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The serotonin transporter gene and disease modification in psychosis: Evidence for systematic differences in allelic directionality at the 5-HTTLPR locus

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ABSTRACT

A 44 base pair insertion ("l")/deletion ("s") polymorphism (called 5-HTTLPR) in the 5′ promoter region of the human serotonin transporter gene (*SLC6A4*) modulates expression and has been associated to anxiety and depressive traits in otherwise healthy individuals. In individuals with psychiatric diagnoses, including schizophrenia, it seems to modulate symptom severity. Thus, it may be a disease modifying gene. In this study, 92 patients with psychosis (including schizophrenia, schizoaffective disorder, bipolar psychosis, and major depression) were assessed at their first hospital admission. Symptom ratings, including SANS negative symptoms, SAPS positive symptoms, and SCID depressive symptoms, were obtained. Stress was also assessed. Bi-allelic genotyping at the 5-HTTLPR locus was done. Using multiple regression models, we found that 5-HTTLPR genotype (especially in dominant models) accounted for a significant portion of the variance in SCID Depression and SANS (about 5%). In particular we found that the l allele was associated with greater psychopathology. This is consistent with our review of the literature and is at variance with findings in healthy controls that the s allele is associated with greater anxiety and depression levels. We believe that this set of findings argues for principled reversal of directionality in associations at the 5-HTTLPR locus and raises the possibility that allelic variation may have very different consequences for personality traits or psychiatric symptoms depending on epistasis or epigenetic context. Furthermore, these results also imply that categorical diagnostic distinctions may still be relevant in understanding some genetic effects.

1. Introduction

A 44 base pair insertion/deletion polymorphism (called 5-HTTLPR) in the 5′ promoter region of the serotonin transporter gene (*SLC6A4*) located in the chromosome 17q11.2 region of the human genome has functional consequences. The insertion variant is associated with greater gene expression than the deletion variant. The polymorphism has received much attention in the literature. It appears to modulate anxiety and depressive traits in otherwise healthy individuals. In individuals with psychiatric diagnoses, including depression and schizophrenia, it seems to modulate symptom severity. Thus, it may be a disease modifying gene. This concept has received recent attention in the literature and could help in understanding the often heterogeneous presentation expression of many psychiatricdisorders (DeRosse et al., 2008; Fanous and Kendler, 2005). Beyond this role, there may be unremarked-upon evidence for a reversal in the directionality of the association in psychiatric cases based on categorical diagnoses. In the present study we intend to review the literature on

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this topic in Caucasians and present new evidence that supports this observation in schizophrenia, and more broadly, psychosis.

As noted, in healthy controls (i.e., individuals who do not meet criteria for a psychiatric diagnosis) the s allele has been shown to be associated with various scales that measure such personality traits as anxiety, depression, stress sensitivity, and worrying (Sen et al., 2004). In particular the Harm Avoidance scale of the Temperament and Character Inventory (TCI) and the Neuroticism scale from the NEO Personality Inventory have proved to be highly sensitive to the 5-HTTLPR polymorphism in meta-analytic studies (Munafo et al., 2005). These reports indicate that individuals with the s allele have more anxiety and depressive symptoms. Several studies that examined neurophysiology also have found evidence consistent with this. Hariri et al. (2005) determined that the amygdala was more reactive (i.e., had a greater BOLD response during fMRI) to threatening faces in individuals who were s carriers than l carriers. While other groups have suggested that the 5-HTTLPR polymorphism may modulate tonic amygdala activation (Canli and Lesch, 2007), it is nevertheless the s allele that is associated with greater activation.

However, when major depression is treated as a categorical diagnostic entity, there is less compelling evidence for the direction of the association, despite consistent personality trait findings and compelling neurobiological findings on how the 5-HTTLPR polymorphism modulates response in key limbic areas in healthy controls. In the largest and most recent study, the odds ratio (OR) of the polymorphism for unipolar depression was 1.05 and not significant (Lasky-Su et al., 2005). Two prior, smaller meta-analyses had come to conflicting conclusions (Anguelova et al., 2003; Lotrich and Pollock, 2004). Furthermore, several studies have reported that among individuals diagnosed with depression l allele carriers may have more severe symptoms (e.g., suicidal acts (Du et al., 1999)) and more abnormal biomarkers (e.g., smaller hippocampi (Frodl et al., 2004; Taylor et al., 2005)). While replications of this result have not been uniform, as there are both negative studies and studies that indicate that s carriers have more severe affective symptoms (reviewed in Arango et al., 2003), the results should be viewed as inconclusive, and perhaps raise issues of the association's directionality.

In the North American/Northern European literature on schizophrenia results are consistent, but perhaps counterintuitive, as the l allele is associated with greater symptom severity. When examined by Malhotra et al. (1998) within a sample of patients, the l allele was associated with greater positive, affective, and negative symptomatology. This was subsequently replicated by Golimbet et al. (2003), who also found that schizophrenia l homozygotes had greater psychopathology on the MMPI's Paranoia scale. In a case control study Kaiser et al. (2001) determined that the l homozygotes had higher rates of schizoaffective disorder (primarily depressed subtype), not schizophrenia. There is a single negative study (Stober et al., 1998). No study has found that the s allele is associated with greater psychopathology. Importantly, the 5-HTTLPR polymorphism is not associated with schizophrenia, as indicated in a meta-analysis in SchizGene (1/20/2008) and in keeping with its presumptive role as a disease modifier. We have not included studies from Asian populations in this review, because of differences in allele frequency leading to concerns about epistasis, epigenetic, or stratification issues.

In the present study we examined the impact of the 5-HTTLPR polymorphism in a group of Caucasian psychotic patients (most of whom suffered from schizophrenia or schizoaffective disorder) on several symptom dimensions: positive, negative, affective. We found that the l allele was associated with more severe negative symptoms and depressive symptomatology in this cohort.

2. Methods

2.1. Participants

Data for this study were collected from 92 patients following first hospitalization for psychosis. This sample was drawn from a larger first admission cohort of patients with psychosis to oversample for schizophrenia. The cohort was recruited from the inpatient units of the 12 psychiatric facilities in Suffolk County between 1989 and 1995 (Bromet and Fennig, 1999; Bromet et al., 1992). The inclusion criteria were aged 15–60, first admission either concurrent or during the six months prior to the index admission, clinical evidence of psychosis, ability to understanding the assessment procedures in English, and capacity to provide written informed consent. The procedures for obtaining informed consent were approved annually by the Committees on Research Involving Human Subjects at Stony Brook University and by the Institutional Review Boards of all hospitals where respondents were recruited. For participants ages 15–17, written consent of parents was also required. Ethnicity was restricted to Caucasian for the purposes of this study. The sample was limited to Caucasians to avoid distortions associated with population stratification. Of the sample 58.7% were men. Age ranged from 16 to 52 (mean 28.4 + 8.4 years). Duration of untreated psychosis (time from onset of symptoms to the first admission) varied from less than a day to 15 years with the average of 2.06 years. However, many patients were admitted soon after illness onset (46.6% with 3 months of onset; Table 1).

Table 1
Comparison of genotypes on demographics.

	Full sample		L-carriers		S-homozygotes		*p*-value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	28.39	8.38	28.62	8.21	27.31	9.39	0.574
DUP (%<3 months)	46.59		47.30		42.86		0.760
Sex (% male)	58.70		57.89		62.50		0.734

$N = 92$ (76 l-carriers, 16 s-homozygotes). DUP is duration of untreated psychosis (time from onset of symptoms to the first admission). *p*-values were computed with *t*-test (age) and chi-square test (sex and DUP).

2.2. Diagnosis and medication

Intake assessment included the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, and First, 1992) and ratings of psychiatric symptoms. All instruments were administered by trained master's level mental health clinicians. The patients were followed for 24 months. Study psychiatrists formulated longitudinal consensus DSM-IV research diagnoses after the 24-month assessment based on information from the SCID interviews, medical records, and significant others (Schwartz et al., 2000). Primary diagnoses were schizophrenia ($N=57$), schizoaffective disorder ($N=8$), schizophreniform disorder ($N=2$), major depression with psychosis ($N=10$), bipolar disorder with psychosis ($N=8$), and other psychotic disorders ($N=7$).

Sixty seven patients were receiving first generation antipsychotic medications, 7 second generation medications, and 7 were receiving mood stabilizers at baseline assessment. Seven patients were receiving tricyclic antidepressants and 12 were receiving serotonin reuptake inhibitors (SRIs). Eleven patients were not receiving any psychotropic medication.

2.3. Measures

Symptoms of schizophrenia in the four-week period preceding the baseline interview were measured with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). The SAPS consists of 31 items tapping four symptom domains and a global rating for each domain. The SANS is composed of 19 items measuring five domains as well as the global ratings. SAPS and SANS items are rated on a six-point scale (0 = none, 5 = severe). The validity of these measures is well established (Andreasen et al., 1995; Blanchard and Cohen, 2006; Grube et al., 1998). Specifically, the SANS is unidimensional, whereas the SAPS taps two factors: psychotic symptoms (hallucinations and delusions) and disorganized symptoms (bizarre behavior and formal thought disorder). Consistent with prior studies, we used individual items but not the global items (Peralta and Cuesta, 2001; Stuart et al., 1999; Toomey et al., 1997). Common factor analysis supported the established structure in the present data. We removed three items that had consistently poor loadings in these analyses: SANS item 13 (inattentiveness during mental status testing), SAPS item 9 (persecutory delusions), and SAPS item 10 (delusions of jealousy). Thus the final SANS composite consisted of 18 items (internal consistency reliability ranged $\alpha=.88$ to .90 over the five waves), SAPS Psychotic of 16 items ($\alpha=.79$ to .85), and SAPS Disorganized of 13 items ($\alpha=.71$ to .76). The inter-rater reliability of these ratings was very good (average inter-rater $r=.72$, based on 18 assessments; Brown et al., 2000).

Symptoms of depression in the month preceding the interview were assessed with the SCID Depression module administered without skip-outs. Depression was operationalized as a sum of nine DSM criterion symptoms. Items were rated on a three-point scale: 1 = not present, 2 = questionable, and 3 = definite, and the total score ranged from 9 to 27. Internal consistency reliability of the total ranged from .83 to .86, and the inter-rater reliability was very good (average kappa = .73, based on 22 interviews; Bromet et al., 1992). This index showed good evidence of validity and strong psychometrics in our previous study (Kotov et al., in press).

Severity of negative life events that precipitated baseline hospitalization was rated by interviewers using Carpenter Prognostic Scale (Strauss and Carpenter, 1974). The rating options were none, mild, moderate, and severe. The rating was based on interviews with patients, review of records, and reports of relatives. We elected to include a measure of life stress in our model because several previous reports have suggested the 5-HTTLPR might interact with stress or negative life events to increase risk of affective disorder or symptomatology (Kendler et al., 2005; Caspi et al., 2003; Zalsman et al., 2006).

2.4. Statistics

We utilized stepwise multiple regression (forward selection) in which three terms served as predictors: genotype, life stress rating, and genotype × life stress interaction. We used a dominant model (l carriers vs. s homozygotics; the l allele conferred risk for increasing psychopathology) in our primary analyses. We controlled for age and gender by forcing their entry. Four different psychiatric rating scales served as dependent measures: SCID-D, SANS, SAPS-P, SAPS-D.

2.5. Genotyping

5-HTTLPR genotyping was performed using the same protocol we have described previously (Smith et al., 2004). Lymphocytes were harvested from whole blood and DNA was extracted (QIAamp; Qiagen Inc., Valencia, CA, USA). Polymerase chain reactions (PCR) were performed using the following primers: FD 50-TGA ATG CCA GCA CCT AAC CC-30 and RV 50 TTC TGG TGC CAC CTA GAC GC 30. Amplification products were resolved by electrophoresis stained with ethidium bromide staining and visualized by UV transillumination.

The frequency of genotypes in the sample is listed in Table 2. They were in H–W equilibrium ($X^2=.22$, $p=.89$). No differences were observed among the genotypes on basic demographic characteristics (Table 1).

3. Results

The correlations among the scales are shown in Table 3. SCID Depression correlated significantly but weakly with the SANS. No other correlations among scales were significant, which indicates that they were largely independent from each other.

Table 2
Pearson's correlations among symptom scales.

	Depression	SANS	SAPS-P
SANS	0.22 *		
SAPS-P	0.04	−0.02	
SAPS-D	−0.10	−0.07	0.17

* $p<.05$.

Table 3
Symptom scores by genotype.

	N	SCID-D		SANS		SAPS-P		SAPS-D	
		M	SD	M	SD	M	SD	M	SD
SS	16	15.69	5.84	15.00	12.50	11.00	10.00	5.63	5.56
SL	42	18.05	4.52	24.83	13.28	13.21	8.64	7.48	7.00
LL	34	18.65	5.32	21.21	15.22	9.21	9.03	9.24	6.93
SLLL	76	18.32	4.87	23.24	14.19	11.42	8.99	8.26	6.98
SS-SL	58	−0.48		−0.75		−0.25		−0.28	
SS-LL	50	−0.54		−0.43		0.19		−0.55	
SS-SLLL	92	−0.52		−0.59		−0.05		−0.39	

Note. SLLL = any l-carrier. The bottom part of the table reports comparisons in terms of Cohen's *d*.

For the SANS we found that 5-HTTLPR genotype was a significant predictor of score (see Table 4). In this analysis, a dominant model indicated that l carriers differed significantly from s homozygotes ($\beta = .22$), accounting for 4.8% of the variance in SANS. Neither life stress nor an interaction between life stress and genotype accounted for additional variance in negative symptoms. Consistent with this analysis, a *t*-test that compared the l carriers to s homozygotesdemonstrated a significant difference on SANS scores ($t = 2.15$, $p = .03$). In a secondary analysis which utilized three levels of genotype we did not find a significant linear trend.

For SCID-D we found that 5-HTTLPR genotype was a significant predictor of score (see Table 4). In this analysis, a dominant model indicated that l carriers differed significantly from s homozygotes ($\beta = .24$). Life stress also contributed significantly to depression ($\beta = .22$). Together these two variables accounted for 10.1% in SCID Depression, of which 5.4% was accounted for by 5-HTTLPR genotype. There was no evidence of interaction between these predictors, as the interaction term did not account for any additional variance. Consistent with this analysis, a *t*-test that compared the l carriers to s homozygotes demonstrated near-significant difference on SCID-D scores ($t = 1.89$, $p = .06$). In a secondary analysis which utilized three levels of genotype we found a near-significant linear trend in which increasing depression was associated with l allele burden ($\beta = .20$, $R^2 = .04$, $p = .06$).

We next assessed the relative independence of these findings. We used a logistic regression in which genotype served as the dependent measure and SCID-D and SANS as the independent predictors. Both entered at near-significant levels (SANS $p = .07$, SCID Depression $p = .10$) and the model was significant overall ($X^2 = 7.18$, $df = 2$, $p = .03$). This suggests that the 5-HTTLPR polymorphism is associated with multiple independent behavioral phenotypes.

For SAPS-P and SAPS-D, no significant findings emerged by multiple regression analysis, nor by *t*-test (see Table 4).

4. Discussion

In this study we found that the l allele of the 5-HTTLPR was associated with greater psychopathology in categorically diagnosed psychotic patients. This is consistent with our review of the literature and is at variance with findings in healthy controls that the s allele is associated with greater anxiety and depression levels. We believe that this set of findings argues for principled reversal of directionality in associations at the locus of the 5-HTTLPR indel polymorphism. These results, also taken in conjunction with results previously described in the literature, raise the possibility that allelic variation may have very different consequences for brain function, personality traits, and psychiatric symptoms depending on epistasis or epigenetic context. Furthermore, and more theoretically, these results also imply that categorical diagnostic distinctions may still be relevant in understanding some genetic effects, even though strong arguments for a dimensional view of psychopathology have been put forward (Widiger and Samuel, 2005). Consistent with prior genetic evidence, we have collapsed individuals with psychosis into a single group (Craddock and Owen, 2007).

Results from the present study indicate that in schizophrenia, it is the l allele that increases some types of psychopathology, including depression and negative symptoms. Interpreted broadly, the l allele appears to be increasing risk for reduced emotional reactivity, anergia, and/or dysphoria. This is the fourth study to report these types of findings in schizophrenia; no study has indicated that the s allele increases symptoms in schizophrenia. Given that the polymorphism appeared to be independently associated with negative symptoms and affective symptoms, and has been associated with positive symptoms in other studies, pleiotropic processes are suggested. This is consistent with the animal literature on serotonin transporter knock-out mice models (Murphy and Lesch, 2008). However, the mechanism by which the 5-HTTLPR polymorphism modulates symptoms is unclear.

Our study may be criticized because it included schizophrenia and schizoaffective patients and patients with affective psychoses. However, we think that this is a strength because it extends findings to "psychosis" and makes them more generalizable. It is also consistent with the literature in both schizophrenia and affective disorder that indicates that the l allele that is associated with greater symptom severity. There are several other possible caveats. First, our review of the literature on the 5-HTTLPR is nonquantitative and we accepted positive and negative results at face value. A variety of methodological issues may have

Table 4
Hierarchical multiple regression analyses controlling for age and sex.

	ΔR^2	β	*p*-value
SANS			
Genotype	**0.048**	**0.22**	**0.036**
Interaction	0.019	−0.20	0.187
Stress	0.001	0.03	0.802
SCID Depression			
Stress	**0.047**	**0.22**	**0.041**
Genotype	**0.054**	**0.24**	**0.025**
Interaction	0.000	0.01	0.943
SAPS-P			
Stress	0.014	−0.12	0.129
Interaction	0.002	0.05	0.365
Genotype	0.002	−0.06	0.309
SAPS-D			
Genotype	0.026	0.16	0.129
Stress	0.009	−0.10	0.365
Interaction	0.012	−0.18	0.309

$N = 92$. Statistically significant ($p < .05$) predictors are rendered bold. The predictors entered the model in forward fashion.

skewed the results, ranging from genotyping accuracy, the proportion of l variants, sample size, occult population substratification, statistical approaches, and measurement instrument. Second, Zalsman et al. (2006) recently found a polymorphism in the promoter region of SLC6A4 that reduces expression in l carriers (i.e., the 5-HTTLPR polymorphism is triallelic). However, the polymorphism is relatively rare (with a frequency of about 7–10% in l alleles) and given the sample size in our study, it likely impacts only 3–4 individuals. Our lack of interaction between genotype and life stress is perhaps not surprising, given prior negative findings (e.g., Gillespie et al., 2005) and that we sought an interaction effect in the context of schizophrenia, unlike other studies that examined this issue in affective disorder. Furthermore, all participants were undergoing their first psychiatric hospitalization, which is a very stressful experience for most, and this omnibus stressor may have obscured other environmental effects. It could also be argued that we were monitoring a pharmacogenetic response, given the relationship between 5-HTTLPR and clinical response to SRIs (Serretti and Kato, 2008). However, only twelve patients were receiving this class of drugs in the sample, making such an explanation unlikely. We did not correct for multiple comparisons as our hypotheses were narrow and theory-driven, but we acknowledge that results should be interpreted with caution. Last, our sample size was small, making all but the most robust effects nonsignificant. However, the careful phenotyping in this sample may partially mitigate this issue by reducing noise in measurement.

To summarize, we have found evidence consistent with earlier findings that the 5-HTTLPR may be a disease modifying gene in psychosis. Perhaps more unexpectedly, we also found strong evidence that in psychosis, the direction of the association may be reversed, such that the l allele is associated with greater depressive and negative symptomatology.

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Contributors

TG interpreted the data, wrote the manuscript, and conducted statistical analyses. RK designed the study, conducted statistical analyses, and was involved in manuscript revisions. TL was involved in study design and manuscript revision. AL was involved in data acquisition and revision of the manuscript. PG was involved in data acquisition and manuscript revision. EB designed the study, wrote the study's protocol, and managed fieldwork and diagnostic consensus conferences. AM designed the study, led the conduct of the project, and assisted with data analysis and manuscript preparation.

Conflict of interest

The authors report no conflicts of interest or financial disclosures relevant to this study.

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