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REVIEW ARTICLE

Association between polymorphisms of NOS1, NOS2 and NOS3 genes and suicide behavior: a systematic review and meta-analysis

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Abstract

The enzyme nitric oxide synthase has been associated with suicide behavior. *NOS1*, *NOS2* and *NOS3* genes are implicated in the production of nitric oxide. However, the association between *NOS* genes and suicide behavior has not yet been established. To assess the association of Nitric Oxide Synthase *(NOS)* genes and suicide behavior we performed a systematic review a meta-analysis. We searched articles published in three electronic databases, PubMed, Scopus and Web of Sciences, up to February 2019. We used keywords and combinations "*NOS*", "*NOS1*", "*NOS2*", "*NOS3*" and "suicide". Only articles that met the inclusion criteria were included. To assess the association between *NOS* genes and suicide behavior we used allelic, dominant and recessive models, as well as homozygous and heterozygous comparisons. The pooled results showed that rs2682826 of Nitric Oxide Synthase 1 gene *(NOS1)* increased the risk for suicide attempt in the allelic (OR: 1.34; 95 CI: 1.00–1.78), recessive (OR: 1.45; 95 CI:1.06–1.98) and heterozygous (OR: 1.41; 95 CI: 1.09–1.81) models. We found that the rs2682826 of *NOS1* could increase the risk for suicide attempt. However, these results should only be taken as exploratory; more studies are necessary to determine the association between *NOS* genes and suicide behavior.

Keywords Suicide · NOS gene · Biological psychiatry · Neuropsychiatry · Biochemical markers

Introduction

The incidence of suicide has increased over time; every year, approximately one million deaths worldwide are caused by suicide (Giegling et al. 2011a; Oliveira et al. 2015; Zhao et al. 2015). Over the last decades, much research has been done to understand the basis of suicidal behavior (SB). It has been supported that the diathesis for suicide includes a genetic

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predisposition with a heritability of 30–55%, and a similar degree of heritability for nonfatal suicidal acts (Giegling et al. 2011a; Reif et al. 2009; Rujescu et al. 2008). Moreover, several genetic studies have been performed to explain this heritability and consequently numerous potential risk genes have been identified. Recently, Nitric Oxide Synthase *(NOS)* genes have been proposed as candidates (Giegling et al. 2011a; Oliveira et al. 2015; Reif et al. 2009; Rujescu et al. 2008; Zhao et al. 2015).

The nitric oxide synthase and its three isoforms: Nitric Oxide Synthase 1 (NOS1), Nitric Oxide Synthase 2 (NOS2) and Nitric Oxide Synthase 3 (NOS3), belong to a family of enzymes that control nitric oxide production. Diverse studies have explored the function of NOS and have observed that its isoforms have several functions and locations (Freudenberg et al. 2015; Gutierrez et al. 2017; Wang et al. 2016; Xu et al. 2016). The NOS1 is distributed in specific neurons of central and peripheral nervous systems; the protein is encoded by the *NOS1* gene located on the chromosome region 12q24.2–24.3 (Bruenig et al. 2017; Cui et al. 2010; Freudenberg et al. 2015; Kudlow et al. 2016; Mirkovic et al. 2017). The NOS2 is induced by immunological and inflammatory stimuli and it is encoded by the *NOS2* gene located on chromosome 17q11.2–q12 (Gutierrez et al. 2017; Lauridsen et al. 2017). Regarding the *NOS3* gene, it is located on chromosome 7q35–36 and it is expressed in the vascular endothelium (Oliveira et al. 2015; Rujescu et al. 2008). Due to the NOS various functions, a nitrergic dysfunction seems to be participant in several neuropsychiatric disorders (Bruenig et al. 2017; Kudlow et al. 2016; Wang et al. 2016).

The idea of a possible association between *NOS* genes and SB came from studies in animals, where a lack of NOS1 resulted in increased impulsivity, aggression or other abnormal social behaviors. Recently, a series of a species involved in oxidative stress and antioxidant status have been studied, as they are involved in neuron damage that seems to be part of the pathology of psychiatric disorders (Bruenig et al. 2017; Cui et al. 2010; Schiavone et al. 2016). Furthermore, post mortem data indicate low levels of NOS proteins in the locus coeruleus of brain of depressive individuals who died by suicide, when compared with normal controls (Karolewicz et al. 2004). Nitric oxide is an important messenger in hypothalamic cell signaling and it is involved in the regulation of the hypothalamic-pituitary-adrenal axis, which turns out to be dysregulated in patients with psychiatric disorders (Altamura et al. 1999; Bernstein et al. 2002; Bernstein et al. 2000; Bernstein et al. 1998). In addition, it has been proposed that an altered function of the anterior cingulate cortex (ACC) is crucial in the pathogenesis of depression; for instance, it has been observed lower levels of NOS1 mRNA in the ACC of depressive patients, suggesting that a decrease of ACC-NOS1 expression may alter ACC activity in depression (Gao et al. 2013; Rolls et al. 2018).

Based on the above mentioned, our primary aim was to gather and evaluate recent evidence, to better understand the associations between *NOS* genes and SB, through a systematic review and meta-analysis, in order to detect associations that individual studies with a small sample sizes could not detect (due to inadequate statistical power). Moreover, we explored the role of nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH oxidase species (NOx) in suicidality.

Methods

Data sources and searches

A systematic search was conducted in three electronic databases to select potentially relevant literature (PubMed, Scopus and Web of Sciences). We used the combination of terms "*NOS*" AND "suicide", "*NOS1*" AND "suicide", "*NOS2*" AND "suicide", "*NOS3*" AND "suicide", "nNOS" AND "suicide", "eNOS" AND "suicide", "iNOS" AND "suicide", "Nitric Oxide Synthase 1" AND "suicide", "Nitric Oxide Synthase 2" AND "suicide" and "Nitric Oxide Synthase 3" AND "suicide". Then, the retrieved articles were manually searched to identify additional relevant publications. In addition, we conducted another search for articles that have explored the role of NADPH and NOx, using the terms "NADPH" AND "suicide" and "NOX" AND "suicide".

Study selection criteria

To be included in the meta-analysis, the studies had to meet the following criteria: (1) to be a comparison study (SB group and control group), (2) to evaluate associations of single nucleotide polymorphisms (SNPs) of *NOS1*, *NOS2* or *NOS3* genes with suicidal behavior risk, (3) the diagnoses of suicidal behavior or mentally healthy individuals had to be performed by psychiatrists, (4) the sample size and genotype frequencies had to be available for cases and controls or at least they could be calculated, (5) had to be published in English and (6) had to be Peer-reviewed Journals. The exclusion criteria were (i) duplicated studies, (ii) reviews, case reports, abstracts of meetings or unpublished articles, and (iii) did not provide sufficient data to calculate odds ratios (OR) and corresponding 95% confidence interval (CI).

Regarding the articles of NADPH and NOx, the inclusion criteria were: (1) association studies of NADPH or NOx with SB, (2) published in English and (3) Peer-reviewed Journals.

Data extraction

Following the inclusion/exclusion criteria, data were extracted from the eligible studies by two investigators, independently. If they could not reach an agreement, the study was assessed

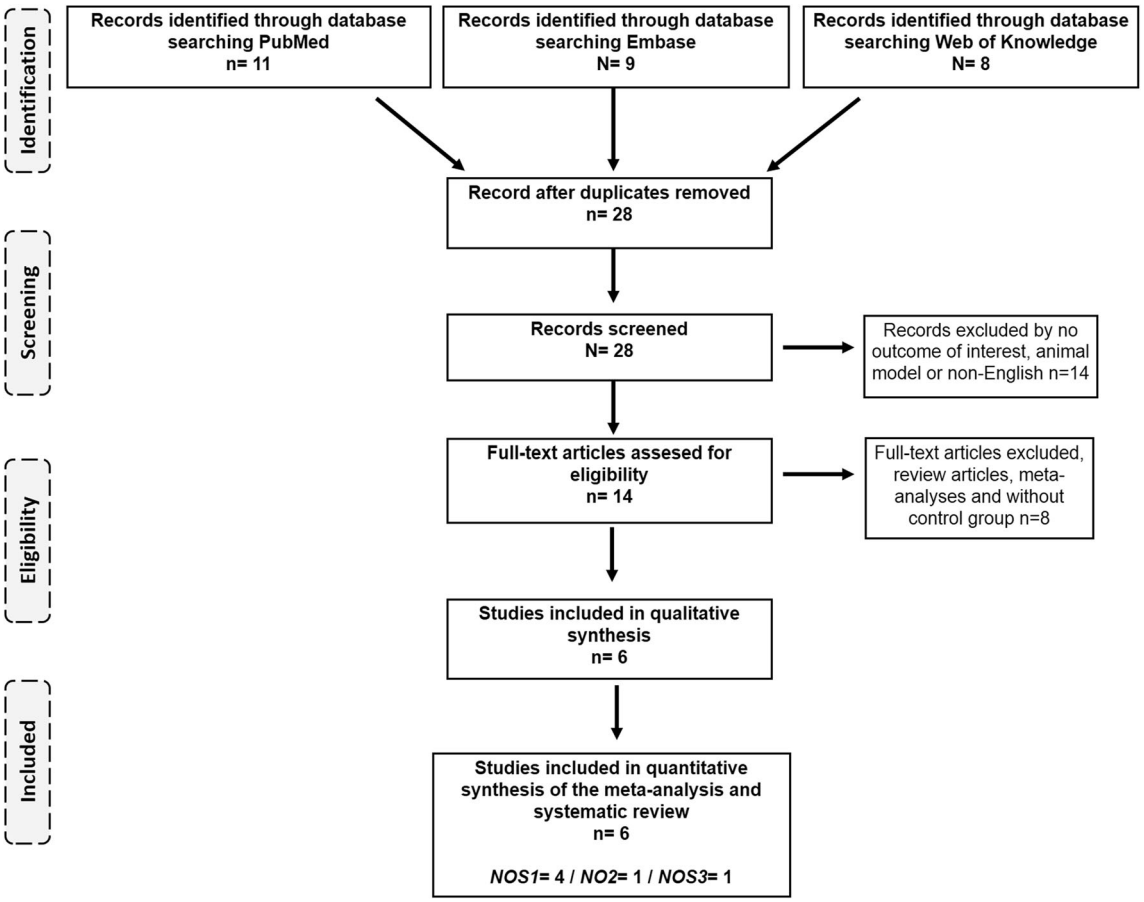

Fig. 1 PRISMA flow diagram of the inclusion/exclusion criteria

by a third investigator, undertaking data extraction and analysis. The following information was gathered from the studies: name of the first author, publication year, country, ethnicity, laboratory measures or techniques, diagnostic tools and features, number of cases and controls, main outcomes, age, gender, genotyping methods, polymorphisms studied and genotype frequencies.

Statistical analysis

The meta-analysis was performed using the Comprehensive Meta-analysis (Biostat V2.2) software. The strength of association between *NOS* gene and risk of SB was assessed by determining the pooled ORs and 95% CIs for allelic (G vs A), dominant (GG vs GA + AA) and recessive (GG + GA vs AA) models, as well as homozygous (GG vs AA) and heterozygous (GA vs AA) comparisons; a $P < 0.05$ was considered statistically significant. Statistical heterogeneity between studies was estimated using Q test and I^2 statistics, heterogeneity was established with a $p \geq 0.10$ or $I^2 \geq 50\%$. For I^2 the degree of the heterogeneity was measured using the criteria: $I^2 = 0$–25% absence, $I^2 = 25$–50% moderate heterogeneity, I2 = 50–75% high heterogeneity and $I^2 = 75$–100% extreme heterogeneity. When significant heterogeneity existed, the random effect model was used; otherwise, the fixed-effect model was adopted as the pooling method. The potential publication bias was evaluated through Begg's and Egger's test; a $p < 0.05$ was considered as significant publication bias.

Results

NOS genes variants

After duplicates were removed, 28 studies were screened for titles and abstracts. After full-text reading, 6 studies were included in the present work. Figure 1 represent the PRISMA record management flowchart. Of the six articles searching for an association between NOS gene variants and suicidal behavior, four studied *NOS1* gene (rs2682826, rs41279104, rs693534, rs1353939, rs6490121, rs3782206, rs561712, rs3782219, rs3782221), one studied *NOS2* gene (rs2779248, rs2779249, rs8078340) and one studied *NOS3* gene (rs1799983). Due to the small number of published studies, we only performed a meta-analysis for the variant rs2682826 of *NOS*1 gene. Nevertheless, a detailed information of all the articles is presented in Tables 1 and 2.

Table 1 Genotyping features of the case-control association studies of the NOS gene variants with SB

Reference	Location	Cases							Controls						
		n	Age	M/F	MM	Mm	mm	HWE	n	Age	M/F	MM	Mm	mm	HWE
NOS 1: rs2682826															
Cui et al. 2010 [13] (overrall)	Japan	284	47.9	193/91	132	120	32	0.587	287	50.4	185/102	97	136	53	0.716
Cui et al. 2010 [13] (males)	Japan	193	48.9	193/0	90	83	20	0.869	185	47.2	185/0	55	94	36	0.767
Cui et al. 2010 [13] (females)	Japan	91	46.9	0/91	42	37	12	0.479	102	53.6	0/102	42	42	17	0.288
Giegling et al. 2011a, b [27]	Germany	111	39.2	43/68	69	33	9	0.105	289	45.2	123/166	177	94	18	0.241
Mirkovic et al. 2017 [12]	France	98	15.4	17/81	53	37	8	0.617	150	25.1	32/118	61	66	21	0.722
NOS1: rs41279104															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	192	86	5	0.288	284	50.4	185/102	184	87	11	0.848
Oliveira et al. 2015 [2]	France	224	42.5	193/91	168	54	2	0.548	160	41	99/61	120	38	2	0.586
NOS1: rs693534															
Giegling et al. 2011a, b [27]	Germany	111	39.2	43/68	50	51	10	0.664	289	45.2	123/166	97	141	51	0.984
Mirkovic et al. 2017 [12]	France	98	15.4	17/81	37	44	17	0.531	150	25.1	32/118	60	69	20	0.981
NOS1: rs1353939															
Giegling et al. 2011a, b [27]	Germany	111	39.2	43/68	58	38	15	0.04*	289	45.2	123/166	149	102	38	0.00*
Mirkovic et al. 2017 [12]	France	98	15.4	17/81	60	33	5	0.775	150	25.1	32/118	77	58	12	0.837
NOS1: rs6490121															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	44	147	93	0.327	287	50.4	185/102	54	137	96	0.717
NOS1: rs3782206															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	172	101	11	0.487	287	50.4	185/102	174	91	20	0.096
NOS1: rs561712															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	184	89	10	0.849	287	50.4	185/102	179	98	8	0.267
NOS1: rs3782219															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	95	142	47	0.713	287	50.4	185/102	90	155	41	0.067
NOS1: rs3782221															
Cui et al. 2010 [13] (overall)	Japan	284	47.9	193/91	83	146	54	0.547	287	50.4	185/102	82	149	55	0.406
NOS2: rs2779248															
Oliveira et al. 2015 [2]	France	224	42.5	193/91	36	103	85	0.673	160	41	99/61	33	71	56	0.258
NOS2: rs2779249															
Oliveira et al. 2015 [2]	France	224	42.5	193/91	106	96	22	0.968	160	41	99/61	71	66	20	0.476
NOS2: rs8078340															
Oliveira et al. 2015 [2]	France	224	42.5	193/91	168	51	5	0.573	160	41	99/61	117	38	5	0.356
NOS3: rs1799983															
Oliveira et al. 2015 [2]	France	224	42.5	193/91	94	93	37	0.115	160	41	99/61	70	63	27	0.069

M/F: male/female; n: age; Age: Mean age

Table 2 Sociodemographic and clinical characteristics of the case-control association studies of NOS gene variants and suicidal behavior

Reference	SB	Features of diagnostic	Scales	Variants	Laboratory techniques	Main outcomes
Cui et al. 2010 [13]	SV	Hanging: 140; jumping from heights: 65, drowning:10; overdose: 8; cutting/stabbing: 7; gas suffocation: 6; jumping in front vehicles: 4; self-burning: 4; drinking poison: 1; and others:6	DSM-IV	NOS1 rs2682826, rs6490121, rs3782206, rs561712, rs3782219, rs3782221, rs41279104	Integrated BeadArray system supplied barcoded DNA microtiter plates	rs2682826 were significantly different between the suicide victims and controls. Gender-based analysis showed that significances appeared in males only.
Giegling et al. 2011a, b [27]	SA	AS: 68.5%; SS: 15.3%; BPD: 16.2%	DSM-IV SCID I y II	NOS 1 rs2682826; rs1353939; rs693534 NOS 3 rs2070744; rs1799983; rs891512	Integrated BeadArray system supplied barcoded DNA microtiter plates	Association between reward dependence trait and rs2682826 in NOS1 in the healthy sample.
Oliveira et al. 2015 [2]	SA	224 SA from these 53 commit a violent attempt	DSM-IV DIGS	NOS1 s41279104 NOS2 rs8078340; rs2779249; rs2779248 NOS3 rs1799983	PCR TaqMan probe assays	rs1799983 NOS3 is associated with violent suicide attempts in bipolar disorder. Moreover, early-onset bipolar disorder patients with a genetically driven low/inefficient production of nitric oxide may be more susceptible to violent suicide attempts.
Mirkovic et al. 2017 [12]	SA	MDD:32%; ADDD:25%; AD: 22%; ODCD:16%; SD: 9%	CCASA CSSRS	NOS1 rs2682826	DNA extracted from saliva AS-PCR	rs2682826 NOS1with significant associations with suicide attempts or with the quantitative hoplessness or impulsivity phenotypes. However, no association withstand statistical correction test.
Reif et al. 2009 [4]	SA	AS: 131 SS: 30 BPD: 28	DSM-IV SCID-I	NOS1 Ex1f VNTR	PCR Microarray expression	Short repeat was more frequent in adult ADHD, autoagressive and heteroagressive behaviors.
Zhao et al. 2015 [1]	SV	GSW: 2, hanging: 8; jumping: 1; overdose: 5; stabbing: 1	DSM-IV	NOS 1 NOS2	DNA extracted from frozen brain PCR expression	MDD-S group, expression levels of CRH and neuronal NOS-interacting DHHC domain-containing protein with dendritic mRNA were increased.
Rujescu et al. 2008 [5]	SA/SV	AS: 64.07%; SS: 20.96%; BPD: 14.97%	DSM-IV SCID-I Intent Score Scale	NOS1 Rs2682826; rs1353939, rs2293049; rs693534 NOS3 rs2070744; rs1799983; rs891512	Integrated BeadArray system supplied barcoded DNA microtiter plates	NOS1 haplotype CTGG (rs2682826-rs1353939-rs693534) was associated with suicidal behavior and more specifically with SA. Sliding window analysis showed similar results for the haplotype GG (rs1353939-rs693534) being a risk factor for suicidal behavior again especially in SA.

SB suicidal behavior, *SA* suicide attempters, *SV* suicide victims, *AS* affective spectrum, *SS* schizophrenia spectrum, *BPD* borderline personality disorder, *ADHD* Attention-Deficit hyperactive disorder, *CCASA* Columbia Classification Algorithm of Suicide Assessment, *CSSRS* Columbia Suicide Severity Rating Scale, *MDD* major depressive disorder, *ADDD* adjustment disorders with depressed mood, *AD* anxiety disorder, *ODCD* oppositional defiant and conduct disorders, *SD* substance related disorders, *MDD-S* major depressive disorder patients who died by suicide, *GSW* gunshot wound

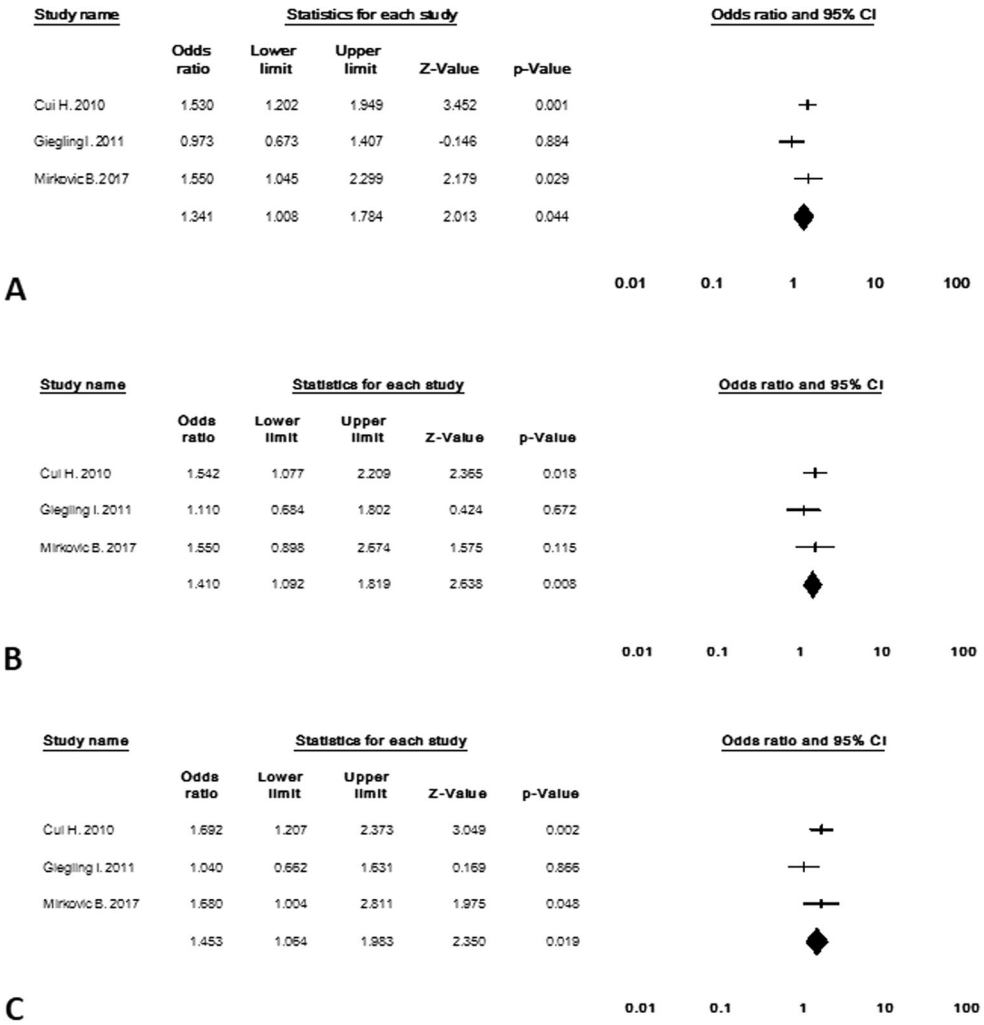

Fig. 2 Forest plot of rs2682826 NOS1 gene variant in the models: **a**) Allelic, **b**) Heterozygous, **c**) Recessive

Association analysis of rs2682826 NOS1 gene variant with SB

The analysis of this polymorphism was performed through the five models previously mentioned. The results revealed that rs2682826 *NOS1* gene variant could be a risk factor of SB in the *allelic* [OR (CI95%): 1.34 (1.00–1.78), Z *p* value 0.044, I^2: 55.458, Egger's test: 0.6662] Fig. 2, *heterozygous* [OR (CI95%): 1.41 (1.09–1.81), Z p value 0.008, I^2: 0.000, Egger's test: 0.7528] and *recessive* [OR (CI95%): 1.45 (1.06–1.98), Z p value 0.019, I^2: 37.367, Egger's test: 0.7555] models, Table 3 and Fig. 3.

NADPH and NOx

Regarding the oxygen species research, only two studies have observed a relation between NADPH and NOx: Vargas et al. 2013a, b (Vargas et al. 2013a; Vargas et al. 2013b) and Schiavone et al. 2016 (Schiavone et al. 2016). From these

Table 3 Meta-analysis results comparing the inherence models between cases and controls

Model	Heterogeneity	Random effects OR (CI95%)	Z *P* value	I^2	Q test *P* value	Egger test *P* value
Allelic	High	1.34 (1.00–1.78)	0.044	55.458	0.1059	0.6662
Homozygous	High	1.65 (0.85–3.19)	0.133	57.986	0.0925	0.6263
Heterozygous	Absence	1.41 (1.09–1.81)	0.008	0.000	0.5250	0.7528
Dominant	Moderate	1.43 (0.84–2.43)	0.178	41.449	0.1812	0.6218
Recessive	Moderate	1.45 (1.06–1.98)	0.019	37.367	0.2026	0.7555

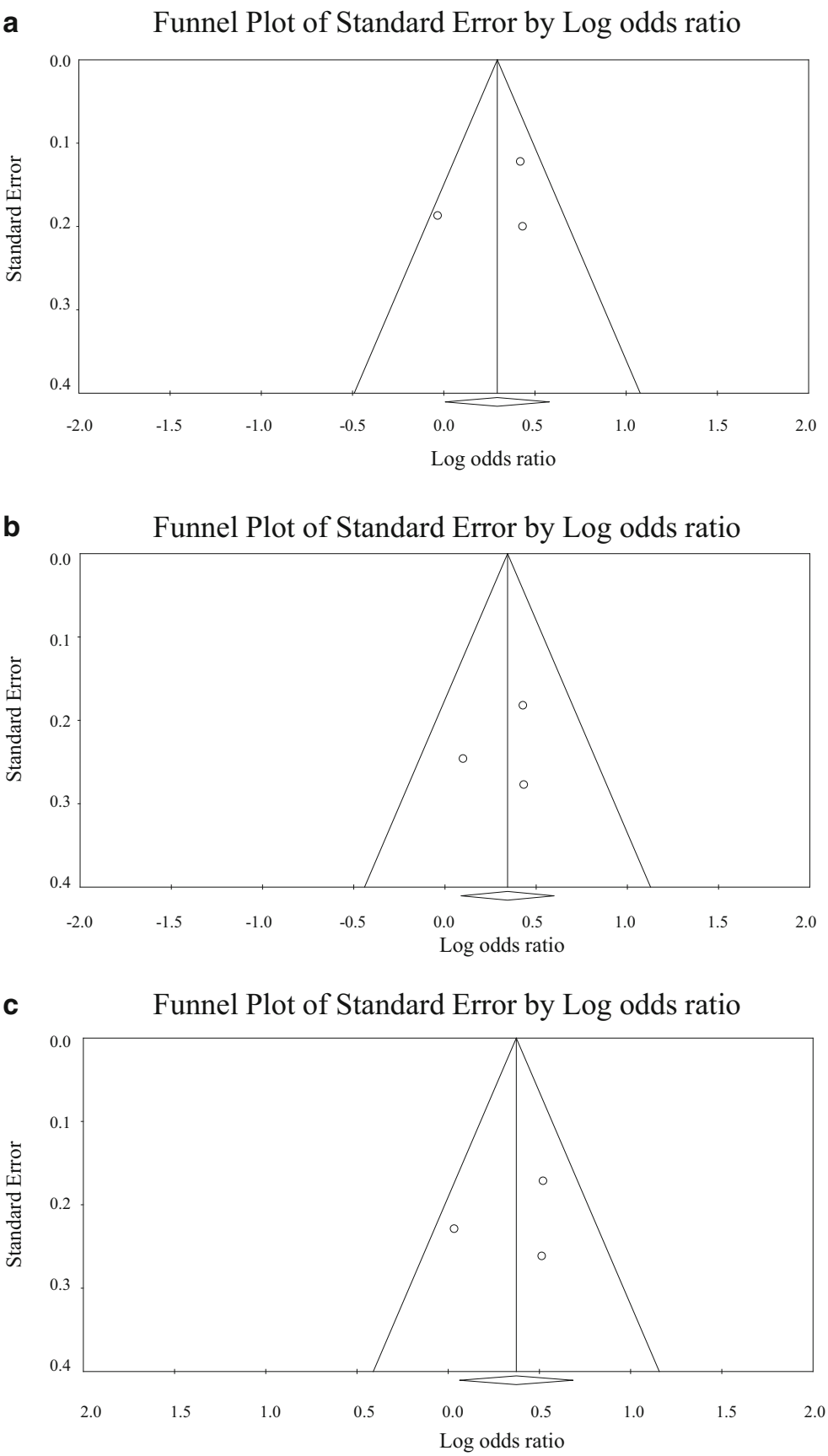

Fig. 3 Funnel plot of rs2682826 NOS1 gene variant in the models: **a**) Allelic, **b**) Heterozygous, **c**) Recessive

Table 4 Characteristics of the association studies of NOx and NADPH with SB

Author	Biomarkers or laboratory techniques	Sample population	Outcomes
Vargas et al. 2013a, b [20]	NOx, MDA, TRAP, AOPP, fibrinogen concentrations, homocysteine, ESR and hs-CRP were assayed from blood specimens.	Smokers ($n = 150$) were recruited from Paraná, Brazil and never smokers ($n = 191$) were recruited from staff of UEL.	Associations were found among depressed smokers who had more severe depressive symptoms, a higher risk of alcohol consumption, more suicide attempts, and more disability for work than non-depressed never smokers. Depressed smokers had significantly higher levels of NOx, fibrinogen, hs-CRP, AOPP, ESR and lower levels of TRAP compared to non-depressed never smokers. Depressed smokers had significant levels of oxidative stress and inflammatory biomarkers after adjusting for gender, age, years of education, disability for work, and laboratory measures.
Vargas et al. 2013a, b [21]	NOx, MDA, AOPP, TRAP; inflamatory biomarkers, including CRP, fibrinogen, IL-6, TNFα and ESR; and metabolic biomarkers, including total cholesterol, LDL and HDL-cholesterol, TG, insulin, glucose, homocysteine, BMI and metabolic syndrome.	Subjects with a history of suicide attempts (n = 150) and without suicide attempts ($n = 201$) were recruited from Paraná, Brazil. All participants were men and women aged 18–60 and all ethnicities were accepted for this study.	Individuals with a history of suicide attempts had significantly higher levels of NOx and lipid hydroperoxides and lowered TRAP as compared to individuals without suicide attempts. Logistic regression showed that both unipolar and bipolar disorder, female gender, smoking behavior and lipid hydroperoxides were significantly associated with a history of suicide attempts.
Schiavone et al. 2016 [19]	NOX2 enzyme and markers of oxidative stress was evaluated using anti-Nox 2. Neuroinflammation was investigated using anti-IL-6, anti-TNF-α, anti-IL-10 and anti-IL-1 beta antibodies.	A total number of 26 post mortem brain samples of AS subjects, 10 post mortem brain samples of controls subjects and 6 post mortem brain samples of NSA subjects were recruited in Italy.	NOX2 expression was significantly higher in the cortex of AS subjects than in the other two experimental groups. NOX2 immunostaining was mainly detected in GABAergic neurons, with a minor presence of NOX2-positive-stained cells in glutamatergic and dopaminergic neurons.

NOx nitric oxide metabolites, *MDA* lipid hydroperoxides, malondialdehyde, *AOPP* advanced oxidation protein products, *TRAP* plasma total antioxidant potential, *ESR* erythrocyte sedimentation rate, *BMI* body mass index, *hs-CRP* high-sensitivity C reactive protein, *AS* suicidal asphyxia, *NSA* non-suicidal asphyxia

studies the outcomes revealed a possible interaction of oxygen species and suicide, Table 4.

Discussion

NO is involved in several pathologies including SB. We performed a meta-analysis and systematic review of *NOS* genes to get a better understanding of their participation in suicidal behavior. To our knowledge, this is the first meta-analysis and up-dated systematic review that addresses the relation of *NOS1*, *NOS2* and *NOS3* genes and the risk of SB.

In 2010, Cui et al. examined 7 SNPs (rs2682826, rs6490121, rs3782206, rs561712, rs3782219, rs3782221, and rs41279104) of the *NOS1* gene in 287 healthy subjects and 284 complete suicides (Cui et al. 2010). They found that both genotypic and allele frequencies distribution of rs2682826 were significantly different between cases (complete suicides) and controls (healthy subjects) even after a correction for multiple testing (Cui et al. 2010). Since then, other studies in Caucasian and Asian population have been performed, using this type of association analysis (Cui et al. 2010; Giegling et al. 2011b; Mirkovic et al. 2017). Our findings revealed a possible relation of rs2682826 *NOS1* gene variant in the pathogenesis of SB. For example, in the *allelic* model we found a 1.24 more risk of SB, and this statistical relation remained and increased in the *heterozygous* (OR = 1.41) and *recessive* (OR = 1.45) inheritance models. We could infer that the rs2682826 of NOS1 gene is a promising candidate polymorphism because the single-tissue eQTLs analysis information shows that it is related with F-Box Protein 21 gene (*FBXO21*) ($p = 8.3e-09$) (GTEx Portal 2019); this gene has been involved in the immune system pathway (Genecards 2019) highly linked with psychiatric disorders (Dickerson

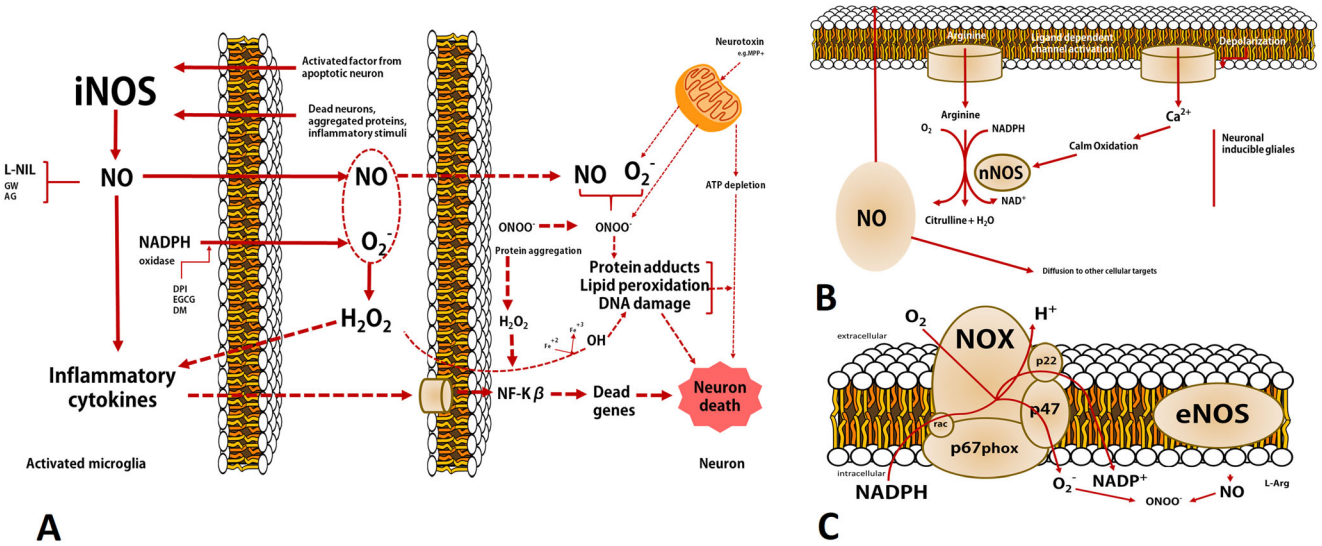

Fig. 4 **a**) *iNOS* and NADPH oxidase and their inhibitors in oxidative stress and neuronal damage. Reactive oxygen species (ROS) can be generated by neurotoxins and mitochondrial dysfunction and protein aggregation. ROS have a role in oxidative stress, thereby causing neuronal injury or cell death which could cause microglial activation. **b**) *nNOS* is activated by a calcium-dependent calmodulin. nNOS produces NO when arginine is oxidized into citrulline. NO diffuses and act on pre-synaptic or post-synaptic targets. **c**) NO produced by *eNOS* not only reacts with superoxide to produce the reactive species peroxynitrite

et al. 2017; Monfrim et al. 2014; Pandey 2017). This evidence agrees with the hypothesis that NOS1 is the main producer of pleiotropic gaseous neurotransmitter NO. NO itself, is considered a risk factor for SB, as nitrergic dysfunctions seem to be involved in several neuropsychiatric disorders (Bruenig et al. 2017; Freudenberg et al. 2015; Wang et al. 2016). In this sense, interactions between NO and dopamine in the striatum, might be crucial in schizophrenia and perhaps bipolar disorder; furthermore, there is a close link between the serotonergic and nitrergic systems (Rujescu et al. 2008; Xu et al. 2016). Even though our meta-analysis presents a statistical significance when evaluating the rs2682826, we understand that the genetic background of patients could have a considerable contribution in the genotype frequency distribution. For example, the allele frequencies of rs2682826 of *NOS1* gene in Utah Residents (CEU), Chinese Dai in Xishuangbanna (CDX) and Esan in Nigeria (ESN) are G = 0.7020 A = 2980 for CEU, G = 0.5484 A = 0.4516 for CDX and G = 0.8990 A = 0.1010 for ESN (1000 Genomes Project 2019) respectively. Therefore, it is necessary to perform more studies in order to get a better view of the role of NOS gene in these populations.

On the other hand, and important mode of NO inactivation is its reaction with superoxide anion to form oxidant peroxynitrite, which cause oxidative damage, nitration and S-nitrosylation of biomolecules (Schiavone et al. 2016; Wang et al. 2016). Therefore, there is also a link between oxidative stress and increased reactive oxygen species with psychiatric diseases. This relation could appear when oxidative stress, nitrosative stress and inflammation induce protein, DNA and mitochondria damage among other alterations; these alterations may lead to brain damage, a pathway for neurodegenerative diseases and neuroprogression of psychiatric disorders (Rujescu et al. 2008; Schiavone et al. 2016; Xu et al. 2016). In addition, the NADPH oxidase 2 (NOX2) enzyme expressed in the central nervous system, is a major generator of reactive oxygen species that has been observed in several disorders, including psychiatric and neurodegenerative diseases; Fig. 4 (Dusting et al. 2005; Forstermann and Sessa 2012; Koppula et al. 2012; Kourosh Masoumeh Arami BJaSAM 2017).

We want to emphasize some limitations in our study. Firstly, meta-analyses depend on the number of articles published, and in this case our sample size is small, so the power of the sample is low and may not detect small effects of gene variants and the heterogeneity could not be discarded. Secondly, we could not perform sub-analyses by socio-demographics and clinical features such as gender, ethnic and age among others that could be involved in the pathogenesis of SB. Nevertheless, we consider that our outcomes are important because they show a possible association between SB and the *NOS1* gene that codifies nNOS (neuronal isoenzyme); meanwhile for the iNOS (inducible isoenzyme) and eNOS (endothelial isoenzyme) we observed a lack relation with SB (Bradley and Steinert 2016; Bruenig et al. 2017; Cui et al. 2010; Rujescu et al. 2008). Hence, these findings suggest an important relation of function, location and activity of NOS enzyme.

In conclusion, our outcomes revealed a possible involvement of rs2682826 *NOS1* gene variant in the development of suicidal behavior; this gene variant could be a risk factor for suicide attempt. We recommend to perform more studies that address the involvement of oxidative stress and reactive oxygen species in SB. Our findings should be taken with caution due to the limitations above mentioned.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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