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Serotonin Transporter Gene Polymorphism, Childhood Trauma, and Cognition in Patients With Psychotic Disorders

Monica Aas[*,1], Srdjan Djurovic[1,2], Lavinia Athanasiu[3], Nils Eiel Steen[3], Ingrid Agartz[1,4], Steinar Lorentzen[4], Kjetil Sundet[5], Ole A. Andreassen[1,3], and Ingrid Melle[1,3]

[1]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [2]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway; [3]Psychosis Research Unit, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; [4]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway; [5]Department of Psychology, University of Oslo, Oslo, Norway

*To whom correspondence should be addressed; Post Doctoral researcher, Thematically Organized Psychosis study group, Division of Mental Health and Addiction, Institute of Clinical Medicine, Bygg 49, Ullevål sykehus, PO Box 4956 Nydalen, 0424 Oslo, Norway; e-mail: monica.aas@medisin.uio.no

Objective: **The functional polymorphism in the promoter region of the SLC6A4/5-HTT serotonin transporter gene (5-HTTLPR) has been linked to altered stress response. Carriers of the short (s-) allele have increased negative psychological reactions and stress hormone release compared with carriers of the long (l-) allele, interacting with severe life events including childhood trauma. High stress levels are associated with cognitive impairments in a variety of clinical and experimental studies. Patients with psychotic disorders are characterized both by more childhood traumatic events and abnormal stress responses and by significant but highly variable cognitive dysfunction. We hypothesize that 5-HTTLPR variations and long-term effects of childhood trauma interact and contribute to some of the variation in cognitive dysfunction seen in patients with psychotic disorders.** ***Methods:*** **Patients with psychotic disorders (schizophrenia and affective spectrums) were recruited from a catchment area–based treatment organization. History of childhood abuse was obtained by the Childhood Trauma Questionnaire. Cognitive function was assessed through a comprehensive, standardized neuropsychological test battery. 5-HTTLPR genotypes were analyzed using standard polymerase chain reaction.** ***Results:*** **We observed a significant interaction between 5-HTTLPR variants and childhood trauma across cognitive domains; here, homozygotic s-carriers exposed to high levels of childhood trauma (physical neglect and abuse) had significantly poorer cognitive functioning than all other groups.** ***Conclusions:*** **Our results need replication but underline the importance of investigating childhood trauma and its interaction with genetic markers when studying cognitive dysfunction in patients with psychotic disorders.**

Key words: psychosis/childhood trauma/serotonin transporter gene/cognitive function

Introduction

The human serotonin transporter gene (SLC6A4/5-HTT/) is extensively studied in psychiatry. A functional polymorphism in the promoter region of the gene (5-HTTLPR) is associated with several psychiatric disorders; here, individuals with the short (s-) allele show increased levels of anxiety compared with persons with long (l-) allele even in neutral situations.[1] A large body of research also shows a relationship between 5-HTTLPR variations and stress response,[2,3] with higher cortisol response in s-carriers already present in newborns.[4] There are also indications that 5-HTTLPR variation interacts with stressful life events, particularly severe childhood adversity, increasing risk of depression and suicidal behavior in s-carriers.[5] While there is some discordance,[5,6] several lines of evidence support an interaction between 5-HTTLPR variations and stressful events on a range of psychiatric symptoms and disorders.[7]

Several studies have also shown associations between childhood trauma and poorer performance on cognitive tasks in adulthood, including measures of intellectual and academic functioning,[8,9] verbal memory and working memory.[8] This effect may partly be mediated through stress response disturbances, as increased stress is associated with cognitive impairments in both clinical and experimental settings.[10–13] Several studies also indicate that 5-HTTLPR variation affects the hypothalamic-pituitary (HPA) axis and may thus mediate or moderate relationships between environmental stress and cortisol response.[3,14–17] The few existing studies of the relationship

between 5-HTTLPR variation and cognition in healthy individuals are however divergent; while 2 small studies indicate better executive functioning in s-carriers compared with homozygotic l-carriers,[18,19] a larger study show worse memory performance in s- carriers.[3]

Cognitive dysfunction is also a core abnormality in schizophrenia spectrum disorders.[20] The majority of patients with schizophrenia function at a level at least 1 SD below healthy comparison groups, even at the time of their first episode[20–22] and the dysfunction endures after successful treatment of psychotic symptoms.[23]In addition to a global cognitive deficit, specific cognitive domains such as episodic memory, working memory, and executive function are particularly affected.[20] Cognitive dysfunction is also observed in similar areas in bipolar disorder, however to a less severe degree.[21,24] In the 2 existing studies of associations between 5-HTTLPR variation and cognitive dysfunction in patients with schizophrenia, one using a test battery without measures of executive functioning found no relationship to cognitive dysfunction,[25] while the other found poorer executive functioning in s-carriers.[26]

Severe childhood adversity is also more common in subjects with psychotic disorders compared with the general population.[27] While the ability to draw conclusions about casual mechanisms here is debated,[28] the increased prevalence of childhood trauma in psychotic patients is widely accepted.[29–31] There is also increasing evidence that stress response disturbances is linked to the precipitation of psychosis in vulnerable individuals.[32] Recent studies also indicate associations between abnormal stress responses and cognitive dysfunctions in psychotic disorders,[22] in addition to possible relationships between childhood trauma and cognitive dysfunction[33] even if there are inconsistent findings.[33,34] Some discrepancies may be due to specific associations between different types of childhood trauma and cognitive domains[35] or differences in associations between trauma types and psychotic symptoms,[36] as indicated by recent studies.

There are thus indications of relationships between trauma exposure, stress response abnormalities and cognition, and a role of 5-HTTLPR variants influencing stress response. These are all key factors in psychotic disorders, but no study to now has investigated the role of 5-HTTLPR variants as a potential modulator in this context. The overall aim of this article is to gain insight into mechanisms behind variations in cognitive impairments in psychotic disorders, by investigating the link between types of childhood trauma, 5-HTTLPR variants, and cognitive dysfunction. Based on previous studies, our hypotheses are as follows: (1) Presence of childhood trauma is related to cognitive dysfunction, particularly in working memory/executive functioning and memory. (2) S-carriers with a history of childhood trauma will have more cognitive dysfunction than homozygotic l-carriers and/or patients without childhood trauma.

Methods

Subjects

The participants were recruited consecutively from psychiatric units in 4 major hospitals in Oslo, as part of the Thematically Organized Psychosis Research study. To minimize genetic variation, only patients with European ancestry were included in this part of the study. Between 2003 and 2010, 118 patients were recruited, 50 with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, (DSM-IV) schizophrenia spectrum disorders (43 schizophrenia/schizophreniform and 7 schizoaffective), 53 psychotic affective disorders (33 bipolar I, 10 bipolar II with psychotic symptoms while depressed, 6 bipolar not otherwise specified (NOS), and 4 major depression with mood incongruent psychotic features), and 15 with other psychoses (delusional disorder, brief psychotic disorder, and psychosis NOS). In addition, 478 healthy persons from the same geographical area without drug abuse or severe mental disorders in their families were recruited as controls. Common exclusion criteria were: hospitalized head injury, neurological disorder, and unstable medical conditions interfering with brain function. To assure valid test performance, all participants had Norwegian as their first language or scored $\geq$15 in the forced recognition trial of the California Verbal Learning Test (CVLT).[37] Of the patients, 12 (10%) used no psychopharmaceuticals, 89 (75%) $\geq$1 antipsychotics, 43 (37%) antidepressants, and 1 (8%) mood stabilizers (one patient with missing data). The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants gave written informed consent.

Clinical Assessment

Clinical assessment was carried out by trained psychiatrists or clinical psychologists. Diagnoses was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Diagnostic reliability was satisfactory with an overall $\kappa = 0.77$ (95% CI: 0.60–0.94) for diagnostic categories.[38] Current positive and negative symptoms were rated using the Positive and Negative Symptom Scale .[39] Interrater reliability was good with intraclass correlation coefficients (ICC 1,1)[40] for subscales ranging from 0.71 to 0.73. Participants were defined as currently psychotic if they scored $\geq$4 on any of items P1, P3, P5, P6, or G9. Participants were considered to have a history of psychosis if they had any previous SCID-verified psychotic episodes. Duration of illness (DI) (years since first contact with psychiatric health services due to psychotic symptoms for the schizophrenia group, psychotic or affective symptoms for the schizoaffective, and bipolar groups), number of affective and psychotic episodes, hospitalizations and suicide attempts, and use of medication at time of testing were determined through clinical interview and medical charts.

Neurocognitive Assessment

Neurocognitive assessment was carried out by psychologists trained in standardized neuropsychological testing. A 3-hour test battery (including measures of estimated premorbid IQ) was administered in fixed order with 2 refreshment breaks. Included in current analyses are measures previously found sensitive to dysfunction in psychotic disorders with emphasis on measures sensitive to stress[9,10,21] comprising the following 4 domains: (1) memory; (2) working memory and executive functioning; (3) perception and visuospatial abilities; and (4) verbal abilities. Individual test scores were converted into standardized *z* scores relative to the healthy controls means and SDs (controls' mean IQ score 113 ± 10.04; range 78-138). Patients *z* scores can thus be read as deviations from scores of the control group. To examine performance by domain, *z* scores within each domain were averaged together. Confirmatory correlational analyses ensured that test scores within each domain shared similar variance and could be considered part of the same cognitive construct (Pearson correlation coefficients ≥ 0.50)[41]; all tests within each domain met this criterion.

The neuropsychological battery was composed as follows:

General Cognitive Function. Full-scale IQ derived from Wechsler Abbreviated Scale of Intelligence[42] from subtests in the neuropsychological battery.

Memory. The California verbal learning test (CVLT) to measure verbal memory at immediate and delayed (30 min) time points.[37]

Working Memory and Executive Function. To measure working memory and executive function, letter-number sequencing, digit span forwards, and digit span backwards was conducted.[43]

Perception and Visuospatial Abilities. Measured with block design task[42] and matrix reasoning.[42]

Verbal Abilities. Measured with similarities (abstract verbal reasoning) and vocabulary (degree of having learned, comprehended and ability to express vocabulary) from the Wechsler Adult Intelligence Scale—Third Edition.[42]

Childhood Trauma Questionnaire

We used the 28-item Childhood Trauma Questionnaire (CTQ) translated to Norwegian; a retrospective questionnaire yielding scores for the 5 subscales childhood physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect; enquiring about traumatic experiences in childhood with answers ranging from "never true," "rarely true," "sometimes true," "often true," to "very true."[44] Reliability and validity of the CTQ have been demonstrated previously.[44] Resulting variables were heavily skewed since many were not exposed to childhood trauma at all while those who were often had been exposed to several types with varying severity. Data from the CTQ are dichotomized by the common method of a median split into low and high levels for each sub scale to facilitate presentations and data analyses.[45] Childhood trauma data were analyzed both for subscales, together with an overall test of childhood trauma with all subscales added together.

Genotyping; 5-HTT-Linked Polymorphism PC

Oligonucleotide primers flanking the 5-HTT-linked polymorphic region (5-HTTLPR) and corresponding to the nucleotide positions ranging from −1416 to −1397 (stpr5; 5′ GGCGTTGCCGCTCTGAATTGC) and from −910 to −889 (stpr3; 5′- GAGGGACTGAGCTGGACAACCCAC) of the h5-HTT gene regulatory region were used to generate a 484/528-hp fragment.[46] Polymerase chain reaction amplification was carried out in a final volume of 30 µl consisting of 50 ng genomic DNA, 2.5 mM of each deoxyribonucleotidetriphosphates, 0.1 µg of sense and antisense primers, 10 mM Tris-HC1 (pH 8.3), 50 mM KCI, 1.5 mM MgCl2, 5% dimethyl sulfoxide, and I U of Taq DNA polymerase. Termal cycling was performed at 95°C for 15 minutes and amplified for 35 cycles (a 30 s denaturation at 95°C, followed by 30 s of annealing at 61°C, and a 60 s extenion at 72°C), with a final extension of 7 minutes at 72°C, as described earlier.[46]

Statistical Analyses

Data were analyzed using the Predictive Analytic software, Version 18 (formerly SPSS Statistics), and Plink (Whole genome association analysis toolset). Continuous variables are presented as mean ± SD. As the childhood data were not normally distributed, we used either nonparametric tests or transformed as previously described under measurements, depending on analysis. For descriptive analyses (tables 1 and 2), we used X^2-test and Univariate ANOVA. To reduce the number of comparisons in the main analyses, we collapsed cognitive measurements into 4 domains as previously described and then used repeated measures ANOVAs with the cognitive domains as within-subjects variables and 5-HTTLPR genotypes (ll, sl, and ss carriers), and childhood trauma experiences (split at the median) as between subject's factors. This approach has been used to reduce the number of analyses and thus the risk of spurious findings in several previous studies, keeping the validity of the results higher while still allowing for small numbers.[41,47,48] The interaction term in the analysis will thus be for the between-subject effect average over cognitive domains. Follow-up analyses of covariance correcting

Table 1. Demographics and Clinical Characteristics of the Patients Grouped by 5-HTTLPR Genotypes

	ll (n = 31)		sl (n = 59)		ss (n = 28)		Statistics	*df*	*P*
	n	%	*n*	%	*n*	%			
Gender (m/f)	12/19	38.7/61.3	35/24	59.3/40.7	17/11	60.7/39.3	$X^2 = 4.10$	2.0	.13
Physical abuse below/above median	17/14	54.8/45.2	31/28	52.5/47.5	21/7	75.0/25.0	$X^2 = 2.31$	1.0	.13
Sexual abuse below/above median	20/11	64.5/35.5	38/21	64.4/35.6	22/6	78.6/21.4	$X^2 = 1.27$	1.0	.26
Physical neglect below/above median	17/14	54.8/45.2	39/20	66.1/33.9	21/7	75.0/25.0	$X^2 = 2.66$	1.0	.10
Emotional abuse below/above median	18/13	58.1/41.9	29/30	49.2/50.8	19/9	67.9/32.1	$X^2 = 0.49$	1.0	.48
Emotional neglect below/above median	13/17	43.3/56.7	35/19	64.8/35.2	19/9	67.9/32.1	$X^2 = 3.17$	1.0	.053
Diagnosis							$X^2 = 2.96$	4.0	.57
Schizophrenia	16	51.6	23	39.0	11	39.3			
Affective psychosis	13	41.9	26	44.1	14	50.0			
Other psychosis	2	6.5	10	16.9	3	10.7			
	Mean	SD	Mean	SD	Mean	SD			
Age	33.0	12.0	32.4	11.2	30.9	1.4	$F = 0.27$	2.0	.76
Years of education	14.0	3.6	13.5	2.9	13.8	3.3	$F = 0.33$	2.0	.72
Current IQ	104.0	15.4	107.7	11.6	101.8	20.3	$F = 2.14$	2.0	.12

for differences in age, gender, and parental education level were conducted since these factors may influence cognitive function.

Results

Sample Characteristics

Patients' demographic and clinical characteristics grouped by 5-HTTLPR allele are presented in table 1 (Table 1 in here). There were no differences between groups in age, gender, years of education, or diagnostic distribution but with a trend for the experience of more emotional neglect in the l- carriers''. The duration of untreated psychosis was 3.2 ± 5.6 years and DI was 2.3 ± 4.2years, both not significantly different across groups ($X^2 = 97.7$, $df = 92$, $P = .32$ and $X^2 = 33.6$, $df = 32$, $P = .39$, respectively).

5-HTTLPR Variation and Cognitive Function

There was a significant association between 5-HTTLPR variations and cognitive dysfunctioning, in particular for memory tests, in the direction that l-carriers performed better than s-carriers (table 2) (Table 2 in here). Overall, the data show that across both cognitive domains and subtests, homozygotic l-carriers did better than homozygotic s-carriers with the heterozygotic group (sl) performed in between.

Table 2. Z Scores With Means and SDs for Cognitive Domains (in Bold) and Cognitive Subtests by 5-HTTLPR Genotype

	ll (n = 31)		sl (n = 59)		ss (n = 28)		Statistics		
Cognitive tests	Mean	SD	Mean	SD	Mean	SD	*f*	*df*	*P*
Memory	−0.15	1.01	−0.54	1.28	−1.16	1.32	5.07	2.0	.008**
CVLT list A trial 5	−0.15	1.07	−0.57	1.37	−1.15	1.39	4.33	2.0	.015*
CVLT short delay free recall	0.00	1.04	−0.53	1.26	−1.05	1.25	5.66	2.0	.005**
CVLT short delay cued recall	−0.11	1.02	−0.57	1.41	−1.07	1.41	3.87	2.0	.024*
CVLT long delay free recall	−0.20	1.06	−0.52	1.32	−1.23	1.36	5.00	2.0	.008**
CVLT long delay cued recall	−0.18	1.01	−0.60	1.43	−1.20	1.41	4.36	2.0	.015*
CVLT recognition	−0.17	1.41	−0.46	1.60	−1.28	2.00	3.51	2.0	.033*
Working memory/executive function	−0.57	0.74	−0.56	0.81	−0.47	0.96	0.14	2.0	.87
WAIS-III digit span forwards	−0.42	0.84	−0.36	0.91	−0.12	1.02	0.85	2.0	.43
WAIS-III digit span backwards	−0.46	0.83	−0.59	0.97	−0.80	0.95	0.98	2.0	.38
WAIS-III letter number sequencing	−0.85	0.99	−0.74	1.11	−0.62	1.17	0.30	2.0	.74
Perception and visuospatial abilities	−0.59	1.11	−0.58	1.09	−0.98	1.29	1.31	2.0	.27
WASI block design	−0.90	1.39	−0.73	1.28	−1.05	1.30	0.61	2.0	.55
WASI matrix reasoning	−0.29	0.98	−0.43	1.15	−0.91	1.62	2.08	2.0	.13
Verbal abilities	−0.62	1.21	−0.58	1.17	−0.91	1.11	0.80	2.0	.45
WASI vocabulary	−0.61	1.38	−0.54	1.38	−0.82	1.28	0.39	2.0	.68
WASI similarities	−0.64	1.29	−0.62	1.14	−1.01	1.20	1.09	2.0	.34

Note: WASI, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition; CVLT, The California Verbal Learning Test.
*$P < .05$; ** $P < .01$; ***$P < .001$.

Table 3. Z Scores for Cognitive Domains (With Means and SDs) for the Groups Formed Based on Presence of Above or Below Median Ratings of Childhood Trauma (Low or High Trauma) and 5-HTTLPR Genotypes (ll, sl, and ss)

	Genotype and trauma groups						
Cognitive domain	ll low trauma (n = 15)	ll high trauma (n = 12)	sl low trauma (n = 29)	sl high trauma (n = 22)	ss low trauma (n = 21)	ss high trauma (n = 7)	Interaction effect (f, df, P)
Physical abuse							3.23, 2.0, .04**
Memory	−0.21 ± 1.28	−0.001 ± 0.74	−0.76 ± 1.25	−0.07 ± 0.65	−1.01 ± 1.26	−1.62 ± 1.50	
Working memory	−0.42 ± 0.84	−0.58 ± 0.62	−0.59 ± 0.77	−0.38 ± 0.91	−0.33 ± 0.97	−0.89 ± 0.85	
Perception and visuospatial abilities	−0.26 ± 1.12	−0.56 ± 0.95	−0.69 ± 1.05	−0.42 ± 1.16	−0.87 ± 1.24	−1.31 ± 1.45	
Verbal abilities	−0.42 ± 1.26	0.54 ± 0.91	−0.64 ± 1.24	−0.45 ± 0.84	−0.68 ± 0.78	−1.59 ± 1.66	
	ll low trauma (n = 18)	ll high trauma (n = 9)	sl low trauma (n = 35)	sl high trauma (n = 16)	ss low trauma (n = 22)	ss high trauma (n = 6)	(f, df, P)
Sexual abuse							0.76, 2.0, .47
Memory	−0.36 ± 1.19	0.37 ± 0.53	−0.47 ± 1.23	−0.45 ± 0.68	−1.20 ± 1.31	−1.01 ± 1.49	
Working memory	−0.40 ± 0.64	−0.67 ± 0.92	−0.46 ± 0.87	−0.58 ± 0.76	−0.45 ± 1.01	−0.56 ± 0.78	
Perception and visuospatial abilities	−0.42 ± 1.20	−0.49 ± 0.66	−0.54 ± 1.04	−0.63 ± 1.24	−0.90 ± 1.40	−1.29 ± 0.72	
Verbal abilities	−0.71 ± 1.15	−0.01 ± 1.10	−0.40 ± 1.13	−0.92 ± 0.88	−1.00 ± 1.21	−0.60 ± 0.53	
	ll low trauma (n = 16)	ll high trauma (n = 11)	sl low trauma (n = 26)	sl high trauma (n = 25)	ss low trauma (n = 19)	ss high trauma (n = 9)	(f, df, P)
Emotional abuse							2.96, 2.0, .057*
Memory	0.07 ± 1.31	−0.19 ± 0.60	−0.69 ± 1.30	−0.23 ± 0.75	−1.07 ± 1.42	−1.36 ± 1.14	
Working memory	−0.38 ± 0.78	0.66 ± 0.68	−0.54 ± 0.87	−0.45 ± 0.80	−0.29 ± 1.00	−0.85 ± 0.80	
Perception and visuospatial abilities	−0.31 ± 1.01	−0.65 ± 1.09	−0.61 ± 1.10	−0.53 ± 1.11	−0.69 ± 1.30	−1.60 ± 1.06	
Verbal abilities	−0.46 ± 1.28	−0.50 ± 1.02	−0.76 ± 1.21	0.36 ± 0.89	−0.66 ± 0.84	−1.45 ± 1.43	
	ll low trauma (n = 15)	ll high trauma (n = 12)	sl low trauma (n = 34)	sl high trauma (n = 17)	ss low trauma (n = 21)	ss high trauma (n = 7)	(f, df, P)
Physical neglect							6.10, 2.0, .003***
Memory	−0.16 ± 0.74	−0.46 ± 1.32	−0.60 ± 1.22	−0.19 ± 0.68	−1.05 ± 1.41	−1.50 ± 1.01	
Working memory	−0.30 ± 0.70	−0.73 ± 0.76	−0.72 ± 0.77	−0.07 ± 0.79	−0.37 ± 0.99	−0.77 ± 0.84	
Perception and visuospatial abilities	−0.23 ± −0.94	−0.72 ± 1.11	−0.78 ± 1.12	−0.16 ± 0.95	−0.81 ± 1.39	−1.51 ± 0.75	
Verbal abilities	−0.20 ± 1.19	−0.82 ± 1.07	−0.71 ± 1.20	−0.26 ± 0.71	−0.91 ± 1.12	−0.91 ± 1.13	
	ll low trauma (n = 12)	ll high trauma (n = 14)	sl low trauma (n = 31)	sl high trauma (n = 15)	ss low trauma (n = 19)	ss high trauma (n = 9)	(f, df, P)
Emotion neglect							2.96, 2.0, .23
Memory	0.11 ± 0.85	−0.21 ± 1.20	−0.61 ± 1.14	−0.06 ± 0.68	−1.05 ± 1.25	−1.40 ± 1.51	
Working memory	−0.28 ± 0.57	−0.67 ± 0.86	−0.46 ± 0.87	−0.46 ± 0.73	−0.46 ± 1.10	−0.49 ± 0.64	
Perception and visuospatial abilities	−0.19 ± 1.03	−0.71 ± 1.04	−0.65 ± 1.12	−0.50 ± 1.21	−1.13 ± 1.36	−0.67 ± 1.12	
Verbal abilities	−0.45 ± 1.11	−0.54 ± 1.27	−0.74 ± 1.20	−0.27 ± 0.90	−1.19 ± 1.22	−0.33 ± 0.44	

To reduce multiple testing, the P value interactions are measured by repeated measures ANOVAs.
*$P < 1.0$; **$P < .05$; ***$P < .01$; test statistics and P value given for the interaction term between type of childhood trauma and 5-HTTLPR genotypes (as the independent variables or between subject's factors), and cognitive domain (as the dependet variable or within subject factors) covariated for age, gender, and paternal education level. High and low trauma are defined as above or below the median score because these may vary for one individual; subgroups are not equal across analyses.

Interactions Between 5-HTTLPR Variations and Childhood Trauma on Cognitive Function

Using a median split of the CTQ data, we found a significant interaction effect between the presence of high levels of either physical abuse or psysical neglect in childhood and 5-HTTLPR variation across cognitive domains that persisted also after simultaneous correction for differences in age, gender, and fathers education level (F = 3.23, df = 2, P = .04 and F = 6.10, df = 2.0, P = .003, respectively; see table 3). Examination of

data and follow-up analyses showed that homozygotic s-carriers had more severe cognitive dysfunction across cognitive domains compared with the l-carriers. We also found a statistical trend level for an intercation effect between emotional abuse and 5-HTTLPR variations across cognitive domains, again in the directions that homozygotic s-carriers that had experienced high levels of emotional abuse performed worse than other groups ($F = 2.96$, $df = 2.0$, $P = .057$). Similar patterns were seen both for childhood sexual abuse and emotional neglect, but this did not reach statistical significance or trend levels (see table 3). Finally, we added information about all types of childhood trauma into one variable and repeated the analyses using this as an allover measurement of trauma. Using this variable, we did no longer observe a significant interaction effect.

Discussion

The novel and most important finding of the current study is the clear indication of an interaction between 5-HTTLPR variations and childhood trauma on cognitive dysfunction in patients with psychotic spectrum disorders. The direction is that homozygotic s-carriers experiencing high levels of childhood trauma—in particular physical trauma—showed more cognitive dysfunction across domains compared with all other groups. The finding was not explained by random differences in possible confounding variables between groups. To our knowledge, this is the first study showing such an interaction effect in patients with psychotic disorders. It is of importance because it may aid our search for mechanisms behind unexplained variations in cognitive dysfunction seen in this patient group.[23]

Since increased stress responses are associated with cognitive impairments,[10] both 5-HTTLPR variations and childhood trauma may influence cognitive deficits through their alteration of the HPA mediated stress response. A possible mechanism is thus that s-carriers experience larger increases in stress hormones compared with l-carriers[3,14–17] interacting with long-standing stress response disturbances seen in persons exposed to childhood trauma.[49] That patients with psychotic disorders show an abnormal HPA axis further supports this theory.[29] If this interaction is specific to persons with an already compromised cognitive functioning or is also seen in otherwise healthy, we unfortunately cannot explore here because we do not have data on childhood trauma for the healthy control group.

The present results expand previous findings of childhood trauma being associated with decreased cognitive performance in adulthood.[9] Several explanations have been proposed for this association, including a link between heritable low parental IQ and a parental style characterized by more abusive behavior as a possible confounder.[9] However, finding that childhood trauma is significantly related to cognitive impairments primarily in s-carriers indicate that other mechanisms must play a role.

A limitation to our findings is that our relatively large sample size ($N = 118$) still is too small to investigating other interaction effects. Our findings should therefore be interpreted with caution, and studies to replicate our findings in larger samples are needed. These should preferably include trauma data from healthy controls. To further explore relationships to stress response abnormalities, additional measures of cortisol and cortisol metabolism genes would be of use, if possible in patient samples large enough to explore interaction effects.

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