

NMDA Receptors and Epileptogenesis in Human Cortical Dysplasia: A Meta-analysis

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Abstract

Cortical dysplasia (CD) is a cerebral disorder caused by disruption of neuronal migration and disorganization of cortex development. The mechanisms of epileptogenicity in CD have been investigated yet still remain unknown. One of the possible reasons is the changes of expression of N-methyl-D-aspartate (NMDA) receptors. Emerging evidences have shown that NR2A/B in the region of focal cortical dysplasia (FCD) cortex may play an important role in the risk of epilepsy and NR1 remains unchanged during epilepsy pathogenesis but recent published studies showed inconclusive results. This meta-analysis aimed to derive a more precise estimation of the associations between NMDA receptors and CD related epilepsy risk. A literature search of PubMed, Embase, Web of Science and China BioMedicine (CBM) databases was conducted on articles published before July 1st, 2013. Crude odds ratio (OR) with 95% confidence intervals (CI) were calculated. Ten studies were included with a total of 170 subjects. 104 of them were diagnosed with FCD and epilepsy while 66 resected specimen were non-CD cerebral tissue. The meta-analysis results showed that the expression of NR2B is increased in FCD cortex, which is indicated might be an important role in FCD related epilepsy pathogenesis. On the other hand, the expression of NR1 showed no significant difference between FCD group and controls, therefore the NR1 might not be a relevant factor. The function of NMDA receptors in development of FCD is not clear yet, a further explanation is still needed. We assume that NMDA receptors might interact with other substances in different signaling pathways to initiate and promote the epileptogenic process. Meanwhile we suggest more research to focus on the causal relationship between NMDA receptors and epileptogenesis.

Keywords: NMDA receptors; Epilepsy; Cortical dysplasia; Meta-analysis

Introduction

Cortical dysplasia is a cerebral disorder caused by disruption of neuronal migration and disorganization of cortex development. They are histologically characterized by changes in neocortical microarchitecture: disturbance of laminar organization, ectopic neurons, and cellular abnormalities such as cytomegalic or dysmorphic neurons [1]. CDs are increasingly recognized as a frequent cause of drug-resistant neocortical epilepsy [2-4], and its surgery outcome is normally worse than other pathologies [5,6]. The mechanisms of epileptogenicity in CD were well documented yet still remain unknown [2,7-8]. One of the possible causes that may lead to abnormal neuronal discharges is an imbalance between the amount of excitatory and inhibitory neurotransmitter receptor such as glutamate N-methyl-D-aspartate (NMDA) receptor [9,10].

In the past decade, the role of NMDA receptor, a excitatory neurotransmitter receptor, as a substrate for cortical hyperexcitability has been investigated [11-14]. Several studies have reported differential changes in NMDA-receptor density and subunit composition in human epilepsy specimens [10,15-17]. And the majority support the theory that the expression of NMDA receptors especially the subunit NR2A/B in epileptogenesis cortex is increased [10,15,17-19].

The reason NMDAR might be a cause of epileptogenesis is because Ca²⁺ could permeate through it and acts as a second messenger in signaling cascades attributed to synaptic plasticity meanwhile it could also display slow kinetics with a long inactivation time constant [20].

However in epileptogenesis related to cortical dysplasia, the expression of NMDA receptors remains controversial about its role and mechanism. Research showed increased NMDAR2A/B subunit protein expression and its coassembly with NR1 subunits dysplastic cortex

[10,15,16,21]. The increased heteromeric coexpression of NR1 and NR2 subunits was hypothesized to account for the enhanced NMDA hyperexcitability in epileptic cortex.

In view of the conflicting results from previous studies, we performed a meta-analysis of all available data to evaluate the association between NMDA receptors and epileptogenesis in human cortical dysplasia.

Materials and Methods

Literature search strategy

Relevant papers published before July 1st, 2013 were identified through a search in Pubmed, Embase, Web of Science and China BioMedicine (CBM) databases using the following terms: ("malformations of cortical development" or "cortical development malformation" or "cortical dysplasia" or "cortical dysplasias" or "cerebral cortical dysplasia" or "focal cortical dysplasia") and ("epilepsy" or "seizures" or "seizure disorder" or "epileptic seizures" or "single seizures" or "cryptogenic epilepsy" or "awakening epilepsy") and ("Receptors, N-Methyl-D-Aspartate" or "NMDA Receptor Ionophore Complex" or

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“N-Methyl-D-Aspartate Receptors” or “N-Methylaspartate Receptors” or “NMDA Receptors” or “Glutamate Receptors”). The references from the eligible articles or textbooks were also reviewed to find other potential sources. Disagreements were resolved through discussions between the authors.

Inclusion and exclusion criteria

1. Types of research design: Studies included in our meta-analysis have to be either randomized blind case-control or cohort studies focused on the association between NMDA receptors and epileptogenesis in human cortical dysplasia; other types should be excluded.
2. Participants: (a) diagnostic criteria: all patients diagnosed with cortical dysplasia should have clinical, radiological and neuropathological confirmations as well as manifestation and electroencephalogram (EEG) evidence for epilepsy. Patients with any other acute or chronic disease, any other progressive neurological disorder or deficiency of liver or kidney function, pregnancy should be ruled out of this study. (b) Basic characteristics of patients: age, gender, race, age of seizure onset, duration of epilepsy, frequency of seizure attacks, whether or not with secondary general tonic-clonic seizures, history of febrile convulsion, type of epilepsy is not limited as a criteria in this study.
3. Interventions and comparisons: we enrolled patients with resection of CD tissue displaying epileptiform discharges as experimental group. Brain tissue with no EEG evidence for abnormal discharges is considered as control group.
4. Outcomes: Results coming from experimental methods as immunocytochemistry and immunoblot analysis for quantifying NR1, NR2A/B or coassembling of both NR1 and NR2A/B should be extracted and analyzed. Experiments on other objects or using other methods should be ruled out.

Additionally, publications with incomplete data; meta-analyses, case reports, letters, reviews or editorial articles should not be included in our study.

Literature screening

The selection process was conducted strictly according to the inclusion and exclusion criteria by two independent authors simultaneously. Cross-verification through two authors to rule out duplicates of publications was our primary step. Then the two investigators screened titles and abstracts to identify potentially relevant citations. A citation was retained for further evaluation if either investigator selected it. Each potentially relevant article was reviewed to determine if it met the above inclusion criteria.

Data extraction

Data from the published studies were extracted independently by two authors into a standardized form. For each study, the following characteristics and numbers were collected: the first author, year of publication, country, study design, ethnicity of subjects, numbers of subjects, gender ratio, age, source of controls, experimental method and subtype of NMDA receptors. In cases of conflicting evaluation, disagreements were resolved through discussions between the authors.

Quality assessment of included studies

Two authors independently assessed the quality of included studies

according to the items below. (1) The subjects were enrolled into study randomly. (2) The study was designed under blind policy. (3) There was preferable comparability between experimental and control group. (4) The identification of methods, outcome index and exposure factors were achieved between experimental and control group. (5) No sample or case dropped out during research. Three or more items achieved were defined as moderate to high quality. Disagreements were also resolved through discussions between the authors.

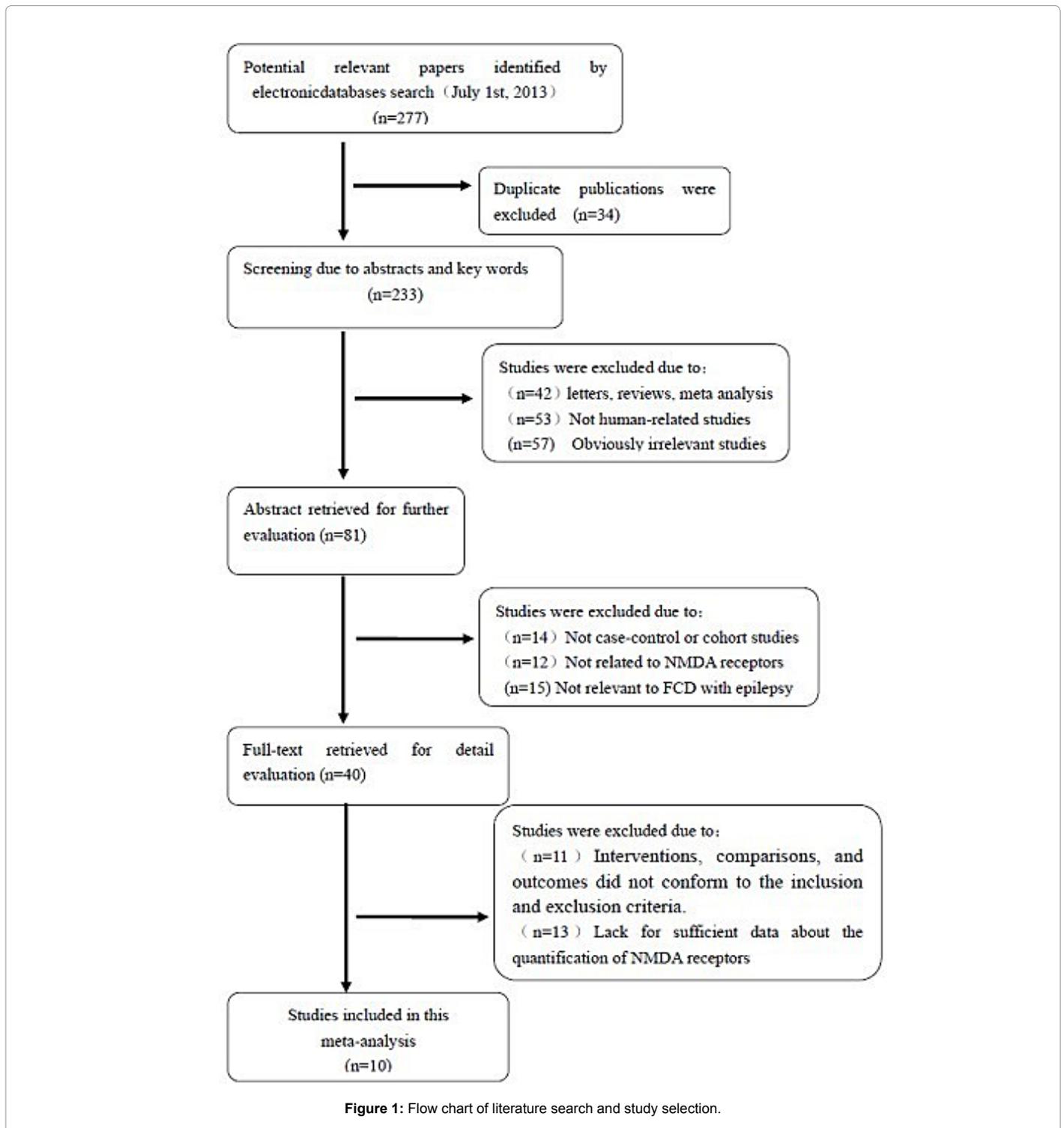
Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were computed as summary statistics. The statistical significance of the pooled ORs was examined using the Z test. Between-study variations and heterogeneities were estimated using Cochran's Q-statistic with a P -value <0.05 as statistically significant heterogeneity [22]. We also quantified the effects of heterogeneity by using the I^2 test (ranges from 0 to 100%), which represents the proportion of inter-study variability that can be contributed to heterogeneity rather than to chance [23]. When a significant Q-test with $P<0.05$ or $I^2>50\%$ indicated that heterogeneity among studies existed, the random effects model [24] was conducted for the meta-analysis; otherwise, the fixed effects model [25] was used. Sensitivity analysis was performed through omitting each study in turn to assess the quality and consistency of the results. Begger's funnel plots were used to detect publication biases [26]. A sensitivity analysis was performed by assessing the contribution of individual studies to the summary effect estimate with respect to the primary outcome. This was done by excluding each trial one at a time and computing meta-analysis estimates for the remaining studies. Results were considered statistically significant at $P<0.05$. All analyses were calculated using the RevMan5.0.

Results

Included studies and their characteristics

In accordance with the inclusion criteria, 10 randomized studies of patients with focal cortical dysplasia and epilepsy treated with surgical resection and post-operational pathological evidence versus other cerebral specimens without epileptiform discharges were selected for this meta-analysis. The flow chart of the screening process is shown in Figure 1. The characteristics and methodological quality of the included studies are summarized in Table 1. A total of 170 subjects were included in these studies, 104 of them were diagnosed with FCD and epilepsy while 66 resected specimen were non-CD cerebral tissue nor with epilepsy. The publication years of the involved studies ranged from 1998 to 2011. Two of ten studies were conducted in Asian populations, and the other eight studies in Caucasian populations. All of the selected studies were designed as case-control. All patients were diagnosed with FCD as well as epilepsy (normally refractory) based on typical clinical manifestation, radiology findings and electroencephalogram (EEG) before surgery. Specimen was achieved through surgical resection of the FCD lesion as experimental group and cortex without epileptiform discharges as control groups. Some surgeries included electrocorticogram (ECoG) monitoring of the suspicious FCD area to verify epileptiform discharges before resection, which obviously increased the quality of the study itself. As for sources of controls, they were mainly normal cortex or adjacent tissue of FCD lesion or abnormalities resected during surgery, neither of which displayed epileptiform discharges during ECoG monitoring, therefore were suitable as comparisons. Meanwhile, there were pathological evidences of these experimental subjects by post-operational pathological examination, which confirmed the diagnosis of FCD. As for experiments to quantify the expression of NMDA



receptors including NR1 and NR2A/B, there are mainly two methods conducted as below by over-reading all the selected studies:

1. Histological and immunocytochemical (ICC) staining [17]: NR1 and NR2A/B ICC staining was qualitatively graded according to the following criteria: (a) the presence and extent of NMDA receptors staining (estimation of the percentage of stained neurons). The extent of NR1 and NR2A/B ICC staining

of neurons was calculated among 100 neurons by observing 2-3 high power field (HPF), then graded according to the following system: 4=receptor-labeled neurons cover more than 70% of the neurons; 3=receptor-labeled neurons cover between 40% and 69% of the neurons; 2=receptor-labeled neurons cover between 20% and 39% of the neurons; 1=receptor-labeled neurons cover less than 20% of the neurons; 0=no receptor-labeled neurons

First author	Year	Country	Ethnicity	Study design	Number		Gender (M/F)		Source of controls	Age	Evidence of FCD	Diagnosis of epilepsy	Methods	NMDA receptors	Quality assessment
					Case	Control	Case	Control							
Nobuhiro Mikuni et al.	1999	USA	Caucasian	Case-control	3	3	2/1	2/1	Non-CD tissue	7-18	Pathology	Symptoms and EEG	ICC and immunoblot analysis	NR1 and NR2B	Middle-high
Nobuhiro Mikuni et al.	1999	USA	Caucasian	Case-control	3	3	2/1	2/1	Non-CD tissue	6-18	Pathology	Symptoms and EEG	ICC and immunoblot analysis	NR1	Middle-high
Ying Z et al.	1999	USA	Caucasian	Case-control	11	11	11	11	Non-CD tissue		Pathology	Symptoms and EEG	Immunoblot analysis	NR1 and NR2B	Middle-high
Thomas L Babb et al.	2000	USA	Caucasian	Case-control	3	3	3	3	Non-CD tissue		Pathology	Symptoms and EEG	Immunoblot analysis	NR1	Middle-high
Iniad M Najm et al.	2000	USA	Caucasian	Case-control	5	5	1/4	1/4	Non-CD tissue	15-29	Pathology	Symptoms and EEG	ICC	NR1 and NR2B	Middle-high
Zhong Ying et al.	2004	USA	Caucasian	Case-control	4	4	1/3	1/3	Non-CD tissue	3.5-17	Pathology	Symptoms and EEG	Immunoblot analysis	NR2B	Middle-high
Gabriel Moddel et al.	2005	USA	Caucasian	Case-control	20	8	8/12	8	Non-CD tissue	0-4	Pathology	Symptoms and EEG	ICC and immunoblot analysis	NR2B	Middle-high
Akira Hodozuka et al.	2006	Japan	Asian	Case-control	15	15	7/8	7/8	Non-CD tissue	0.6-8	Pathology	Symptoms and EEG	Immunohistochemical staining	NR1 and NR2A/B	Middle-high
Lei Liu et al.	2008	China	Asian	Case-control	20	4	14/6	4	Non-CD tissue	1-17	Pathology	Symptoms and EEG	En Vision	NR1 and NR2A/B	Middle-high
Jie Zheng et al.	2011	China	Asian	Case-control	20	10	12/8	10	Non-CD tissue	18-45	Pathology	Symptoms and EEG	ICC	NR1 and NR2A/B	Middle-high

Table 1: Characteristics of included studies in this meta-analysis.

Study	Country	Ethnicity	Experimental			Control		
			Mean	SD	Number	Mean	SD	Number
Gabriel Moddel 2005	USA	Caucasian	5.3	0.3	20	3	0.37	8
Iniad M Najm 2000	USA	Caucasian	7.9	0.59	5	5.7	1.9	5
Jie Zheng 2011	China	Asian	5	4.44	20	3	2.22	10

Table 2: Outcomes of included studies under experimental methods (NR2B, ICC).

Study	Country	Ethnicity	Experimental			Control		
			Mean	SD	Number	Mean	SD	Number
Nobuhiro Mikuni 1999	USA	Caucasian	169	0	3	75	21	3
Ying Z 1999	USA	Caucasian	168	13	11	76	9	11
Zhong Ying 2004	USA	Caucasian	195	23	4	125	9	4
Gabriel Moddel 2005	USA	Caucasian	90	14	20	41	13	8

Table 3: Outcomes of included studies under experimental methods (NR2B, immunoblot).

Study	Country	Ethnicity	Experimental			Control		
			Mean	SD	Number	Mean	SD	Number
Iniad M Najm 2000	USA	Caucasian	6.3	1.78	5	5.7	1.33	5
Jie Zheng 2011	USA	Caucasian	5	4.44	20	3.5	2.96	10

Table 4: Outcomes of included studies under experimental methods (NR1, ICC).

Study	Country	Ethnicity	Experimental			Control		
			Mean	SD	Number	Mean	SD	Number
Nobuhiro Mikuni 1999	USA	Caucasian	147	23	3	139	18	3
Nobuhiro Mikuni 1999'	USA	Caucasian	106	16	3	97	17	3
Ying Z 1999	USA	Caucasian	193	19	11	187	16	11
Thomas L Babb 2000	USA	Caucasian	135	20	3	122	19	3

Table 5: Outcomes of included studies under experimental methods (NR1, immunoblot).

in 100 neurons. (b) The intensity of cellular staining of various dysplastic areas. ICC density of NR1 and NR2A/B staining was graded according to the following system: 3=dark; 2=mildly dark; 1=faint; 0=no labeling. The final grade was obtained by adding the scores for extent and density (maximum grade of 7 for the most severe protein expression).

2. Immunoblot analysis: The tissue was prepared for Western immunoblot as previously described [27] with minor modifications. CD or non-CD specimens were firstly processed for immunoblotting, then incubated with polyclonal NR1 or NR2A/B primary antibody, and subsequently with secondary antibody (Jackson ImmunoResearch, West Grove,

PA, USA). Protein-antibody complexes were visualized with enhanced chemiluminescence reagents (ECL-PLUS; Amersham, Arlington Heights, IL, USA). To quantify the protein densities, blots were scanned, and the digitized images of the bands imported into NIH Image v.1.58 densitometry software. The digitized gray values of each band were used as a semiquantitative parameter for the amount of NMDA receptors protein.

More specifically, ICC alone was conducted in two trials while immunoblot analysis in three, and both of them were used in other three studies. There were the other two studies conducted immunohistochemistry yet did not have detailed data. We discussed them in subgroup. As for the NMDA receptors investigated among the selected studies, NR1 was tested alone in two trials as well as NR2B, and both of them were tested in 6 studies. The specific data of each trial was displayed in Table 2-5.

All quality of included studies were satisfied for meta-analysis (moderate-high quality).

Quantitative data synthesis and outcomes

Odds ratios and their 95% CIs for FCD and control group outcomes are displayed in Figures 2-6. Only fixed-effects model results are shown because of the lack of heterogeneity across trails included in this meta-

analysis. Outcomes for studies involved in investigating NR2B by ICC staining analysis was shown in Figure 2. The pooled OR was 2.29 (95%CI 2.01-2.58; $P < 0.00001$). There were no heterogeneity between trials ($P = 0.96$). Begger's funnel plots were used to detect publication biases shown in Figure 7. Meanwhile outcomes of NR2B by immunoblot analysis was displayed in Figure 3 as the pooled OR was 73.49 (95%CI 66.68-80.29; $P < 0.00001$). However the heterogeneity did exist ($P < 0.00001$). Sensitivity analysis was then performed through omitting each study indicated the Model 2005 study generated the most relevant influence on heterogeneity, therefore the omission of this individual led to a more satisfactory result in Figure 4. The pooled OR was 89.15 (95%CI 80.43-97.86; $P < 0.00001$) while the heterogeneity test came back negatively ($P = 0.10$). Both of the subgroups indicate that expression of NR2B is increased in patients' FCD cortex with epileptiform discharges. As for NR1 investigation, only two studies were involved in the subgroup of NR1 with ICC method shown in Figure 5 and the pooled OR was 0.91 (95%CI -0.66-2.49; $P = 0.26$) indicating there were no significant difference of expression of NR1 between FCD lesion with epilepsy and normal brain tissue, while subgroup analyzing immunoblot method had the similar result shown in Figure 6 (the pooled OR was 7.66, 95%CI -3.51-18.83; $P = 0.18$). Tests for heterogeneity of these two subgroups turned out negatively ($P = 0.59$ for subgroup of NR1 with ICC; $P = 0.98$ for subgroup of NR1 with immunoblot analysis). The Begger's funnel plots of them were symmetrical therefore there was

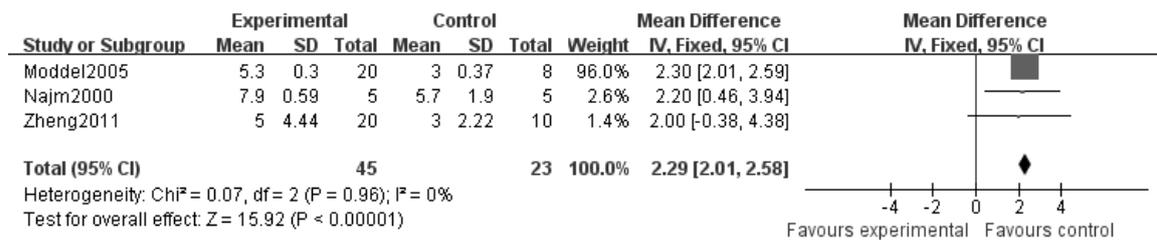


Figure 2: Forest plot for the association between expression of NR2B and susceptibility to epilepsy in FCD cortex under ICC staining.

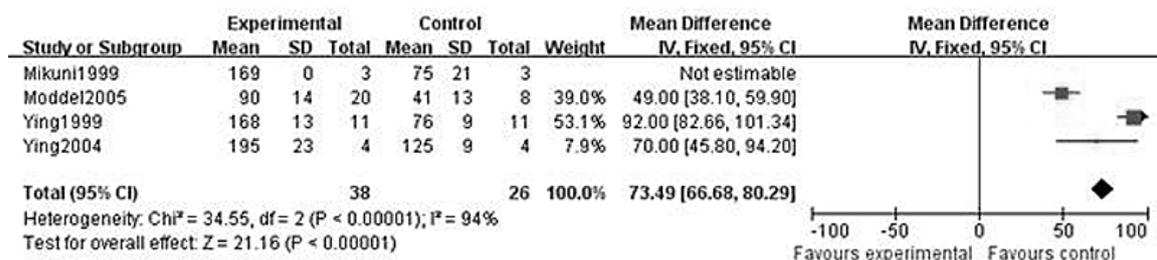


Figure 3: Forest plot for the association between expression of NR2B and susceptibility to epilepsy in FCD cortex under immunoblot analysis.

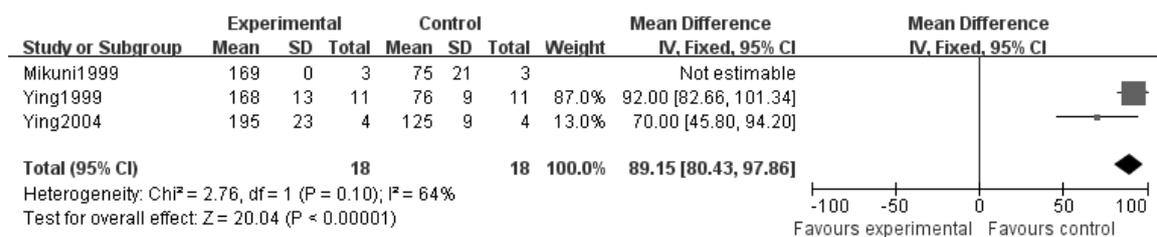


Figure 4: Forest plot for the association between expression of NR2B and susceptibility to epilepsy in FCD cortex under immunoblot analysis after omission of the potential heterogeneity generated trail.

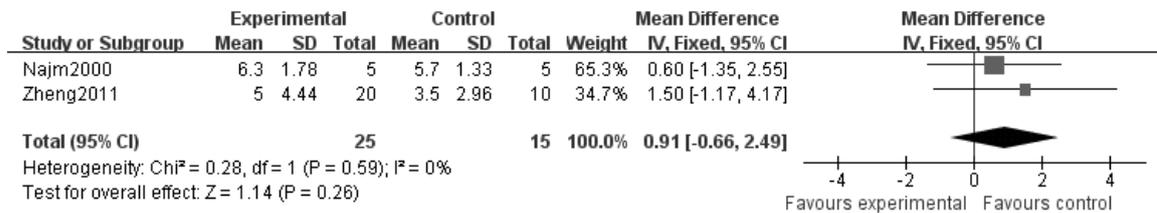


Figure 5: Forest plot for the association between expression of NR1 and susceptibility to epilepsy in FCD cortex under ICC staining.

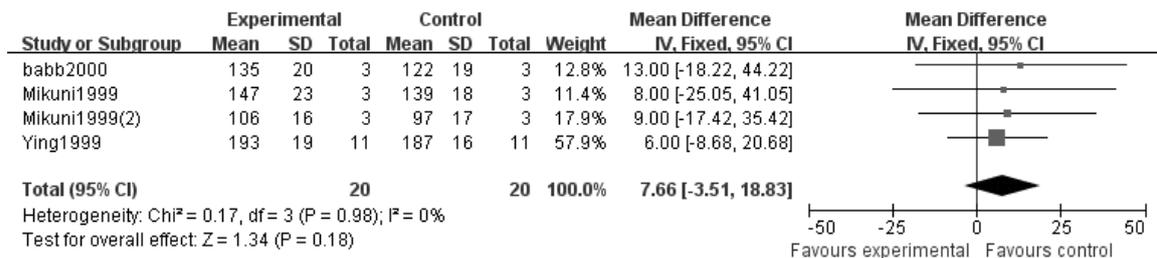


Figure 6: Forest plot for the association between expression of NR1 and susceptibility to epilepsy in FCD cortex under immunoblot analysis.

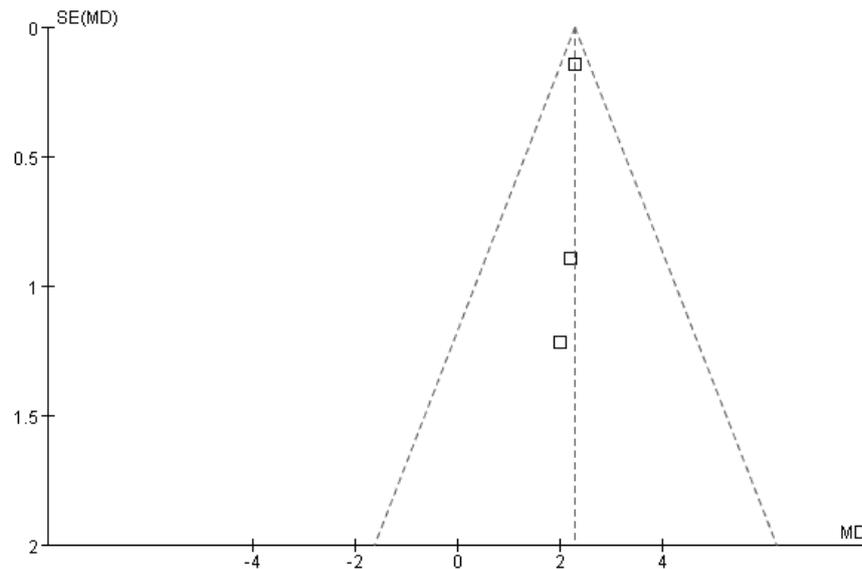
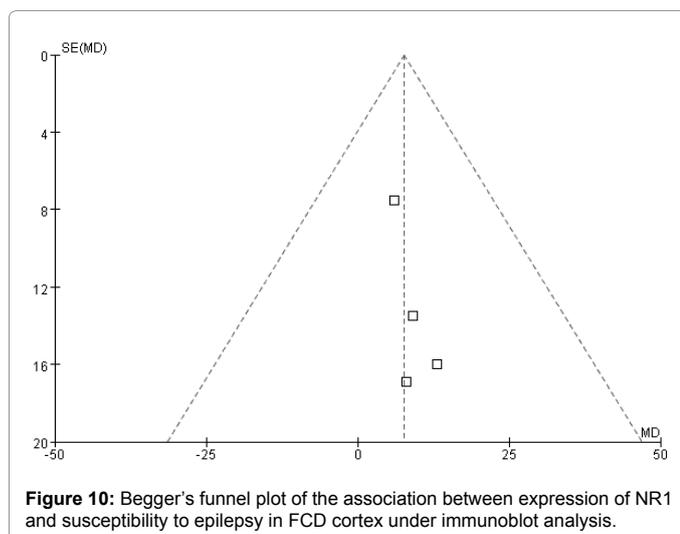
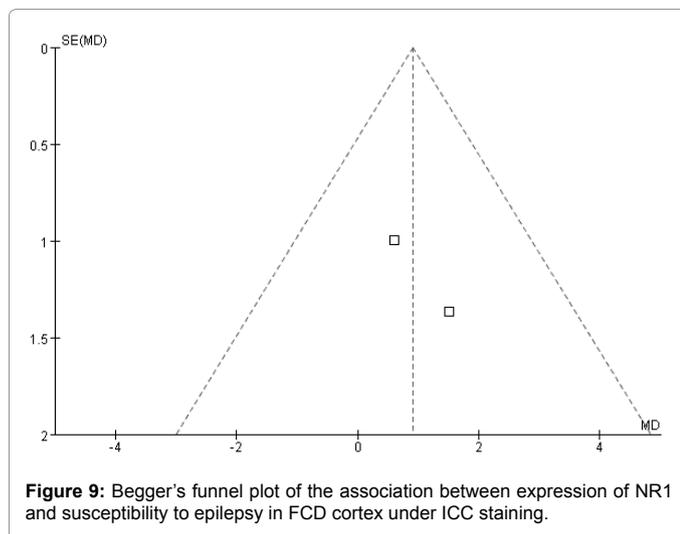
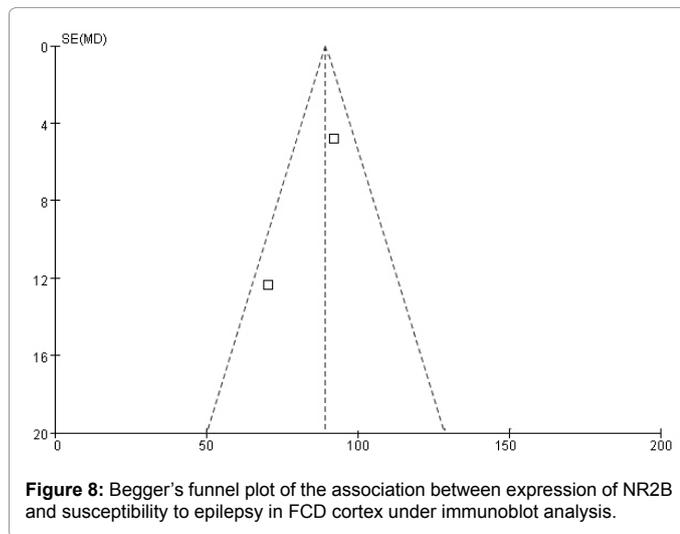


Figure 7: Begger's funnel plot of the associations of the association between expression of NR2B and susceptibility to epilepsy in FCD cortex under ICC staining.

no obvious publication biases (Figures 8-10). As mentioned before, there were two studies conducted immunohistochemistry yet did not have detailed data which was Liu 2008 and Hodozuka 2006. Based on the literatures, they both applied immunohistochemistry experimental methods yet their quantification techniques did not coincide with the others' and they mainly displayed the results as positive/negative or increased/decreased when describing the difference of expression of NMDA receptors between experimental and control groups. Although their outcomes couldn't be involved into meta-analysis, we still feel it necessary to extract the data and displayed it Table 6.

Discussion

Overwhelming evidence indicates the significance of NMDA receptors in FCD related epileptogenesis. However it is still unclear about which subtype of NMDA receptors being the most relevant factor inducing epileptiform discharges. Numbers of studies suggested that NR2A/B found in FCD cortex may play an important role in epileptogenesis. However NR1 remains unchanged during epilepsy pathogenesis [17]. However recent trails found no convincing evidence of NR2A/B expression changes in increasing susceptibility to epilepsy as well as NR1 might increase in FCD cortex [16]. This controversy



especially on the effect of different subtype of NMDA receptors could be explained with several reasons, such as the differences in study designs,

sample size, ethnicity, source of subjects, immunohistochemical methods, etc. Therefore, we performed a meta-analysis to provide a comprehensive and reliable conclusion on the association between NMDA Receptors and epileptogenesis in human cortical dysplasia.

In this meta-analysis, 10 case-control studies were included with a total of 170 subjects. 104 of them were diagnosed with FCD and epilepsy while 66 resected specimen were non-CD cerebral tissue. When all the eligible studies were pooled into the meta-analysis, the results showed that the expression of NR2B is increased in FCD cortex on patient with epilepsy, which indicates that the increased NR2B might play an important role in FCD related epilepsy pathogenesis. On the other hand, the expression of NR1 was investigated in this meta-analysis, which showed no significant difference between FCD group and controls. Therefore the NR1 might not be a relevant factor that affect the epileptiform discharges in patient's cortex with FCD. Although the exact function of NMDA receptors in the development of FCD related epilepsy is not yet clear, a possible explanation could be referred to by our meta-analysis, we also assume that NMDA receptors might interact with other substances in different signaling pathways to initiate and promote the epileptogenic process.

Some limitations of this meta-analysis should be acknowledged. First, there were only ten articles included in the present meta-analysis, so the sample size was relatively small and may not provide sufficient statistical power. Therefore, more studies with larger sample size are needed to accurately provide a more representative statistical analysis. Second, as a type of a retrospective study, a meta-analysis may encounter recall or selection bias, possibly influencing the reliability of our study results [28,29]. Third, our lack of access to the original data from the studies limited further evaluation of potential interactions between other factors and liver disease risks, such as gene-environment and gene-gene interactions [11]. Fourth, there are some controversies about the effecting period of NMDA receptors during epileptogenesis. Epileptogenesis is considered to induce the onset of spontaneous recurrent seizures, which, in other terms, the receptor modification observed might well be due to seizures more than being a cause[12-14]. We suggest more research to focus on this issue. Therefore we could improve our meta-analysis from understanding the correlation between NMDA receptors and epileptogenesis to their specific role. In spite of these limitations, however, this is the first meta-analysis of the relationship between NMDA Receptors and epileptogenesis in human cortical dysplasia.

In conclusion, our meta-analysis suggests that NR2B might be a significant factor affecting epileptogenesis in human cortical dysplasia while NR1 might not be relevant. Further studies are still required to warrant and validate the association between NMDA receptors and CD related epilepsy risk.

Acknowledgement

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Study	Country	Ethnicity	NR1		NR2A/B	
			FCD cortex	Non-FCD cortex	FCD cortex	Non-FCD cortex
Lei Liu 2008	China	Asian	Increased	Normal	Increased	Normal
Jie Zheng 2011	China	Asian	Negative	Negative	Negative	Negative

Table 6: Outcomes without specific data.

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