Genetic Variations of the NR3A Subunit of the NMDA Receptor Modulate Prefrontal Cerebral Activity in Humans

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Abstract

■ *Introduction:* Recently, a novel *N*-methyl-D-aspartate (NMDA) receptor subunit, NR3A, has been discovered in the brain. This subunit decreases NMDA receptor activity by modulating the calcium permeability of the receptor channel and current density in cortical cells. Because the NR3A is expressed in the human prefrontal cortex, we hypothesized that genetic variations of the NR3A subunit modulate prefrontal activation. *Methods:* Electromagnetic activity during selective attention (auditory oddball task with target processing) was measured in 281 healthy subjects. Genotyping of a missense variation (rs10989591, Val362Met) of the *NR3A* gene was performed. *Results:* Individuals carrying Val/Val genotype showed significantly reduced frontal P300 amplitudes compared with Met/Met subjects. Subsequent low-resolution electromagnetic source analysis revealed that this group difference is likely caused by reduced activation in the inferior frontal gyrus. *Conclusions:* It was shown for the first time that the genetic constitution of the subunit composition of NMDA receptor regulation might be relevant for prefrontal information processing in humans. The results underline the pivotal role of glutamate in frontal lobe function and indicate that the NR3A subunit could be a plausible candidate gene for diseases with prefrontal dysfunctions. ■

INTRODUCTION

Glutamate is the most important excitatory neurotransmitter in the central nervous system (CNS) and it is involved in neuronal development, brain function, as well as learning and memory (Gallinat et al., in press; Gallinat et al., 2006; Harrison & Weinberger, 2005; Javitt, 2004; Tamminga, 1998). Glutamate acts via different receptors, including the *N*-methyl-D-aspartate (NMDA) receptor, which has been implicated in several physiological CNS functions as well as pathological conditions (Olney & Farber, 1995). For instance, subanesthetic doses of the noncompetitive NMDA receptor antagonist ketamine cause a decline of immediate and delayed recall, verbal fluency, and performance on the Wisconsin Card Sorting Test (Krystal et al., 1994; Ghoneim, Hinrichs, Mewaldt, & Petersen, 1985). The achievement on these tests largely depends on the proper function of the prefrontal cortex (PFC), which is in line with the topography of the NMDA receptor density shown to be highest in the PFC and hippocampus and lowest in primary sensory regions (Maragos, Penney, & Young, 1988; Monaghan & Cotman, 1985). Furthermore, positron emission tomography investigations in healthy subjects showed increased metabolic activity of the prefrontal and cingulate cortex under ketamine exposure (Breier, Malhotra, Pinals, Weisenfeld, & Pickar, 1997; Vollenweider, Leenders, Oye, Hell, & Angst, 1997; Vollenweider, Leenders, Scharfetter, et al., 1997). Together, these findings indicate that the NMDA receptor function is essential in PFC activation and related cognitive functions.

The NMDA receptor is a heteromeric complex primarily composed of NR1 subunits and a family of NR2 subunits (NR2A–NR2D) (Hollmann & Heinemann, 1994; McBain & Mayer, 1994; Monyer, Burnashev, Laurie, Sakmann, & Seeburg, 1994; Kutsuwada et al., 1992). Both the NR1 subunit and the NR2 subunit contribute to the molecular diversity of NMDA receptors by generating receptors with unique properties that alter the activity, sensitivity, and efficiency of NMDA receptors (Hollmann & Heinemann, 1994). Subunit composition is thus an important feature of NMDA receptor regulation, and NMDA receptor dysfunction may reflect changes in receptor stoichiometry due to changes in the expression of particular NMDA receptor subunits (Monyer et al., 1994).

Several years ago, a new NMDA subunit, NR3A (previously named chi-1 or NMDAR-L), was identified (Das et al., 1998; Ciabarra et al., 1995; Sucher et al., 1995),

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which was shown to be enriched at the postsynaptic density (Das et al., 1998). More recently, it was found that the NR3A subunit is expressed in human fetal and adult cortex (Mueller & Meador-Woodruff, 2003, 2004). In addition, NR3A subunits are known to act as dominant negative regulator of the NMDA receptor current and they have been shown to alter the two most prominent properties of the NMDA receptor: calcium permeability and magnesium sensitivity (Chatterton et al., 2002; Perez-Otano et al., 2001; Das et al., 1998). The NR3A subunit is the first subunit attenuating the NMDA receptor function and is therefore relevant for understanding the NMDA receptor function. Moreover, in NR3A, knockout mice cortical cells were morphologically altered and had a greater number of dendritic spines in layer V compared to wild-type mice (Das et al., 1998). This suggests that the NR3A subunit plays a role in CNS development and plasticity via modulation of NMDA receptor activity.

The *NR3A* gene localizes to chromosome 9q34 and consists of nine exons (Andersson, Stenqvist, Attersand, & vonEuler, 2001). A common missense variation in exon 2 of the *NR3A* gene has been identified that alters the amino acid valine to methionine at position 362 (dbSNP: rs10989591; Val362Met) (Andersson et al., 2001). Due to the attenuating effect of the NR3A subunit in NMDA receptor function, including neuronal development and plasticity, this missense variation could modulate cerebral function. In the present study, we hypothesized that this genetic variation of the NR3A subunit affects the activity of the frontal cortex in humans. To measure cortical activity in a large sample, an auditory oddball task was chosen because the evoked P300 component (1) is generated by cortical areas in which the NR3A subunit is expressed including the frontal lobe (Halgren, Baudena, Clarke, Heit, Liegeois, et al., 1995; Wood & McCarthy, 1985; Knight, 1984); (2) The P300 amplitude is reduced in healthy subjects after ketamine exposure (Oranje et al., 2000) and has been found to be abnormally changed in disorders associated with glutamatergic dysfunctions such as schizophrenia (Gallinat, Winterer, Herrmann, & Senkowski, 2004; Gallinat et al., 2003; Winterer et al., 2003); (3) The P300 amplitude is to a substantial proportion genetically determined and has trait character with high retest stability (van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1998; Segalowitz & Barnes, 1993). Evoked responses (P300 amplitude) to auditory target stimuli as well as NR3A genotype were determined in 281 healthy subjects carefully screened for mental health. Differences in the cortical activation between NR3A genotype groups were investigated in realistic head models with current source density measures employing a voxel-by-voxel *t*-statistics.

METHODS

Subjects

The study was approved by the ethics committee of the University Hospital Benjamin-Franklin, Free University of Berlin (Germany). All subjects gave written informed consent. All participants, who were of German descent, were interviewed by a research psychiatrist with structured clinical interviews (Mini-International Neuropsychiatric Interview) (Sheehan et al., 1998). Exclusion criteria were *DSM-IV* axis-I or axis-II disorders, including alcohol or illegal drug abuse as well as neurological disorders, hearing disorders or any other significant cardiovascular, hepatic, renal, gastrointestinal, metabolic, or systemic disease which might have interfered with the purpose of the study. Demographic and clinical data are given in Table 1.

Genotyping

Genomic DNA was extracted from anticoagulated venous blood samples according to standard protocols. Genotyping of the missense variation rs10989591 (Val362Met) in exon 2 of the *NR3A* gene was carried out by a TaqMan nuclease assay (Livak, 1999), using TaqMan MGB probes and primers provided by the Assays-on-Demand service (Applied Biosystems, Foster City, CA, USA). The samples were amplified with GeneAmp PCR System 9700 thermocyclers (Applied Biosystems). Allelic discrimination was performed by measuring the fluorescence intensity

Table 1. Clinical Data of Subjects Separated by Genotype

	Met/Met	*Met/Val*	*Val/Val*	*Test Results*
n	41	118	122	
Age (*SD*), years	40.2 (14.6)	39.1 (15.3)	42.6 (15.2)	$F = 1.687$, $df = 2$, $p = .187$[a]
Sex (M/F)	17/24	53/65	72/50	$\chi^2 = 6.351$, $df = 2$, $p = .042$[b]
Handedness (R/L)	39/2	109/9	110/12	$\chi^2 = 3.946$, $df = 4$, $p = .413$[b]

SD in parentheses.

[a]One-way ANOVA.

[b]χ^2 test.

of reporters at the PCR end point, using an ABI Prism 7900 HT System and the SDS software version 2.1 (Applied Biosystems).

Task and ERP Recording

Recording took place in a sound-attenuated and electrically shielded room adjacent to the recording apparatus. Subjects were seated in a slightly reclined chair with a head rest. Evoked responses were recorded with 32 tin electrodes referred to Cz, using an electrode cap. The electrodes were positioned according to the International 10/20 system with the additional electrodes FC1, FC2, FC5, FC6, T1, T2, CP5, CP6, PO9, PO10. Fpz served as ground. Eye movements were recorded across an electrode 1 cm lateral to the left eye (Lo1). Electrode impedance was less than 10 kΩ. Event-related potentials (ERPs) were recorded (Synamps-Neuroscan; 500 Hz sampling rate; gain 75,000; analogous bandpass filter 0.16–50 Hz) with eyes closed and using an auditory oddball paradigm with pseudorandomized presentation of frequent nontargets (175 double-clicks with 500-msec interstimulus interval [ISI], 1-msec square waves at 83 dB) and rare targets (55 sinus-tones at 1000 Hz, 83 dB sound pressure level [SPL]; 40-msec duration including 10 msec rise and 10 msec fall time), with an overall ISI between 1.5 and 4.6 sec presented binaurally by headphones. Subjects were required to respond to targets by a button press. Post hoc data analysis was performed with Brain Vision Analyzer Version 1.05. A prestimulus period of 350 msec and a poststimulus period of 800 msec were evaluated for every sweep. For artifact suppression, all sweeps were automatically excluded from averaging when the voltage exceeded 100 μV in any one of the 32 channels at any point during the averaging period. For each subject, the remaining sweeps were averaged. Targets with a button press response later than 1800 msec were not averaged. Only waveshapes, based on at least 30 averages, were accepted. Nine subjects had to be excluded due to an insufficient number of artifact-free sweeps. The P300 amplitude was determined as the most positive amplitude between 250 and 500 msec poststimulus automatically by the analysis software (Brain Vision Analyzer Version 1.05) at the electrode positions Fz (frontal), Cz (frontocentral), and Pz (parietal), each referred to linked mastoids. A visual inspection of the results was performed to control for erroneous determinations.

Electromagnetic Source Analysis

A current density analysis was performed in 3-D Talairach space of the event-related electrooculogram (EEG) using the LORETA-software package (Low Resolution Electromagnetic Tomography, version 2003 June) (Pascual-Marqui, Michel, & Lehmann, 1994). LORETA images represent the electrical activity at each voxel in neuroanatomic Talairach space as amplitude of the computed current source density ($\mu A/mm^2$). The characteristic feature of the resulting solution is its relatively low spatial resolution, which is a direct consequence of the smoothness constraint. Specifically, the solution produces a ''blurred-localized'' image of a point source, conserving the location of maximal activity, but with a certain degree of dispersion. The version of LORETA used in the present study used the digitized Talairach atlas (Talairach & Tournoux, 1988), available as digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute, estimating the current source density distribution for either single time-points or epochs of brain electric activity on a dense grid of 2394 voxels at 7 mm spatial resolution (Pascual-Marqui et al., 1999). The solution space (the three-dimensional space where the inverse EEG problem is solved) was restricted to the gray matter and parts of the hippocampus and amygdala in the Talairach atlas. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al. (1993). A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% (Pascual-Marqui, 1999).

Statistical Analyses

The LORETA current density distribution was performed as a comparison of the event-related current density values between genotype groups using a nonparametric statistical analysis based on voxel-by-voxel t tests (Holmes, Blair, Watson, & Ford, 1996). This ''maximum t-statistic'' is a nonparametric analysis that offers—after a procedure of randomizations (e.g., 5000 randomly created groups across conditions)—a randomization distribution of the maximal statistic and produces threshold values for single voxel ps. The consideration of a maximal statistic deals with the multiple-comparison problem. Let T_{max} be the maximum of the observed statistic image T, searched over the intracerebral voxels. If the omnibus null hypothesis H_Ω (no activation anywhere in the brain) is true, T_{max} is as likely as any of the randomization values. The probability (under H_Ω) of observing a statistic image with maximum intracerebral value as or more extreme than the observed value T_{max} is simply the proportion of randomization values greater than or equal to it. This gives a p value for the omnibus null hypothesis. This p value will be $<.05$ if T_{max} is in the largest 5% of the randomization values, which is the case if and only if it is greater than the 95th percentile of the randomization values (Holmes et al., 1996). We compared the electrical activity during the P300 time range between genotypes on the basis of the estimated electric current density. These calculations were based on

Table 2. MANOVA and Post Hoc ANOVA

Analysis	*Dependent Variables*	*Age*	*Gender*	*NR3A Genotype*
MANOVA	P300 amplitude Fz, Cz, Pz	$F = 35.310$ $df = 3, p < .0001$	$F = 8.366$, $df = 3, p < .0001$	$F = 3.077$[a], $df = 6, p = .006$
Post hoc ANOVA	Fz	$F = 8.767$, $df = 1, p = .003$	$F = 3.974$, $df = 1, p = .047$	$F = 4.479$, $df = 2, p = .012$
	Cz	$F = 5.471$, $df = 1, p = .020$	$F = 4.452$, $df = 1, p = .036$	$F = 3.093$, $df = 2, p = .047$
	Pz	$F = 50.465$, $df = 1, p < .0001$	$F = 18.496$, $df = 1, p < .0001$	$F = 1.817$, $df = 2, p = .164$

P300 amplitude at electrode positions Fz, Cz, and Pz are the dependent variables for the MANOVA and the post hoc ANOVA. Factor is NR3A genotype with the covariates age and sex ($n = 281$).

[a]The effect size (partial η^2) of the NR3A genotype accounted for 3.2% of the variance.

the average waves of each subject (i.e., current source density).The time frames of interest were preselected on the basis of the expectations from the prior conventional ERP analysis (for further details, see Reischies et al., 2005; Gallinat et al., 2002; Winterer et al., 2001).

Statistical calculations were carried out as indicated in the Results section using SPSS for Windows (Release 12.0). Between-genotype comparisons of demographic data were performed with one-way analysis of variance (ANOVA) or χ^2 test as appropriate. The effect of the NR3A genotype on P300 peak amplitudes (dependent variables measured at frontocentral [Fz], centrocentral [Cz], and parietocentral [Pz] positions) was assessed by a multivariate analysis of variance (MANOVA) using ''NR3A'' and ''diagnosis'' as factors and ''age'' and ''sex'' as covariates. Further details are given in the Results section. All tests were performed with a two-sided $p < .05$.

RESULTS

Genotype

Genotype frequencies of Val/Val ($n = 122$), Val/Met ($n = 118$), and Met/Met ($n = 41$) were 43.4%, 42.0%, and 14.6%, respectively. Allele frequencies were 0.36 (A, Met362) and 0.64 (G, Val362). The genotype distribution did not significantly deviate from that expected according to the Hardy–Weinberg equilibrium ($\chi^2 = 1.984$, $df = 1, p = .159$). One-way ANOVA revealed a significant difference between genotype groups with respect to sex. No age differences were observed for the genotype groups (Table 1).

P300 Amplitude Analysis

MANOVA revealed that the dependent variables (P300 amplitudes at Fz, Cz, Pz) were significantly affected by the factor ''genotype'' (Met/Met, Met/Val, Val/Val) and the covariates ''age'' and ''sex.'' Post hoc ANOVA showed a significant effect of the factor genotype on the P300 amplitudes (*dependent variables*) at the electrodes Fz and Cz, but not Pz (Table 2). Contrast analysis showed higher P300 amplitudes at Fz in Met/Met subjects compared with Met/Val and Val/Val individuals, and higher amplitudes of Met/Met versus Val/Val subjects at the Cz electrode (Table 3; Figures 1 and 2). In this model, estimates of effect sizes (partial η^2) revealed that the genotype accounted for 3.2% of the variance. Because a gender difference was observed between the groups (Table 1), an additional MANOVA was carried out to investigate possible effects of the Genotype × Sex interaction on the P300 amplitudes. Again, the dependent variables (P300 amplitudes at Fz, Cz, Pz) were significantly affected by the factor ''sex'' ($F = 2.957$, $df = 6, p = .008$, explaining 3.1% of the variance), and the covariate ''age'' ($F = 34.968$, $df = 3, p < .0001$, explaining 27.8% of the variance), but not by the Genotype × Sex interaction ($F = 1.333$, $df = 6, p = .240$, explaining 1.4% of the variance).

Electromagnetic Source Analysis

To localize with higher accuracy the active brain regions during target detection, an intragroup comparison of

Table 3. Contrast Analyses between Genotypes Computed within the MANOVA Model

		Fz	*Cz*	*Pz*
Healthy subjects	Met/Val ($n = 118$) vs. Met/Met ($n = 41$)	$F = -2.495, p = .033$[a]	$F = -1.874, p = .105$	$F = 0.713, p = .488$
	Val/Val ($n = 122$) vs. Met/Met ($n = 41$)	$F = -3.488, p = .003$[a]	$F = -2.857, p = .014$[a]	$F = -0.701, p = .497$

[a]P300 amplitude in Met/Met subjects higher than in Met/Val as well as in Val/Val subjects (also see Table 2 and Figures 1 and 2).

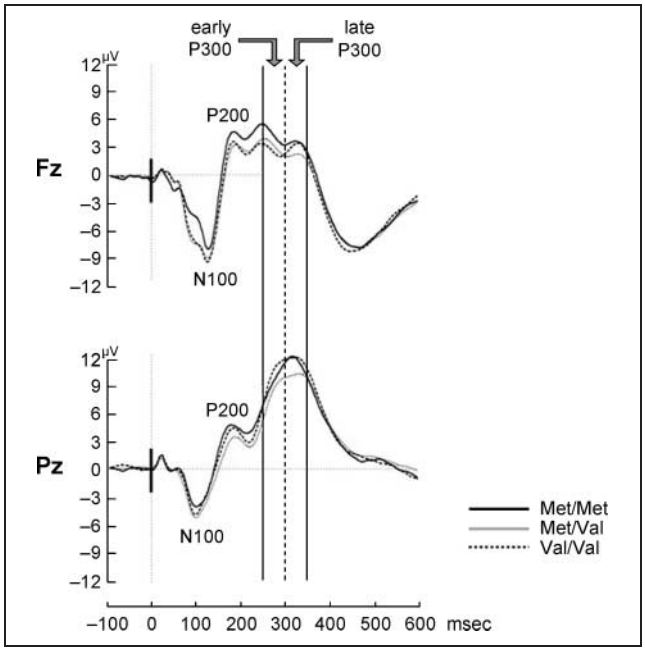

Figure 1. Grand-average curves of the ERP separated by genotype. A higher amplitude of the Met/Met group relative to the other genotype groups can be observed for the P300 amplitude at the Fz electrode. At the Pz electrode, the Met/Val group shows a smaller P300 amplitude than the other genotypes which was not statistically significant.

electrical current densities was performed for the time frames 250–300 msec (early P300) and 300–350 msec (late P300), in contrast to prestimulus baseline activity in 100 healthy subjects. The two time frames were determined according to different generators constituting the early and the late part of the P300 wave (Gallinat et al., 2001; Winterer et al., 2001; Baudena, Halgren, Heit, & Clarke, 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995). *t* Statistics showed widespread significant activations in the frontal, temporal, and parietal cortices for the early as well as for the late time frames (Figure 3 and Table 4).

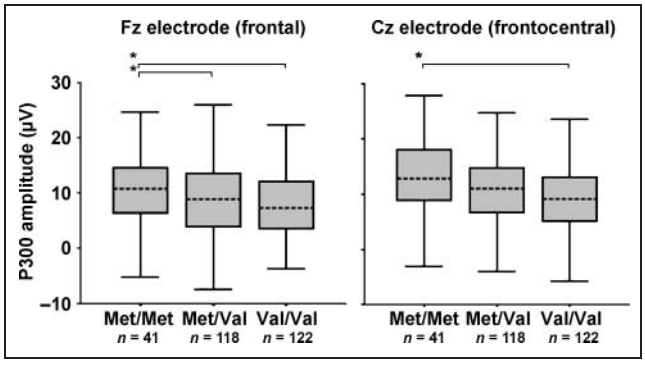

Figure 2. Box plot of the P300 amplitudes at frontal (Fz) and frontocentral (Cz) recording sites separated by genotype. *Significant differences as revealed by contrast analysis ($p < .05$; see Results section).

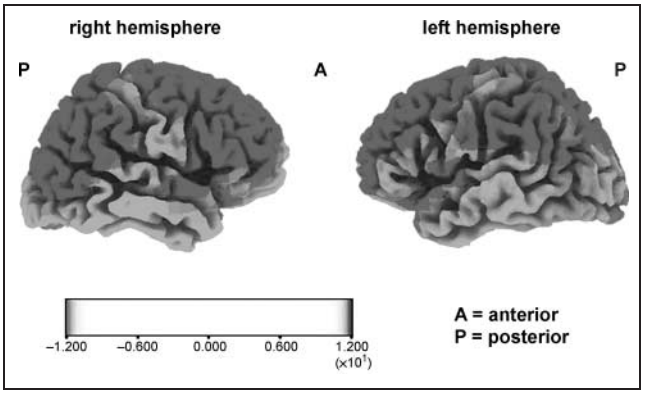

Figure 3. Current density maxima of healthy subjects ($n = 100$) at 250–300 msec poststimulus compared to baseline (prestimulus interval −150 to −100 msec). Red color indicates statistically significant higher activity poststimulus relative to prestimulus. 1% *p* value threshold: $t = 3.527$; *p* for maximum difference <.001.

Electromagnetic source analysis of brain activation differences between genotypes was performed as a *t*-map comparison of Met/Met versus Val/Val subjects. For the early P300, subjects with the Val/Val genotype showed a significant lower activation in the right lateral PFC (inferior frontal gyrus; BA 47 and BA 45) as compared to the Met/Met individuals (Figure 4). In contrast, the analysis of the activation differences in the late P300 time frame revealed no significant result.

DISCUSSION

The present study indicates that prefrontal activation during auditory target processing is modulated by genetic variation of the NR3A subunit of the NMDA receptor. The results are compatible with the pivotal role of glutamate in frontal lobe function, together with the high expression of the NR3A subunit in prefrontal cortical areas. In our investigation, it was shown for the first time in humans that the subunit composition of NMDA receptor regulation might be relevant in cortical function and that it may depend on a common genetic variation.

ANOVA with covariation of age and sex showed a significant effect of the *NR3A* missense variation Val362Met on the P300 amplitude at Fz and Cz electrodes. This indicates a functional effect of the N3RA genotype on glutamatergic neurotransmission. Compatible to this, NMDA receptor antagonists (ketamine, MK-801) were shown to reduce the P300 amplitude in animals and humans (Ehlers & Somes, 2002; Oranje et al., 2000). This is in accordance with the role of glutamate as the major excitatory neurotransmitter mediating excitatory postsynaptic potentials, which are essential for EEG oscillations and evoked potentials (Gallinat et al., 2006; Kandel & Siegelbaum, 2000; Mitzdorf, 1991; Wood & Allison, 1981).

For further spatio-temporal determination of involved cerebral regions, current source density analysis was

Table 4. *t* Statistics of Mean Current Density during Scalp P300 Activity (Time Frames 250–300 and 300–350 msec) versus Baseline (Time Frame 150–100 msec) in 100 Healthy Subjects

			Talairach			
Poststimulus Time Frame	*Cortical Area*	*BA*	*x*	*y*	*z*	*t Value*
250–300 msec	Posterior cingulate cortex	29	−3	−39	22	17.90
	Precuneus (r)	40	25	−67	50	15.36
	Inferior parietal lobule (r)	9	25	−67	57	15.34
	Angular gyrus (r)	22	32	−67	36	15.21
	Supramarginal gyrus (l)	46	−59	−46	29	14.10
	Superior temporal gyrus (l)	41	−38	−18	1	14.94
	Superior temporal gyrus (r)	39	32	−25	15	12.25
	Middle temporal gyrus (l)	10	−45	−53	15	12.68
	Anterior cingulate cortex	24	4	−4	29	16.49
	Superior frontal gyrus (l)	8	−17	59	29	14.93
		6	4	31	57	14.93
		40	−24	−11	71	13.40
	Medial frontal gyrus (r)	39	11	31	29	15.22
	Middle frontal gyrus (l)	45	−38	45	22	13.81
	Inferior frontal gyrus (r)	47	32	24	8	13.10
			32	17	−6	13.10
	Hippocampus (l)		−24	−39	1	11.41
300–350 msec	Posterior cingulate cortex	29	−3	−39	22	20.71
	Precuneus (l)	31	−10	−74	29	19.25
	Inferior parietal lobule (r)	40	53	−39	36	12.56
	Angular gyrus (r)	8	46	−74	29	13.54
	Superior temporal gyrus (l)	22	−38	−25	1	13.70
	Insula (r)	13	39	−4	1	14.52
	Precentral gyrus (r)	4	25	−11	57	12.89
	Cingulate gyrus	32	11	31	29	15.33
	Superior frontal gyrus (l)	9	−17	45	43	16.00
	Middle frontal gyrus (l)	8	−45	24	43	15.33
	Inferior frontal gyrus (l)	47	−38	31	−20	12.56

Exact $p_{max} < .0001$ for both time frames, *t*-thresholds for $p < .01$ are 3.527 and 3.390 for time frames 250–300 and 300–350 msec, respectively. Values below $t = 11.0$ are not indicated. Laterality is not indicated for midline structures. BA = Brodmann's area; (l) = left; (r) = right.

performed for the two major time frames of the P300 component. According to different generators constituting the early and late parts of the P300 (Gallinat et al., 2001; Winterer et al., 2001; Baudena et al., 1995; Halgren, Baudena, Clarke, Heit, Liegeois, et al., 1995), source analysis was performed for an early (250–300 msec) and a late time frame (300–350 msec). The analysis showed activation of various cortical areas in the frontal lobe, the temporo-parietal junction, and the hippocampus, which is in good accordance with a series of intracerebral depth electrode recordings during target detection in an oddball paradigm (Baudena et al., 1995; Halgren, Baudena, Clarke, Heit, Liegeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995). The latter authors described a distinct triphasic waveform termed N2a/P3a/SW, which was found to be most prominent in the frontal cortex, in the anterior and posterior cingulate cortex, and in the supramarginal

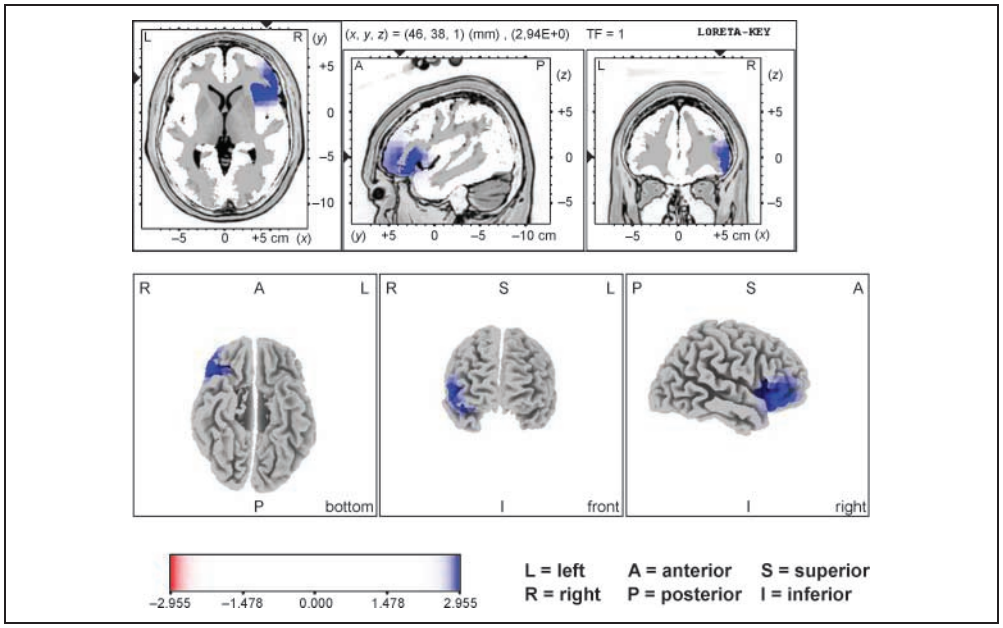

Figure 4. Top: Group comparison of absolute current density values between Met/Met and Val/Val individuals in the time range 250–300 msec. Blue color indicates significant lower activity in the Val/Val genotype group as compared to the Met/Met group. 5% p value threshold: $t = 2.966$. The maximum t values and their Talairach coordinates (x, y, z) are: 3.170 ($x = 46$, $y = 31$, $z = -6$) and 3.070 ($x = 32$, $y = 31$, $z = 1$) for the inferior frontal gyrus, and Brodmann's area 47 and 45, respectively. No other cortex area showed significant group differences. No significant t values for the later time range (300–350 msec) were observed. Bottom: 3-D view of the significant cortical activation differences.

gyrus. The P3a time course of generator activation was about 280 msec for the frontal cortex (Baudena et al., 1995) and 300–320 msec for posterior areas including the temporal and parietal cortex (Halgren, Baudena, Clarke, Heit, Liegeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995), which is very similar to the early and late time frames of our P300. Similar cortical activation patterns during oddball-like paradigm have consistently been described in fMRI investigations (Mulert et al., 2004; Winterer, Adams, Jones, & Knutson, 2002; Linden et al., 1999) as well as with the LORETA approach (Neuhaus et al., 2006).

Comparing the genotype groups homozygous for the A or G allele revealed significant differences in the inferior frontal gyrus of the lateral PFC. Activation of this region during the oddball task has been observed in intracerebral recordings (Halgren, Marinkovic, & Chauvel, 1998; Baudena et al., 1995), brain imaging studies (Ohyama, Senda, Kitamura, & Terashi, 1993), as well as electromagnetic source analyses (Prabhu et al., 2001; Winterer et al., 2001), and plays an important role in the network for directed attention and evaluation of stimulus significance (Mesulam, 1981, 1990). This particular localization is also in line with the high density of NMDA receptors in the PFC and hippocampus (Maragos et al., 1988; Monaghan & Cotman, 1985) and, more specifically, with the prefrontal expression of the NR3A subunit in humans (Mueller & Meador-Woodruff, 2003, 2004).

Although frontal lobe activation during target stimuli processing was largely symmetrical (Figure 3), the activation differences between genotypes were lateralized to the right side. This may indicate a lateralization of the NR3A subunit topography. For the NMDA receptor NR2B subunit, asymmetrical allocations have been observed previously (Kawakami et al., 2003), whereas asymmetries for the NR3A subunit have not been reported until today. However, some evidence for a lateralization of glutamatergic neurotransmission has been observed in a positron emission tomography investigation revealing an asymmetrical activation pattern of the prefrontal lobe after administration of the NMDA receptor antagonist ketamine (Breier et al., 1997). Moreover, evidence for an asymmetry in glutamatergic neurotransmission exists in schizophrenia, as right-sided abnormalities in MK-801 binding were found in a postmortem brain investigation (Kornhuber et al., 1989).

In animal experiments, direct evidence for the role of NR3A in synaptic transmission comes from *NR3A* knockout mice in which the NMDA-induced current density in cerebrocortical cells was found to be 2.8-fold greater than in wild-type cells (Das et al., 1998). Moreover, single-channel recordings in oocytes and embryonic kidney 293T cells reported a smaller unitary conductance, altered mean open time, and five-fold lower calcium permeability when NR1 and NR2A are coexpressed with NR3A (Chatterton et al., 2002; Sasaki et al., 2002; Perez-Otano et al., 2001; Das et al., 1998). Several lines of evidence indicate that NMDA receptor function is essential for the local EEG and spontaneous spiking of the neocortex (Ludvig et al., 1992; Sherwin et al., 1988; Gratton, Hoffer, & Freedman, 1987). More recently, it was found that NMDA antagonist application produces a profound potentiation of disorganized spike activity in most PFC neurons of freely moving rats (Jackson, Homayoun, & Moghaddam, 2004). This was interpreted as a possible increase of cortical noise (Jackson et al.,

2004), which is relevant for evoked potential amplitudes (Gallinat et al., 2003; Winterer et al., 1999). Moreover, NMDA receptor antagonism resulted in a reduction in organized burst activity (Jackson et al., 2004), which was previously related to an impaired neurotransmitter release and information processing (Cooper, 2002; O'Donnell & Grace, 1995). This is in line with the observation that a higher concentration of in vivo measured cerebral glutamate is associated with higher frontal theta oscillations in humans (Gallinat et al., 2006). In this context, it is interesting to speculate that the reduced prefrontal activation in individuals with the Val/Val genotype in the present study is caused by a more pronounced attenuation of the NMDA receptor function compared to Met/Met subjects. However, we consider the present association of the Val/Val genotype of the NR3A subunit with a reduced glutamatergic neurotransmission in the PFC as a hypothesis-generating finding that warrants further replication studies.

Cognitive deficits associated with frontal lobe dysfunction are a determinant of long-term disability in schizophrenia. Recent genetic linkage studies strongly implicate NMDA receptor deficiency in schizophrenia (Harrison & Weinberger, 2005) and postmortem investigations reported decreased glutamate concentrations (Tsai et al., 1995) and an up-regulation of NMDA receptors in the PFC of schizophrenic subjects (Chen et al., 1998; Simpson et al., 1992). More specifically, an elevation of the NR3A subunit transcript levels in the PFC of schizophrenic patients relative to controls has been observed in postmortem brains (Mueller & Meador-Woodruff, 2004). These reports indicate a possible role of dysfunctional glutamatergic neurotransmission (and an involvement of NR3A subunits) in frontal lobe deficits of schizophrenia (Carlsson et al., 1999). Interestingly, the prepulse inhibition of the startle response, which was found to be dysfunctional in schizophrenia (Wynn et al., 2004), is also dependent on the function of the NR3A subunit as determined in animal experiments with NR3A knockout mice (Brody, Nakanishi, Tu, Lipton, & Geyer, 2005). The reported genetic variation of the NR3A subunit may be important for sensory processing and frontal lobe function, and therefore, is a candidate gene for schizophrenia research.

A methodological limitation of the study is a possible inaccuracy of the LORETA approach. Mislocalization of sources is a principal problem of inverse solutions, particularly for simultaneously active sources (de Peralta Menendez & Andino, 2000). In the present investigation, a moderate number of electrodes were used (32 channels), and only a few electrodes were positioned below the temporal row. This may be another potential source of error variance for basal cerebral activity in particular (Michel et al., 2004; Gallinat et al., 2002; Scherg, 1994). Finally, prefrontal generators located back-to-back across the midline will cancel out and cannot be detected. Moreover, the back-to-back position of two generators may result in a lateralization effect when the two generators do not have the same strength. Together, it is possible that the right-sided genotype effect may reflect the net activation of simultaneous active bifrontal sources. Taken together, even when considering the potential drawbacks of the present study, our investigation provides some evidence that PFC activity is modulated by genetic variations of the NMDA receptor.

Acknowledgments

This work is part of the doctoral thesis of Susanne Prinz.

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