Neuropsychopharmacology (2004) 29, 1506–1511

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Allelic Variation of Serotonin Transporter Function Modulates the Brain Electrical Response for Error Processing

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A functional length variation in the transcriptional control region of the serotonin transporter gene (5-HTTLPR) influences brain function, personality traits, and susceptibility to psychiatric disorders. Here we measured prefrontal brain function by means of event-related potentials during an error processing paradigm. Physiologically, occurrence of an error elicits two specific electrical responses in the prefrontal cortex, the early error related negativity (Ne/ERN) and the later occurring error positivity (Pe), reflecting different components of error processing. Healthy subjects with one or two copies of the low-activity 5-HTTLPR short variant showed significantly higher amplitudes of the Ne/ERN and a trend to higher amplitudes of the Pe as compared to age- and gender-matched individuals homozygous for the long allele. Performance measures and latencies of these ERP-components did not differ between groups. These results indicate that the 5-HTTLPR short variant is associated with enhanced responsiveness of the brain and further supports the notion that prefrontal brain function is influenced by allelic variation in serotonin transporter function.
Neuropsychopharmacology (2004) **29,** 1506–1511, advance online publication, 9 June 2004; doi:10.1038/sj.npp.1300409

Keywords: serotonin transporter promoter polymorphism; event-related potentials; error related negativity; prefrontal brain function; Ne/ERN; Pe

INTRODUCTION

In the investigation of inherited physiological and pathophysiological brain function, the search for so-called endophenotypes has become a major focus of interest and is increasingly replacing the classical candidate gene association approach using psychometric assessment of behavioral traits. An endophenotype, for example a characteristic difference in brain function, is believed to be more directly linked to genomic variation than a highly variable behavioral phenotype. One obvious advantage of the concept of endophenotypes is that brain function is tightly controlled, resulting in increased effect sizes of genomic variation (Gottesman and Gould, 2003). Compared to association studies with genetically complex behavioral traits, which frequently comprise several hundreds of subjects, robust gene–brain activity correlations allow the investigation of substantially smaller sample sizes. Endophenotype approaches therefore attempt to associate distinct patterns of either simple brain processes, like the decreased inhibition of the P50 auditory evoked response in schizophrenic patients (eg Freedman *et al*, 1997) or more complex cognitive functions, like the brain electrical response for error processing in this study, with common functional polymorphisms in genes coding for pivotal regulatory proteins of neurocircuits. A functional length variation in the transcriptional control region of the serotonin transporter (5-HTT) gene (5-HTTLPR) has previously been shown to influence both personality traits (neuroticism: Lesch *et al*, 1996; Jang *et al*, 2001 with the 5-HTT gene accounting for 10% of the variance) and brain function related to emotionality (Hariri *et al*, 2002) as well as susceptibility to psychiatric disorders (for review, see, Lesch and Mossner, 1998; Lesch, 2003). Moreover, a recent study revealed evidence for gene × environment interaction at the 5-HTT locus, suggesting that the 5-HTTLPR genotype modulates the influence of stressful life events on depression (Caspi *et al*, 2003). Furthermore, several studies implicate the prefrontal cortex with a dysfunction of serotonergic neurotransmission in depressive patients (Mann *et al*, 2000; Wu *et al*, 2001; Arango *et al*, 2002).

Our group has previously employed an event-related potentials (ERPs) technique to investigate the relationship between cognitive brain function and allelic variation of 5-HTT function. A significant association of the 5-HTTLPR genotype with an ERP-measure of cognitive response

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Received 6 August 2003; revised 2 January 2004; accepted 13 January 2004
Online Publication: 15 January 2004 at http://www.acnp.org/citations/Npp01150403355/default.pdf

control was found in 23 healthy subjects, revealing a more pronounced frontal brain electrical activity during this task in individuals with low 5-HTT function (Fallgatter *et al*, 1999). Another stable and reliable ERP measure of prefrontal brain function, especially the anterior cingulate cortex (ACC), is the error-related negativity (Ne/ERN; Falkenstein *et al*, 1991; Gehring *et al*, 1993). This negative ERP typically appears about 80 ms after a subject commits an error in a cognitive task. Recent results favor the interpretation that the Ne/ERN reflects the output of an evaluative system engaged in monitoring conflict, as the Ne/ERN has been found also after correct responses in tasks requiring conflict monitoring (Rodriguez-Fornells *et al*, 2002). Physiologically, this negative Ne/ERN is followed by a positive component denoted Pe about 250 ms after the error which is supposed to reflect cognitive processes like conscious error processing (Nieuwenhuis *et al*, 2001) or updating of error context (Leuthold and Sommer, 1999). Moreover, several source location analyses indicate that the Ne/ERN originates in neighboring but slightly different areas within the prefrontal cortex as compared to the Pe (van Veen and Carter, 2002; Herrmann *et al*, in press), qualifying the ERN as an electrophysiological endophenotype of prefrontal brain function. Furthermore, a recent study found a larger frontal error negativity during a Stroop task in patients with geriatric depression, who did not respond to antidepressive therapy with selective serotonin reuptake inhibitors as compared to the responders (Kalayam and Alexopoulos, 2003). Based on these findings, we hypothesized that healthy subjects with one or two copies of the low-activity short (s) variant of the 5-HTTLPR display a more pronounced Ne/ERN as well as Pe, expressed by a higher amplitude of these electrophysiological indicators of prefrontal brain function, as compared to individuals homozygous for the long (l) form.

MATERIALS AND METHODS

Subjects

In total, 39 healthy subjects were included after thorough description of the study and giving informed consent to 5-HTTLPR genotyping and electrophysiological assessment. Without knowledge of the electrophysiological analysis, all 11 carriers of a l/l genotype were selected (eight female; mean age, 24.82 ± 1.08; range, 23–27 years) and contrasted with 11 age- and gender-matched s/s and s/l subjects (eight female; mean age, 24.55 ± 1.04; range, 23–27 years). All subjects were self-reported right hander and medication-free, none had a lifetime or actual history of any neurologic or psychiatric disorders.

Stimulation Paradigm

The electrophysiological investigation was conducted in an electrically shielded, sound-attenuated and dimly illuminated room. The subjects were seated in a relaxed position on a comfortable chair in a distance of 1.2 m to a monitor. The Ne/ERN paradigm was adopted from Luu *et al* (2000) and was similar to the paradigms used by Gehring *et al* (1993) and Scheffers and Coles (2000). After a warning signal (a star presented for 700 ms in the middle of the screen with a vertical and horizontal visual angle of 0.52°), a combination of five letters was shown for 800 ms (HHHHH, HHSHH, SSHSS or SSSSS; visual angle vertically 0.69°, horizontally 3.44°). Subjects were instructed to put their right index finger on the right and their left index finger on the left response button and to press the right response button as fast as possible whenever an S was the middle letter and the left response button whenever an H was the middle letter. Feedback about the correctness and the speed of the response was provided by following signals, lasting for 1000 ms on the monitor. A plus sign (+; visual angle vertically and horizontally 0.57°) was presented when the response was both correct and fast (within a time window of 400 ms after the stimulus). A correct but slow response (reaction time more than 400 ms) was followed by the German word for 'faster' (visual angle vertically 0.69° and horizontally 4.01°). An erroneous response prompted a minus sign (−, visual angle vertically 0.06° and horizontally 0.69°). The flanking letters have been implemented to increase the difficulty of the task and the error rate. All participants performed a training session consisting of 40 combinations of letters to ensure correct understanding of the instructions. Moreover, this training session was used to calculate the individual median reaction time. In the experiment the time window of 400 ms was replaced by the individual median reaction time in order to increase the error rate in faster subjects and to avoid a demotivation of slower subjects by the continuous request to respond faster (compare Stemmer *et al*, 2001). In order to enlarge the motivation, subjects were informed that they would be able to manipulate the amount of financial compensation for participating in the task. Participants were told that they would start the task with a score of 3200 points, that for each error eight points and for each feedback 'faster' 1 point per 100 ms response delay would be subtracted, and that the resulting score would influence the amount of financial compensation.

Four runs of the paradigm each consisting of 200 stimuli and lasting about 13 min were presented. Short breaks of 2–3 min were allowed between the runs. In each run occurrence of the priming star, the four stimuli and the three feedbacks as well as the motor responses with the left and the right index finger were recorded with different markers in the ongoing EEG.

EEG Recording

The EEG was recorded with 21 gold cup electrodes placed according to the International 10/20-System and three additional channels at the outer canthi of both eyes and below the right eye for the registration of eye movements. The presentation of each stimulus was registrated in a separate trigger channel with a specific marker for each condition. A 32-channel DC-amplifier (brain-star system) and a data acquisition software (Neuroscan), calibrated with an external 100 μV/10 Hz signal, were used. The hardware filter was set to a bandpass from 0.1–70 Hz, the A/D rate was 256 Hz. Recording references were linked mastoids with compensating resistors of 10 kΩ each. All electrode impedances were below 5 kΩ.

Analysis of EEG Data

The four runs per subject were analyzed together with the software 'Vision Analyser' (Brain Products, Munich, Germany). Data were transformed to average reference and filtered with a bandpass from 0.1 to 50 Hz. The data set was divided into sequences of 60 s to perform an eye movement artifact correction with the algorithm of Gratton *et al* (1983), with amplitudes of more than 100 μV considered as artifacts. The artifact-free epochs were divided into segments lasting from 200 ms before until 500 ms after each marker. Only the response locked ERPs for the conditions correct response and erroneous response are presented. Subjects with the S/S or S/L genotype had 44.4 ± 34.5 artifact-free error responses and 621.4 ± 72.9 artifact-free correct responses, carriers of the L/L genotype had 48.3 ± 22.9 artifact-free error responses and 589.8 ± 84.4 artifact-free correct responses, which did not differ between both groups (incorrect responses: $t[20] = -0.3$, $p = 0.76$; correct responses: $t[20] = -0.94$, $p = 0.36$]. A grand average with all subjects and conditions was calculated and a peak analysis of the ERP at the electrode Cz was calculated. Cz is considered as the standard position for calculating Ne/ERN measures and also in our sample the most pronounced Ne/ERN was found at this electrode. One negative peak was identified within a time segment starting at 20 ms before the response and lasting until 130 ms after the response, which was used for the calculation of the Ne/ERN amplitude, and the positive peak in the time segment from 130–450 ms was used for the calculation of the Pe-amplitude. According to Luu *et al* (2000) the amplitude of the response to erroneous and correct responses was defined as the maximal difference from minimum to zero line (peak-to-baseline amplitude). The Ne/ERN was defined as the difference between amplitude after erroneous responses minus amplitude after correct responses in μV. Correspondingly, the Pe was calculated as the amplitude-difference in the ERP elicited by erroneous as compared to correct responses in μV.

Genotyping

DNA was extracted from EDTA blood using the QIAamp Blood Kit (Qiagen, Hilden, Germany). Analysis of 5-HTTLPR genotypes was carried out with minor modifications as previously described (Lesch *et al*, 1996). Briefly, oligonucleotide primers flanking the 5-HTTLPR (sense, 5′-GAG GGA CTG AGC TGG ACA AC and antisense, 5′-GCA GCA GAC AAC TGT GTT CAT C) were used to generate 585- and/or 629-bp fragments. PCR amplification was carried out in a final volume of 25 μl consisting of 50 ng of genomic DNA, 2.5 mM deoxyribonucleotides, 8 pmoles of sense and antisense primers, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 25 mM $MgCl_2$, and 1 U of Taq DNA polymerase. After an initial denaturation step for 5 min at 95°C, 30 cycles of denaturation at 95°C for 30 s, annealing at 61°C for 45 s, and extension of 72°C for 1 min were perfomed, followed by a final extension step of 72°C for 5 min.

Statistical Analysis

All statistical analyses were performed by SPSS for Windows, version 11.5. Based on data from the functional analysis of the 5-HTTLPR effect on 5-HTT gene expression (Lesch *et al*, 1996), all analyses were performed by dichotomizing the genotypes into two groups: group S for l/s and s/s genotypes and group L for the l/l genotype. As both neurophysiological parameters were not normally distributed, the nonparametric Whitney–Mann *U*-test was used to compare the amplitudes and latencies of Ne/ERN and Pe between groups. Spearman correlation was applied to correlate genotype with Ne/ERN amplitudes. In an additional exploratory analysis error rates and reaction times were contrasted between groups by two-tailed *t*-tests for unpaired samples.

RESULTS

Performance measures of subjects in the S group (l/s and s/s genotypes) did not differ significantly from subjects in the L group (l/l genotype) with respect to number of errors (44.4 ± 34.5 *vs* 48.3 ± 22.9; $t[19] = -0.31$; NS) and reaction times for incorrect responses (325.0 ± 25.4 *vs* 330.2 ± 40.2 ms; $t[19] = -0.35$; NS). Subjects of the S group showed a significantly higher amplitude of the Ne/ERN (−5.44 ± 2.99 *vs* −3.77 ± 2.53 μV; Mann–Whitney $U = 30.0$, $Z = -2.00$, $p < 0.05$) and a trend to a higher amplitude of the Pe (4.06 ± 2.88 *vs* 2.61 ± 3.82 μV; Mann–Whitney $U = 35.0$, $Z = -1.67$, $p < 0.10$) than carriers of the l/l genotype in the L group (Figures 1 and 2). An additional analysis with linked mastoids as reference instead of average reference yielded very similar results. The latencies did not differ significantly between the S group (Ne/ERN: 51.1 ± 13.2 ms; Pe: 210.2 ± 48.8 ms) and the L group (Ne/ERN: 54.0 ± 16.4 ms; $Z = -0.70$, NS; Pe: 197.8 ± 75.7 ms; $Z = -0.76$, NS).

The *post hoc* power of the statistical analysis at an alpha-level of 0.05 was 0.95 for the Ne/ERN and 0.69 for the Pe amplitudes, with medium-range effect sizes of 0.60 and 0.43, respectively (Faul and Erdfelder, 1992). The Spearman correlation between genotype and Ne/ERN (amplitude differences) was $r = 0.437$, $p < 0.05$. Therefore, the genotype explains about 19.1% of the variance of the Ne/ERN amplitudes.

DISCUSSION

The results of this study confirm the *a priori* hypothesis by revealing significantly higher amplitudes of the Ne/ERN in subjects with one or two copies of the low-activity 5-HTTLPR short variant as compared to age- and gender-matched individuals homozygous for the long allele. This finding indicates greater brain electrical activity shortly after an erroneous response in individuals characterized by low 5-HTT activity. The evidence for enhanced brain excitability is further underscored by a trend for a higher Pe-amplitude in the same subjects, indicating also a more pronounced brain electrical activity during a later cognitive evaluation of an erroneous response. Based on results of source localization studies (Van Veen and Carter, 2002; Hermann *et al*, in press), these genetically driven differences in brain function may be attributed to different areas within the prefrontal cortex. The evidence of greater excitability of the prefrontal cortex corresponds to the findings from a previous electrophysiological study with a

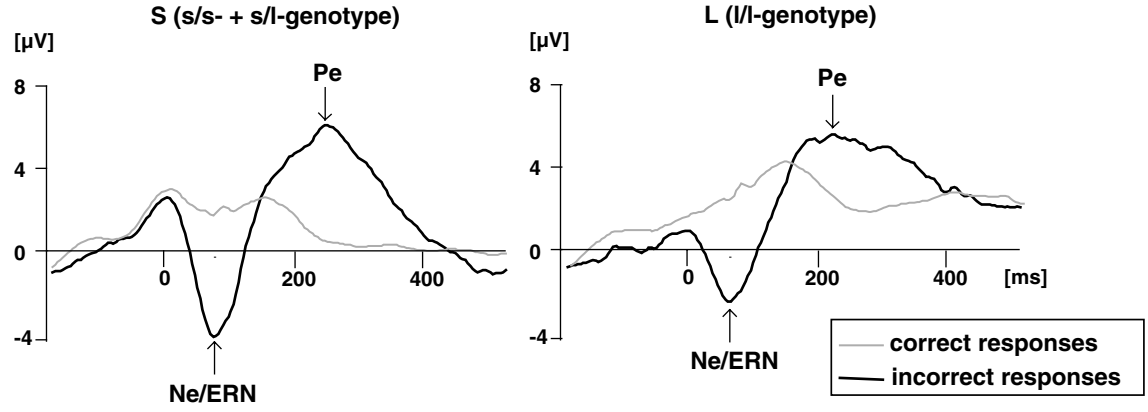

Figure 1 Response-locked grand-averaged ERPs. Left panel: Comparison between the ERPs of correct (thin line) and incorrect responses (bold line) of 11 subjects with one or two copies of the low-activity short 5-HTTLPR variant. Right panel: Comparison between the ERPs to correct (thin line) and incorrect responses (bold line) of 11 subjects homozygous for the long allele.

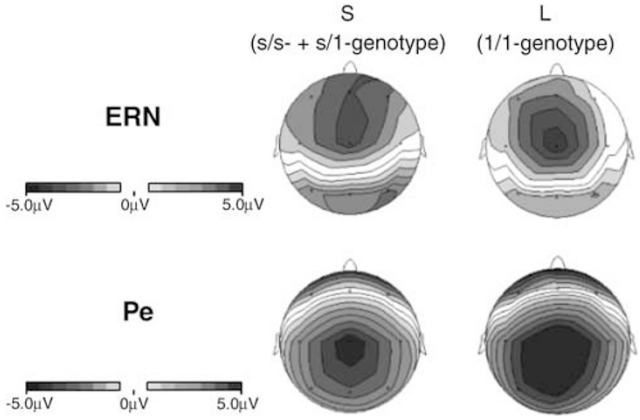

Figure 2 Scalp topographic voltage maps showing the topography at the peak of the Ne/ERN (upper panel) and at the peak of the Pe (lower panel) of both allelic groups for incorrect responses.

different cognitive task (Go-NoGo task), also suggesting a higher prefrontal brain activity in a group of 15 healthy individuals with at least one s allele of the 5-HTTPLR as compared to eight subjects homozygous for the long variant (Fallgatter *et al*, 1999).

Surprisingly, the functional status of serotonergic neurotransmission has not been implicated in the mechanisms of Ne/ERN before. In a recent theoretical model of the neural basis of human error processing (Holroyd and Coles, 2002), only the dopaminergic neurotransmission was discussed as functionally relevant, the mesencephalic dopamine system conveying a negative reinforcement learning signal to the ACC, thereby generating the Ne/ERN. However, given the manifold interactions of dopaminergic and serotonergic systems within the prefrontal cortex (Benes *et al*, 2000; Vermetten and Bremner, 2002), a role of serotonin system function in error-processing seems likely.

Allelic variation in 5-HTT function was previously found to account for approximately 4% of total variance in anxiety and depression-related personality traits in individuals as well as sibships (Lesch *et al*, 1996). In addition to studies of the low-activity s variant's effect on personality traits, a role of the 5HTTLPR has been suggested in a variety of psychiatric diseases including major depression and bipolar disorders (Collier *et al*, 1996; Lesch, 2003). Rates of major depression were found to be strongly influenced by the number of stressful life events in carriers of s alleles of the 5-HTTLPR, but not in those individuals with the l/l genotype (Caspi *et al*, 2003).

Furthermore, healthy volunteers with one or two copies of the low-activity s allele of the 5-HTTLPR exhibit greater neuronal activity of the amygdala in response to fearful stimuli when compared with individuals homozygous for the long allele, as assessed by functional magnetic resonance imaging (fMRI; Hariri *et al*, 2002). Amygdala hyperresponsivity provoked by fearful stimuli in carriers of the low-activity 5-HTTLPR s allele indicates a greater tendency to express anxiety-related traits in a subgroup with low 5-HTT function and associated activity status of the serotonin system. In addition to the exaggerated stress reactivity and associated with increased risk to suffer from depression or other emotional disorders, in these individuals carrying low-activity 5-HTTLPR allele(s), anxiety-provoking stimuli may further enhance genuine amygdala hyperexcitability or physiologic amygdala activity may lack the restrictive control by prefrontal cortical circuits caused by increased excitatory neurotransmission (Davidson, 2002).

The genetic cause for this prefrontal cortex-limbic hyperexcitability — except for allelic variation in 5-HTT function — remains, however, elusive. Notably, genetic influences are not the only pathway that lead to individual differences in personality dimensions, behavior, and psychopathology. Complex traits like error processing are most likely generated by a complex interaction of environmental and experiential factors with a number of genes and their products as documented extensively for the 5-HTT in both non-human primates and humans (Bennett *et al*, 2002; Caspi *et al*, 2003; Champoux *et al*, 2002; Lesch, 2003).

Analogous to fMRI studies, the considerably high effect sizes for applied ERP measures (Fallgatter *et al*, 2000) and their unique ability to assay information processing at the level of brain function during cognitive tasks in relatively small samples of individuals and in the absence of noticeable behavioral differences, offers another powerful

approach to functional genomics of the brain. The consistent results derived from electrophysiological paradigms underscore the power of direct assessment of brain physiology in exploring the functional impact of genomic variation. Moreover, they also support the notion of a critical link between functional gene variation and robust differences in information processing within distinct neurocircuits that have been linked to the manifestation of distinct behavioral traits and psychiatric disorders (Hariri and Weinberger 2003).

It has to be taken into account that such a small case–control study is vulnerable to generating false positive results and, therefore, definitely needs an independent replication in a larger sample with more emphasis laid on problems related to population stratification. However, the findings of this study hopefully should stimulate further investigations of psychiatric patient cohorts employing the endophenotype approach.

ACKNOWLEDGEMENTS

This research was supported in part by a grant from the Deutsche Forschungsgemeinschaft (SFB 581).

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