Genetic variants of the NMDA receptor influence cortical excitability and plasticity in humans

Francesco Mori¹,², Michele Ribolsi³, Hajime Kusayanagi¹,², Alberto Siracusano³, Vilma Mantovani⁴, Elena Marasco⁴, Giorgio Bernardi¹,², Diego Centonze¹,²

¹Clinica Neurologica, Dipartimento di Neuroscienze, Università Tor Vergata, 00133 Rome, Italy
²Fondazione Santa Lucia/Centro Europeo per la Ricerca sul Cervello (CERC), 00143 Rome, Italy
³Clinica Psichiatrica, Dipartimento di Neuroscienze, Università Tor Vergata, 00133 Rome, Italy
⁴Centro Ricerca Biomedica Applicata, Policlinico S. Orsola-Malpighi, 40138 Bologna, Italy

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Author for correspondence:
Diego Centonze, Clinica Neurologica, Dipartimento di Neuroscienze, Università Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. Tel. +39-06-7259-6010; Fax: +39-06-7259-6006; Email: centonze@uniroma2.it
Abbreviations list

AMT, active motor threshold; CEU, Utah residents with ancestry from northern and western Europe; CS, conditioning stimulus; FDI, first dorsal interosseus; ICF, intracortical facilitation; ISI, interstimulus interval; iTBS, intermittent theta burst stimulation; LICI, long-interval intracortical inhibition; LTP, long term potentiation; M1, primary motor cortex; MEP, motor evoked potential; PD, Parkinson’s disease; RMT, resting motor threshold; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; SNP, single nucleotide polymorphism; TMS, transcranial magnetic stimulation; TS, test stimulus.
Abstract

NMDA receptors play crucial roles in glutamate-mediated synaptic transmission and plasticity, and are involved in a variety of brain functions. Specific single nucleotide polymorphisms (SNPs) in the genes encoding NMDA receptor subunits have been associated with some neuropsychiatric disorders involving altered glutamate transmission, but how these polymorphisms impact on synaptic function in humans is unknown.

Here, the role of NMDA receptors in the control of cortical excitability and plasticity was explored by comparing the response to single, paired, and repetitive transcranial magnetic stimulations of the motor cortex in 77 healthy subjects carrying specific allelic variants of the NR1 subunit gene (GRIN1 rs4880213 and rs6293) or of the NR2B subunit gene (GRIN2B rs7301328, rs3764028, rs1805247).

Our results showed that individuals homozygous for the T allele in the rs4880213 GRIN1 SNP had reduced intracortical inhibition, as expected for enhanced glutamatergic excitation in these subjects. Furthermore, individuals carrying the G allele in the rs1805247 GRIN2B SNP show greater intracortical facilitation and greater long-term potentiation (LTP)-like cortical plasticity after intermittent theta burst stimulation.

Our results provide novel insights into the function of NMDA receptors in the human brain, and might contribute to the clarification of the synaptic bases of severe neuropsychiatric disorders associated with defective glutamate transmission.

Key words: glutamate, synaptic plasticity, transcranial magnetic stimulation.
Introduction

N-methyl-D-aspartate (NMDA) and other glutamate receptors form the major molecular determinants of excitatory synapses in the central nervous system (CNS), and play crucial roles in synaptic transmission and plasticity (Dingledine et al. 2009; Paoletti and Neyton 2007). Functional NMDA receptors are composed of a NR1 subunit (GRIN1), and one of the four NR2 subunits (GRIN2A, GRIN2B, GRIN2C and GRIN2D) (Erreger et al. 2007; Gielen et al. 2009; Li et al. 2007). The different subunits determine the binding properties of the receptor, and its permeability to extracellular cations. Furthermore, they influence the interaction of the receptor with intracellular scaffolding, anchoring and signaling molecules associated with the postsynaptic density (Liu et al. 2007).

Signaling through NMDA receptors has been associated with a variety of brain activities also including learning and memory (Barkus et al. 2010; Lovinger, 2010), and its alteration leads to severe neurological and psychiatric conditions spanning from neurodevelopment and neurodegenerative disorders to schizophrenia, mood disorders, and drug addiction (Kantrowitz and Javitt, 2010; Ma et al. 2009), as extensively documented in animal studies. In recent years, association studies have explored the role of NMDA receptors in the pathophysiology of neuropsychiatric conditions, showing that specific single nucleotide polymorphisms (SNPs) of NMDA receptor subunits impact on the risk or the severity of these disorders. GRIN1 and GRIN2B polymorphisms, in particular, have been found to be associated with infantile spasms (Ding et al. 2010), neurodevelopmental disorders (Endele et al. 2010), Alzheimer’s Disease (Chen et al. 2010), Parkinson’s Disease (Wu et al. 2010), schizophrenia (Galehdari et al. 2009), obsessive-compulsive disorder (Arnold et al. 2009), attention/deficit hyperactivity disorder (Dorval et al. 2007), and bipolar disorder (Mundo et al. 2003), confirming a widespread and essential role of NMDA receptors in brain function and dysfunction.

Together, the above results also suggest that NMDA receptor activity is modulated at excitatory synapses by some SNP variants of NR1 or NR2B subunits, but this demonstration is still lacking.
Notably, transcranial magnetic stimulation (TMS) offers the possibility of exploring in the human cortex synaptic transmission and plasticity mediated by glutamate receptors, by applying specific protocols of single, paired, or repetitive stimulations (Rossini et al. 2010). Thus, in the present study the role of NMDA receptors in the control of cortical excitability and plasticity was explored by comparing the response to single (TMS), paired-pulse (ppTMS), and intermittent theta burst stimulation (iTBS) in subjects carrying specific allelic variants of the NR1 subunit gene (GRIN1 rs4880213 and rs6293) or of the NR2B subunit gene (GRIN2B rs7301328, rs3764028 and rs1805247).

Methods

The study was approved by the Ethics Committee of the University Hospital Tor Vergata, Rome.

Subjects and SNP genotyping

We studied 77 drug free, healthy volunteers (31 males; mean age, 38.3 ± 10.2 years), submitted to SNP genotyping. All subjects gave written informed consent and were right-handed (Oldfield 1971).

The MassARRAY Assay Design 3.1 software was used to design a single 20-multiplex reaction in which the two SNPs rs4880213 and rs6293 of GRIN1 gene and the three SNPs rs7301328, rs3764028 and rs1805247 of the GRIN2B gene were included. Genotyping was performed using iPLEX Gold technology (Jurinke et al. 2002) and MassARRAY high-throughput DNA analysis with Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Sequenom, Inc., San Diego, CA), according to manufacturer’s instructions. The five SNPs of the NMDA receptor showed a call rate higher than 95%, with no significant departure from Hardy-Weinberg equilibrium.
Electromyographic (EMG) traces were recorded from the first dorsal interosseous (FDI) muscles of the left hand with 9-mm diameter, silver–silver chloride (Ag–AgCl) surface cup electrodes. The active electrode was placed over the muscle belly, and the reference electrode was placed over the metacarpophalangeal joint of the index finger. Responses were amplified with a Digitimer D360 amplifier (Digitimer, Welwyn Garden City, Hertfordshire, United Kingdom) through filters set at 20 Hz and 2 kHz with a sampling rate of 5 kHz, then recorded by a computer with SIGNAL software (Cambridge Electronic Devices, Cambridge, United Kingdom).

Motor evoked potentials (MEPs) were evoked through a figure-of-eight coil with external loop diameter of 70 mm connected to a Magstim 200² magnetic stimulator (Magstim Company, Whitland, Wales, UK). The hand motor area of right M1 was defined as the point where stimulation evoked the largest MEP from the contralateral FDI muscle. The motor hot spot was identified at the beginning of each experimental session and marked over the patients scalp with a pencil. The coil was held tangentially to the scalp surface with the handle pointing posteriorly and laterally at about 45° with respect to the mid-sagittal axis of the head. We defined the resting motor threshold (RMT) as the lowest intensity that evoked five small responses (approximately 50 µV) in a series of 10 stimuli when the subject kept the FDI muscles relaxed in both hands, according to international standards. Active motor threshold (AMT) was defined as the lowest intensity that evoked five small responses (about 200 µV) in a series of 10 stimulations when the subject made a 10% of maximal voluntary contraction. Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned test pulse.

Paired-pulse TMS was used to assess short-interval intracortical facilitation (SICF, believed to follow the activation of glutamatergic cortical interneurons) (Ziemann et al. 1998b), short-interval
intracortical inhibition and intracortical facilitation (SICI and ICF, mediated by intrinsic
GABAergic or excitatory circuits) (Kujirai et al. 1993), and long-interval intracortical inhibition
(LICI, mediated by local GABAB pathways) (Valls-Solé et al. 1992) of the right M1.

To assess SICF, the conditioning stimulus (CS) was delivered at 90% of right RMT (Ziemann et al.
1998b) following the test stimulus (TS) at interstimulus intervals (ISI) of 1.5 ms, 2.1 ms, 2.7 ms,
3.7 ms and 4.5 ms.

To assess SICI/ICF, a sub-threshold CS, delivered 2 and 3 ms (for SICI) or 10 and 15 ms (for ICF)
prior to the TS, was used to preferentially excite M1 intracortical inhibitory or excitatory fibers, and
the subsequent reduction or potentiation in contralateral MEP amplitude compared to the non-
conditioned MEP provided a measure of SICI or ICF, respectively. The CS was delivered at 80% of
right AMT (Kujirai et al. 1993; Peurala et al. 2008).

LICI was tested following the protocol adopted by (Valls-Solé et al. 1992). The intensity of CS was
set at 120% RMT. Three conditions were presented in a random order: control (TS given alone) and
two paired-pulse conditions (TS preceded by CS) at one of three different ISI (50, 100 and 150 ms).
For all ppTMS experiments ten non-conditioned MEPs and ten conditioned MEPs, at each ISI, were
collected in a randomized order at a rate of 0.2 Hz. The intensity of the TS corresponded to the
intensity required to elicit MEPs of 1mV peak-to-peak mean amplitude in the relaxed FDI.

iTBS

Intermittent TBS (iTBS) was delivered, after ppTMS experiments, over the motor M1 through a
Magstim Rapid^2 stimulator. Stimulation intensity was 80% of AMT. The iTBS protocol consisted
of 10 bursts, each burst composed of three stimuli at 50 Hz, repeated at a theta frequency of 5 Hz
every 10 s for a total of 600 stimuli (200 s). Twenty-five MEPs were collected before (baseline) and
every five minutes after iTBS for 20 minutes. Stimulation intensity was set to induce a stable MEP
of approximately 1 mV peak-to-peak amplitude in the relaxed right FDI at baseline and remained
unchanged until end of recordings. MEP amplitudes were then averaged at each time point and normalized to the mean baseline amplitude (Huang et al. 2005; Mori et al. 2011). Investigators performing TMS experiments and subjects were all blinded to genotyping during the study. TMS experiments were all performed between 2.30 p.m. and 6 p.m. to minimize cortisol negative effects on cortical plasticity.

**Data analysis**

Repeated measures ANOVA with within-subject factor ISI and between-subjects factor GENOTYPE was used on normalized peak–peak amplitudes of the mean MEPs of each subject to compare variables before and after each experimental intervention. *Post hoc* paired *t* tests were applied when necessary. Duncan’s test was used to correct for multiple comparisons. In all figures, error bars refer to the standard error.

**Results**

**Allele frequencies**

The TMS procedure was well tolerated by all subjects. Allele frequencies of the five SNPs of our sample and of the group selected for the assessment of cortical excitability are shown in table 1. The allele frequencies found are comparable to HapMap studies in CEU population (http://hapmap.ncbi.nlm.nih.gov/index.html.en).

**GRIN1 rs4880213**

Mean RMT, AMT, and stimulus intensity required to elicit a MEP of 1 mV amplitude were not significantly different among “CC”, “CT”, and “TT” subjects, suggesting that the SNP rs4880213 variants do not affect the intrinsic excitability of cortical neurons (Ziemann et al. 1996). We also addressed the possible role of SNP rs4880213 in the regulation of synaptic excitability by means of ppTMS experiments. Analysis was performed using a repeated measures ANOVA design
on the normalized data with GENOTYPE as between-subjects and ISI as within-subject main
factors. The analysis showed a significant main effect of ISI (F=3.50, p<0.05) and GENOTYPE
(F=2.42, p<0.05) and a significant GENOTYPE x ISI interaction (F=3.15, p<0.05) on SICI values.
Post hoc contrasts revealed that the “TT” group had less SICI than the other two groups at ISIs 2 ms
and 3 ms. ICF, LICI and SICF showed a significant effect of ISI (F=12.13, p<0.01 for ICF, F=5.21,
p<0.01 for SICF, and F=7.18, p<0.01 for LICI), but no significant effect of GENOTYPE and
GENOTYPE x ISI interaction (Fig. 1A-C).

In iTBS experiments we tested whether the rs4880213 polymorphism affected LTP-like synaptic
plasticity. ANOVA on the normalized data revealed a significant effect of TIME (F=3.10, P<0.05).
Conversely GENOTYPE and GENOTYPE x TIME interaction were not significant (Fig. 1D).
Additional analysis was performed by stratifying the population according to age z-scores and
gender. No significant differences emerged from this analysis.

**GRIN2B rs1805247**

Mean RMT, AMT, and stimulus intensity required to elicit a MEP of 1 mV amplitude were not
significantly different among “AA” and “AG” subjects. In our sample there were no “GG” subjects.
The analysis showed a significant main effect of ISI (F=15.10, p<0.01) and GENOTYPE (F=4.55,
p<0.05) and a significant GENOTYPE x ISI interaction (F=2.48, p<0.05) on ICF values. Post hoc
contrasts revealed that ICF elicited in the “AG” group was significantly larger than in the “AA”
group at ISI 15 ms. SICI, LICI and SICF showed a significant effect of ISI (F=22.48, p<0.01 for
SICI, F=30.90, p<0.01 for LICI and F=6.65, p<0.01 for SICF), but no significant effect of
GENOTYPE and GENOTYPE x ISI interaction (Fig. 2A-C).

In iTBS experiments we found a significant effect of TIME (F=6.45, P<0.05) and a significant
effect of GENOTYPE (F=5.2, P<0.05) and GENOTYPE x TIME interaction (F=3.2, P<0.05). Post
hoc contrasts revealed that MEP amplitudes in response to iTBS elicited in the “AG” group were
significantly larger than in the “AA” group at all times (Fig. 2D).
No significant differences emerged by stratifying the population according to age z-scores and gender (not shown).

GRIN1 rs6293, GRIN2B rs7301328, GRIN2B rs3764028

Unlike SNP rs4880213 and rs1805247, no differences were found on SICF, SICI/ICF, and LICI among the allele groups in the SNP rs6293, SNP rs7301328, SNP rs3764028. Also in iTBS experiments, the normalized data did not reveal any statistical difference among the allele groups of these SNPs (Table 2).

Discussion

The present study provides the first indication that NR1 and NR2B subunits of NMDA receptors are involved in the regulation of cortical excitability and plasticity in the human cortex. Individuals homozygous for the T allele in the GRIN1 rs4880213 SNP, in fact, showed less intracortical inhibition, while individuals carrying the G allele of the GRIN2B rs1805247 SNP showed greater synaptic facilitation and greater LTP-like synaptic plasticity after iTBS.

We propose that the TT genotype of GRIN1 rs4880213 SNP affects SICI at 2 and 3 ms by favoring glutamate transmission. In fact, SICI has been extensively investigated, and is widely regarded as a main inhibitory system in the M1 (Kujirai et al. 1993). There are two phases of SICI with maximum inhibition at ISI of about 1 and 2.5 ms (Fisher et al. 2002; Roshan et al. 2003; Vucic et al. 2009). Inhibition at ISI of 1 ms may partly be due to neuronal refractoriness (Fisher et al. 2002), but synaptic inhibition may also contribute (Ilic et al. 2002; Roshan et al. 2003). On the contrary, SICI at 2-3 ms ISI is mainly due to GABAA receptor-mediated synaptic inhibition, as suggested by several pharmacological studies (Ziemann et al. 1996). However, at this ISI, SICI does not result from a pure inhibition. Instead it reflects a balance between GABAA receptor-mediated inhibition and glutamate-mediated facilitation. The resultant inhibition or facilitation represents a complex interplay between stimulation parameters such as CS intensity and the ISI used (Ilic et al. 2002;
Indeed, it has been well established that the relationship between the degree of SICI and the intensity of the CS is a U-shaped curve (Illic et al. 2002; Kujirai et al. 1993; Peurala et al. 2008). At low levels, an increment of CS intensity leads to greater SICI, likely due to the recruitment of inhibitory interneurons. Conversely, further increase in CS intensity leads to reduced inhibition and eventually causes facilitation. Increasing CS intensity above 90% AMT, SICI at the first peak remains stable, while the peak at 2-3 ms ISI, decreases. This reduction correlates with the degree of facilitation, strongly suggesting contamination by glutamate-mediated facilitation (Peurala et al. 2008). Accordingly, drugs that reduce facilitation, such as glutamate receptor antagonists lead to an apparent increase of SICI, in particular at higher intensities of the conditioning pulse (Schwenkreis et al. 1999, 2000; Ziemann et al. 1998a). Our results provide a further indication in favor of the simultaneous engagement of GABA and glutamate synapses at 2-3 ms ISIs, because we showed that a specific SNP of the glutamate NMDA receptors enhances cortical excitation over inhibition at these intervals. Our results also suggest that the TT genotype of GRIN1 rs4880213 SNP enhances glutamate NMDA receptor function, although a final demonstration of this hypothesis is still lacking. Notably, according to recent studies the TT genotype of SNP rs4880213 is associated with increased risk of Parkinson’s Disease (PD) (Wu et al. 2010), while in schizophrenia patients with a lifetime history of depression the T allele of this SNP is less frequent than in controls (Georgi et al. 2007). As we have shown that the homozygous TT genotype may potentiate glutamatergic transmission, it may be speculated that increased frequency of T allele, and thus increased NMDA receptor function, may play a role in PD possibly through excitotoxic damage of dopamine neurons (Greenamyre et al. 2001; Porter et al. 1994; Rodriguez et al. 1998), while the lower frequency of the same allele in schizophrenia seems consistent with the hypoglutamatergic hypothesis and with the well-known dysregulation of NMDA receptor function in the pathophysiology of this disorder (Halene et al. 2009; Qin et al. 2005).

However, other NMDA-dependent neuronal adaptations might be involved in both disorders. For instance, in the attempt of recovering a function loss, an increase of cortical excitability may be
needed in order to recruit silent synapses and networks to vicariate the lost ones (Nitsche et al. 2007, Wittenberg 2009). Indeed increased excitability is encountered whenever there is a site of lesion, either acute -like in stroke- or slowly progressive, in the CNS (Butefisch et al. 2003, Delvaux et al. 2003).

Individuals carrying the G allele of the GRIN2B rs1805247 SNP showed greater ICF at 15 ms, and greater LTP-like enhancement of MEP amplitude after iTBS. These results are compatible with the idea that glutamate NMDA receptor function is enhanced in these subjects, as also suggested by pharmacological studies showing that both ICF and iTBS-induced plasticity are NMDA receptor-dependent phenomena, since blockade of NMDA receptors reduces both ICF (Reis et al. 2006; Schwenkreis et al. 2000) and iTBS-induced LTP (Huang et al. 2007; Teo et al. 2007). Notably, the permissive role of the NR2B subunit in the induction of LTP has been demonstrated in animal studies (Foster et al. 2010; Hogsden and Dringenberg 2009), and further confirmed in the present investigation in humans. The rs1805247 SNP does not alter the respective encoded amino acid of the NR2B NMDA receptor subunit. However this SNP may still influence the level of gene transcription and respective protein expression and thus influence cortical excitability and induction of plasticity in the human motor cortex.

GRIN2B rs1805247 SNP has been associated with mood disturbances (Zhao et al. 2011). In this respect, there is growing evidence for glutamatergic abnormalities and defective synaptic plasticity at the basis of depression and bipolar disorders (Diazgranados et al. 2010; Yuksel et al. 2010), and our data demonstrating altered intracortical facilitation and plasticity associated with the GRIN2B rs1805247 SNP variant might contribute to the understanding of the pathogenesis of these disorders.

A limitation of the present work may be that the data have been analyzed as if the influence of each of the SNPs was independent. Indeed, it may be argued that the response pattern to TMS may also be heavily influenced by specific combinations of SNPs within individual subjects. Unfortunately this important issue could not be properly addressed due to the small size of our sample, limiting
the conclusions that can be drawn from our study. In this respect it is also interesting to note that also the brain derived neurotrophic factor (BDNF) has been implicated in the control of NMDA-receptor dependent synaptic plasticity and its homeostatic regulation (Figurov et al. 1996). Animal studies have shown that, mature BDNF (mBDNF) plays an important role in all stages of long-term potentiation (LTP), while the precursor peptide (pro-BDNF) has been associated with long-term depression (LTD) (Lu et al. 2005). Recent work suggests that the BDNF val66met genotype influences the direction and magnitude of TMS induced corticospinal excitability even if the results are contradictory (Cheeran et al. 2009). It is therefore conceivable that the BDNF polymorphism may interfere with GRIN1 and GRIN2B SNPs in the regulation of cortical excitability.

In conclusion, in this investigation we have matched information on NMDA receptor genes with an extensive neurophysiologic evaluation of synaptic transmission and plasticity in the human cortex, and found that some NMDA receptor SNP variants affect cortical excitability. Our results might be helpful for a more comprehensive understanding of NMDA receptor function in the human brain, and for the clarification of the synaptic bases of severe neuropsychiatric disorders associated with defective glutamate transmission.
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Disclosures

The authors have no conflicts of interest to disclose
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Figure legends

**Figure 1.** rs4880213 polymorphism influences short-interval intracortical inhibition. In respect of the polymorphism rs4880213, post hoc analysis revealed that in ‘TT’ carriers, SICI at 2 and 3 ms ISIs was significantly reduced. No significant effect was found on LICI (B), SICF (C), and iTBS (D). In A, B, and C, the x-axis indicates the interstimulus interval in ms (ISI), and the y-axis represents the normalized MEP mean amplitudes elicited by paired-pulse stimulations. In the x-axis of D, “pre” refers to the normalized MEP before the iTBS stimulation. * = p<0.05

**Figure 2.** rs1805247 polymorphism influences intracortical facilitation and LTP-like plasticity. In respect of the polymorphism rs1805247, post hoc analysis revealed that in ‘AG’ genotype, ICF at ISI 15 ms was significantly increased compared to the ‘AA’ subjects (A). No significant effect was found on LICI (B), and on SICF (C). D. In the G carriers, iTBS effect was significantly increased compared to ‘AA’ carriers. In A, B, and C, the x-axis indicates the interstimulus interval in ms (ISI) and the y-axis represents the normalized MEP mean amplitudes elicited by paired-pulse stimulations, as in figure 1. In the x-axis of D, “pre” refers to the normalized MEP before the iTBS stimulation. * = p<0.05
**Table legends**

**Table 1:** Allele frequencies of the 5 analyzed SNPs. The frequency genotype data for SNPs rs4880213, rs1805247, rs6293 and rs7301328 are taken from the public database based on HapMap data for European-Americans (CEU) (http://www.hapmap.org). *SNP frequency data for rs3764028 are not available for CEU population, data shown in the table are taken from Jiang et al. (2009) based on a Han Chinese population.

**Table 2.** Effects of GRIN1 rs6293; GRIN2B rs7301328 and rs3764028 SNPs on neurophysiological measures of cortical excitability and plasticity. Based on the results of rs4880213 and rs1805247 SNPs only most relevant data are shown. Data are expressed as mean ± standard error. Differences between genotypes within each SNP are all p>0.05.
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