Allelic Variation in the Serotonin Transporter Promoter Modulates Cortical Excitability

Berthold Langguth, Philipp Sand, Roger Marek, Michael Landgrebe, Elmar Frank, Göran Hajak, and Peter Eichhammer

Background: Transcranial magnetic stimulation (TMS) is a noninvasive procedure that may be used to study individual differences in motor cortex excitability. Such differences are assumed to reflect serotonergic and other inputs to the motor cortex.

Methods: Here we investigate the impact of a functional polymorphism in the promoter region of the 5-hydro[illegible]amine transporter gene (5-HTTLPR) on measures of motor cortex excitability.

Results: Sixty healthy subjects carrying one or two copies of the short 5-HTTLPR allele (s/s and s/l) showed [illegible]ignificant redu[illegible]tion in short intracortical inhibition (SICI, $p = .012$) and an increased cortical silent period ($p = .042$) compared with [illegible]age- a[illegible] sex-match[illegible]d individuals homozygous for the long allele (l/l). In contrast, motor threshold and intracortical facilitation did n[illegible] differ signifi[illegible]tly be[illegible]een groups.

Conclusions: These results provide further evidence of a role for serotonergic transmissio[illegible] the m[illegible]ulation of [illegible]ortical excitability. Differential effects on the measures under study suggest a pattern of prioritization in bioa[illegible]e re[illegible]la[illegible]n of corti[illegible]l inhibition.

Key Words: Excitability, human motor cortex, paired pulse transcranial magnetic stimulation, serotonin transporter polymorphism

In the investigation of inherited physiologic and pathologic brain function, the search for electrophysiologic or neuroimaging markers related to genetic variation has become a major focus of interest (1–5). These well-defined surrogate markers of brain function offer numerous advantages over complex behavioral traits or diagnostic categories. Specifi[illegible]y, the investigation of gene–brain activity relationships can[illegible]e conducted using samples that are smaller than in settings b[illegible] dened by nosological issues and phenotypic heter[illegible]ity (1,2).

Serotonergic transmission has long been i[illegible]plicate[illegible] in the etiology of affective disorders, anxiety disor[illegible]rs, and a[illegible]diction, among other conditions. At the cellular leve[illegible] lengt[illegible] phism in the promoter of the seroto[illegible]n tra[illegible]er gene (5-HTTLPR) accounts for differences i[illegible] clearing th[illegible] monoamine from the synaptic cleft in vitro (6). [illegible]s short (s) a[illegible]es impair gene transcription and lead to reduce[illegible] serotonin transporter levels compared with cells e[illegible]pressing the [illegible]g (l) allele. Phenotypes that have previousl[illegible]een associated wi[illegible]5-HTTLPR status include personality tr[illegible] (6,7), [illegible]motional processing (2), and susceptibility to dep[illegible]sion (8). Among parameters reflecting serotonergic activity in [illegible]ntral ner[illegible]s system, an effect of the 5-HTTLPR [illegible]type [illegible] been [illegible]own on brain electrical responses o[illegible]respons[illegible] control[illegible]) and error processing (3), startle response[illegible]9), and [illegible]udness de[illegible]endence of auditory evoked potential[illegible]10,11). [illegible]some of these findings have been challenged [illegible]ore recent research (12).

Transcrania[illegible]magnetic stimulation (TMS) can be used to investigate the e[illegible]itability of neuronal circuits in the motor cortex (13). We hypothesized that intracortical excitability may also reflect genetic variation in serotonergic function. TMS measures exhibit considerable interindividual variability but are more stable [illegible] [illegible]-degree rela[illegible] (14). 5-HTT genotype and TMS measu[illegible]es have [illegible]merged independently as predictors of the personality trait neuro[illegible]ism (15,16), suggesting a common biologi[illegible] framework. This [illegible]study addresses in more detail the p[illegible]ative relationship of 5-HTTLPR and selected measures of c[illegible]rtical excitabi[illegible]y.

Pharmacolog[illegible] studies have shown that modulators of serotoner[illegible]ic transm[illegible]ion elicit changes in short-interval intracortical inhibi[illegible] (SICI) (17–19). We therefore hypothesized that SICI will be most sensitive for detecting differences related to the [illegible]PR. Three additional parameters were also investigated (resting motor thresholds, RMT; cortical silent period, CSP; and intracortical facilitation, ICF).

Methods and Materials

Healthy volunteers ($n = 137$; 65 men; mean age 28.4 ± 7.5 years) were recruited through advertisements. Written informed consent was obtained from each subject. The study protocol was approved by the local ethics committee. All participants were unrelated Caucasians, free of medication, and free of any DSM-IV diagnosis as verified during an interview by board-certified specialists (B.L. and P.E.).

DNA was extracted from blood by routine methods. Amplification of genetic variants of the 5-HTT gene linked polymorphic region (5-HTTLPR) was accomplished as described elsewhere (20). Amplification products were analyzed on a 3% agarose gel (NuSieve 3:1) by electrophoresis. Following genotyping of the entire sample, all 60 subjects from the l/l group (29 men; mean age 27.0 ± 7.0 years; range 20–44 years) were contrasted with 60 age- and sex-matched subjects from the non-l/l group (43 with s/l genotype and 17 with s/s genotype; 29 men; mean age 27.0 ± 5.5 years; range 20–38 years). This procedure was chosen because age and sex have previously been shown to influence TMS measures (21,22). Genotype distributions conformed to the Hardy-Weinberg equilibrium before and after matching.

For measurement of cortical excitability, the participants were seated in a reclining chair. TMS was delivered by two Magstim 200 stimulators (Magstim, Whiteland, Dyfed, United Kingdom) connected through a Bistim module (Magstim) to a figure-of-eight coil (double-circular 70-mm coil). The coil was held tangential to the skull and with the handle pointing backward

From the Department of Psychiatry, University of Regensburg, Germany.
Address reprint requests to Berthold Langguth, MD, Department of Psychiatry, University of Regensburg, Universitaetsstrasse 84, D-93053 Regensburg, Germany; E-mail: Berthold.Langguth@medbo.de.
Received December 23, 2008; revised January 30, 2009; accepted February 4, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.02.005

© 2009 Society of Biological Psychiatry

RETRACTED

and ~45° away from the midline. Motor-evoked potentials (MEP) of the abductor digiti minimi (ADM) muscle of the right hand were recorded with surface electrodes, bandpass filtered between 20 Hz and 10 kHz, digitized at a frequency of 5 kHz and analyzed offline. RMT and active motor threshold (AMT) were determined according to Rossini (23). CSP was measured in 10 trials (stimulus intensity: 150% RMT; intersweep interval: 5 sec) in the moderately active ADM as the interval between the end of the MEP and first reappearance of voluntary EMG activity on the nonrectified recording of every individual sweep and then averaged.

SICI and ICF were measured with a paired-pulse TMS protocol (24). The intensity of the first (conditioning) stimulus was 90% of the AMT. The second (test) stimulus was delivered at an intensity that produced MEPs of about 1 mV in the resting ADM. An interstimulus interval (ISI) of 2 msec was used to measure SICI and an ISI of 15 msec to measure ICF (24,25). The conditioned stimuli and the control condition (test pulse alone) were each tested 10 times in random order (intersweep interval: 4 sec). The effect of conditioning stimuli on MEP amplitude at each ISI was determined as the ratio of the average amplitude of conditioned MEP to the average amplitude of unconditioned test MEP.

On the basis of data from the functional analysis of the 5-HTTLPR effect on 5-HTT gene expression (6), all analyses were performed by dichotomizing genotypes as follows: "l/l" for homozygous carriers of the l allele, and "non-l/l" for the remaining subjects. The RMT, CSP, SICI, and ICF of both groups were analyzed separately using two-tailed *t* tests for unpaired samples. For all statistical tests, significance was assumed at the 5% level. Statistical analysis was performed with SPSS 16.0. Unless otherwise indicated, data are given as mean ± SD.

Results

All TMS procedures were well tolerated without any side effects. For technical reasons, data for CSP were only available for 107 subjects (55 l/l and 52 non-l/l). Subjects with the l/l genotype displayed significantly higher SICI and lower CSP values than non-l/l subjects (T = –2.5, *df* = 118; *p* = .012, Table 1, Figure 1; CSP: T = –2.06; *df* = 1[illegible], *p* = .042; Table 1, Figure 2). The other parameters of cortical excitability, RMT, and ICF did not differ significantly between groups (Table 1).

Discussion

The aim of this study was to assess whether measures of cortical excitability vary with 5-HTTLPR genotype. Subjects homozygous for the high-activity 5-HTTLPR long variant exhibited a significantly higher SICI and lower CSP than did age- and sex-matched individuals with one or two copies of the short allele. This result is in line with earlier studies demonstrating a regulatory role of the serotonin transporter gene on excitability in the auditory cortex (4,5,11) or the frontal cortex (1,3). As in previous studies, a significant difference emerged between carriers of at least one short allele and carriers of two long alleles, underscoring the functional relevance of 5-HTTLPR genotype for brain cortical phenotypes.

Our finding of reduced SICI in the non-l/l group extends

Table 1. Demographic Data and Measures of Cortical Excitability in Both Groups

	l/l Genotype	Non-l/l Genotype	*p*
n	60	60	
Sex	29 m/31 f	29 m/31 f	
Age (years)	27.0 ± 7.0	27.0 ± 5.5	1
RMT (%max SO)	42.2 ± 6.7	42.9 ± 6.8	.56
CSP (msec)	127 ± 39	141 ± 30	.042[a]
SICI	.52 ± .30	.66 ± .29	.012[a]
ICF	1.29 ± .35	1.24 ± .22	.34

All data are given as mean ± SD.

CSP, cortical silent period; ICF, intracortical facilitation; f, female; m, male; max SO, maximal stimulator output; RMT, resting motor threshold; SICI, short intracortical inhibition.

[a]Statistically significant *p* values.

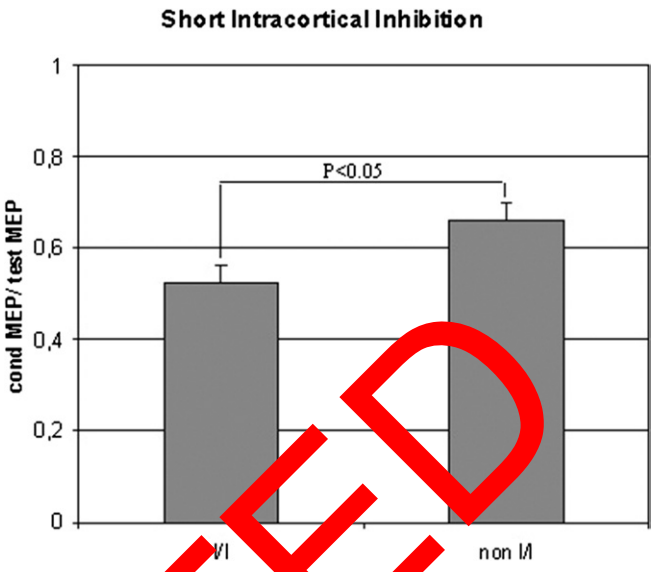

Figure 1. Short intracortical inhibition (SICI) is significantly increased in subjects with the l/l genotype compared with other subjects (non-l/l; $p = .012$). (By definition, increased SICI is reflected by lower values.) SICI is given as conditioned motor-evoked potentials (cMEP)/unconditioned MEP (uMEP) at an interstimulus interval of 2 msec. Error bars represent standard errors.

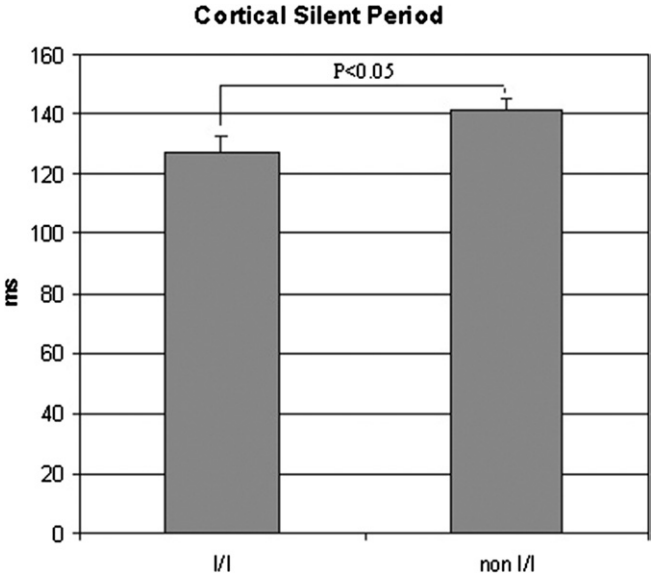

Figure 2. Cortical silent period (CSP) is significantly reduced in subjects with the l/l genotype compared with other subjects (non-l/l; $p = .042$). Error bars represent standard errors.

RETRACTED

Download English Version:

https://daneshyari.com/en/article/4178911

Download Persian Version:

https://daneshyari.com/article/4178911

Daneshyari.com