., 2013) is unlikely to be restricted solely to interneurons.

We have demonstrated by meta-analysis direct postmortem evidence of NMDA receptor hypofunction in schizophrenia, at least in the PFC. We have also argued that NMDA receptor-related neurotransmission is critical for the generation of MMN and that pre-clinical models of NMDA receptor hypofunction are associated with MMN deficits similar to those observed in schizophrenia. We now address the unanswered question: can we link the two lines of research to create a framework for elucidating the neuropathology of schizophrenia through an understanding of the neurobiology of MMN? Within each level of description, schizophrenia and MMN have corresponding characteristics to suggest that an understanding of one will inform the nature of the other. Structurally, the most dominant pattern of reduced grey matter volume associated with schizophrenia affects the STG and prefrontal regions (Gupta et al., 2015), the same neuroanatomical areas that house primary MMN generators, and not surprisingly in schizophrenia MMN deficits correlate with grey matter reductions in the STG (Rasser et al., 2011; Salisbury et al., 2007). Functionally, MMN activates the same networks (Alho, 1995; Fulham et al., 2014) that show altered connectivity in schizophrenia (Friston & Frith, 1995; Liu et al., 2008): these networks are also altered in relation to the MMN deficits in schizophrenia (Gaebler et al., 2015). At the level of circuitry, the same intra-cortical and inter-cortical circuits involved in MMN generation (Javitt, 2015; Javitt & Sweet, 2015; Todd et al., 2013) appear to be altered in schizophrenia (Lewis, 2012; Moghaddam & Javitt, 2012). At the cellular level, models for MMN generation are impressively similar to models for schizophrenia, namely as an alteration in the balance between glutamatergic (pyramidal cell) excitation and GABAergic (interneuronal cell) inhibition (reviewed in Todd et al., 2013). While this formulation is far too imprecise to guide a research program aimed at linking the two lines of research, it does clearly indicate that the focus of such a program should be on comparing and contrasting NMDA receptor dysfunction in specific interneurons and in pyramidal cells in the cortex.

Reinforcing this notion is the literature on EEG oscillatory activity (resting state and steady state oscillations), particularly the gamma band frequency band (25–100 Hz but typically 40 Hz). Fast-firing parvalbumin positive (inhibitory GABAergic) interneurons are essential for the production of synchronised neuronal firing and network oscillations (Gonzalez-Burgos & Lewis, 2008), but recent evidence emphasises interactions between interneurons and pyramidal cells and the centrality of the role of the NMDA receptor in production of cortical oscillations (Cardin et al., 2009; Carlen et al., 2012; Carracedo et al., 2013; Kirli, Ermentrout, & Cho, 2014; Sivarao, 2015). In schizophrenia: task-induced gamma-band oscillations have reduced power and synchronisation (reviewed in Andreou et al., 2015); steady state auditory evoked potentials have reduced power, particularly in the gamma frequency (O'Donnell et al., 2013); and resting state gamma band connectivity increased (Andreou et al., 2015). Importantly, MMN and its schizophrenia-related deficits are tightly linked with oscillatory activity both at the gamma (Ballesteros et al., 2013; Nicol et al., 2012) and theta (Kaser et al., 2013) frequencies, these frequencies being highly inter-dependent in response to novel stimuli (Haenschel, Baldeweg, Croft, Whittington, & Gruzelier, 2000). Despite this rich electrophysiological literature and an emerging picture of the key molecular and cellular abnormalities in schizophrenia, we are still faced with the need to link the currently poorly linked pieces of evidence in order to initiate a systematic investigation of the pathophysiology of MMN in schizophrenia.

In light of the correspondence of within-level mechanistic features that MMN generation and schizophrenia have in common, what recommendations does the literature support in relation to a strategic or coordinated research approach to linking findings across one level to another? First an across-species translational approach is suggested, especially in relation to phenotype assessment. Ideal measures are ones that can be made in humans, non-human primates, and rodents. Examples are spatial memory, task-independent connectivity (e.g., resting-state gamma-band connectivity analysis; Andreou et al., 2015), and neuronal synchrony (e.g., the auditory steady-state response; Sivarao, 2015) measures, and of course MMN. Second, models that link mechanisms across at least two levels of description are essential. Examples of such model building include computational studies of how synaptic NMDA receptor hypofunction might give rise network level oscillatory deficits indexed in entrainment paradigms (Kirli et al., 2014) and MMN (Wacongne, Changeux, & Dehaene, 2012) or experimental studies linking theta oscillatory activity to somatostatin expressing (Womelsdorf, Valiante, Sahin, Miller, & Tiesinga, 2014) and multipolar bursting-type (Blatow et al., 2003) GABAergic interneurons. In relation to recording MMN, a number of recommendations have been made (Todd et al., 2013) including, (1) use of the random control stimulus sequence to separate adaptation and deviance detection processes, (2) use of a very rare

deviant event at least in clinical studies, (3) use of epidural-placed electrodes in rodent studies, and (4) the reporting of standard and deviant waveforms separately in addition to difference waveforms. Todd et al. (2013) drew attention to the dose-dependency of NMDA receptor antagonist effects and recommended use of a larger dosage range in pharmacologically-induced preclinical models. An emerging theme in the MMN literature is the value of source-level modelling of MMN measures (Fulham et al., 2014; Rissling et al., 2014). The effect of different source modelling methodologies is illustrated by studies that implicate gamma band oscillation in the MMN-evoked response (Ballesteros et al., 2013; Nicol et al., 2012) versus those that implicate theta band oscillations (Fuentemilla, Marco-Pallares, Munte, & Grau, 2008; Kaser et al., 2013; Ko et al., 2012). Thirdly, there is a need for longitudinal studies of human development and disease and developmentally and pathophysiologically relevant animal models. The literature draws attention to the need to investigate a range of animal models that can assist in localising the NMDA receptor hypofunction to specific cell types and elucidate the temporal order of the glutamatergic pathologies observed in postmortem studies of individuals with chronic schizophrenia. Validated models are now available to assess the NMDA receptor hypofunction across both interneurons and pyramidal cells (Featherstone et al., 2015b), in interneurons only (Billingslea et al., 2014; Carlen et al., 2012; Korotkova et al., 2010) or in pyramidal cells only (Tatard-Leitman et al., 2015).

Our review also highlights the importance of stage of illness effects: in clinical studies, with contrasting results for deviance type elicitation of MMN (Michie et al., 2000); resting state gamma band connectivity studies (Andreou et al., 2015); source modelling of MMN (Fulham et al., 2014); and in pharmacological models of early-stage (single dose NMDA receptor antagonist) and late-stage (repeated dose NMDA receptor antagonist) disease (Catts & Catts 2010). Importantly, stage-of-illness appears to affect therapeutic response to glutamatergic therapy (Kinon et al., 2015). Our meta-analysis revealed a poverty of postmortem studies of the NMDA receptor in the auditory cortex in schizophrenia and the need for postmortem researchers to broaden their research focus beyond prefrontal and hippocampal regions to include molecular studies of NMDA receptor in the auditory cortex. Research focus may need to go beyond the NMDA receptor to include its synaptic and dendritic partners (e.g., Shelton et al., 2015) as suggested by genetics studies (Fromer et al., 2014; Purcell et al., 2014). We also highlighted the limitations of molecular studies in schizophrenia reported to date, which have mainly assayed homogenized tissue. There is an urgent need for fine grained approaches which allow specification of NMDA receptor abnormalities to specific subunits in specific cells, layers and regions at specific stages of illness. On a more positive note, our meta-analysis showed for the first time the overall consistency of the direct postmortem evidence for deficits in NMDA receptor expression in schizophrenia, a necessary first step in any endeavor to link these abnormalities to either MMN deficits or the pathophysiology of schizophrenia.

In conclusion, while the field has begun to identify what may be consistent molecular changes in NMDA receptor expression in chronically ill patients with schizophrenia, we still seem a long way off from directly linking the observed NMDA receptor hypofunction in schizophrenia with MMN changes. Most of the postmortem studies on NMDA receptor expression in schizophrenia done to date have serious limitations, especially in terms of power, and results are understandably inconclusive. But the most striking limitation of the research to date is that few studies have attempted to localize deficits in NMDA receptor expression to either interneurons or pyramidal cells or investigate whether changes occur in the same people, in the same cell or change according to stage of illness. While mice with a ~30% reduction in NR1 expression across both interneurons and pyramidal cells show a decreased MMN amplitude (Featherstone et al., 2015b), it remains unknown whether reduced expression of NMDA receptors in interneurons or in pyramidal cells on their own is sufficient to elicit reduced MMN amplitude as seen in individuals with schizophrenia. If so, would these effects be recapitulated by gene deletion in the auditory cortex alone, or is a cortex-wide expression deficit necessary? What are the specific NMDA receptor subunits and downstream signaling processes involved in these effects? The answers to questions such as these are essential in order to link molecular abnormalities in schizophrenia to mismatch negativity deficits.

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