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Brief report

Harm avoidance moderates the influence of serotonin transporter gene variants on treatment outcome in bipolar patients

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ABSTRACT

Response to pharmacological treatments is moderated by both genetic and environmental factors. The contribution of such factors is relatively small and complex interactions are likely to be involved. Serotonin transporter gene (SLC6A4) is a major candidate gene associated to response to antidepressant treatment. Moreover, the 5-HTTLPR polymorphism has been associated with anxiety-related traits such as neuroticism and harm avoidance (HA), which are known to influence the risk to develop mood disorders and response to treatments. In the present study we aimed to investigate the interaction between 3 SLC6A4 variants and HA on medium term antidepressant response in a sample of depressed bipolar-spectrum patients followed for 12 months. Contrary to expectations, SLC6A4 variants did significantly influence neither the course of depressive symptoms nor HA scores. However, a significant interaction was observed between HA and 5-HTTLPR genotype. Indeed, a high HA impaired outcome in patients carrying the L_G/S or the S/S genotype more than in L_A/L_A patients. Though a number of limitations characterize the present study, our results indicate HA as a potential moderator of the effect of 5-HTTLPR on the outcome of depression. Given that many factors may influence response to pharmacological treatments, studies that consider personality and other individual characteristics are warranted also in pharmacogenetic investigations.

1. Introduction

Much evidence indicate a genetic influence on response to pharmacological treatments (Serretti and Artioli, 2003; Serretti et al., 2005a). However, it has proven difficult to identify individual genetic risk factors, possibly because the contribution of such factors is relatively small, and complex interactions may be involved (Craddock and Jones, 1999). However, while a growing body of evidence is indicating that a model linking genetic variations, individual and environmental features with psychopathology is the best strategy, the study of response to psychopharmacological treatments is still split between the search of biological factors on a hand, and clinical predictors on the other.

A feature consistently associated to the risk for mood disorder and response to treatment is personality. In particular, many studies focused on neuroticism and harm avoidance (HA). Overall, these studies evidence high scores in patients with a history of depressive disorders. Moreover, patients who fail to respond to antidepressant treatments are likely to have high scores before treatment (Pelissolo and Corruble, 2002). Accordingly, in a previous investigation on this same sample of bipolar (BP) spectrum patients, we found that HA scores significantly influenced the outcome of a depressive episode over a follow-up period of 12 months (unpublished data).

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Individuals' variation in HA has been originally postulated to depend on the functioning of the serotonin system (Cloninger, 1987) and a number of studies reported a significant association between the gene coding for serotonin transporter (SLC6A4) and HA (Benjamin et al., 2002). Given the involvement of SLC6A4 in the risk for mood disorders (Cho et al., 2005) and response to treatments (Serretti et al., 2005b; Serretti and Kato, 2008), it has been hypothesized that SLC6A4 modulates a wide range of anatomical and behavioural aspects (Serretti et al., 2006). Thus, if genetic factors underlying depression, response to treatments and HA are shared rather than unique is a reasonable question. Recently, Munafò et al. (Munafo et al., 2006) reported that neuroticism accounted for 42.3% of the effect of the promoter

Table 1
Clinical and demographic features of the sample.

		5-HTTLPR				rs25533			STin2				
	Overall BP ($n=86$)	La/La ($n=15$)	La/S ($n=47$)	Lg/S or S/S ($n=24$)		T/T ($n=78$)	T/C ($n=8$)		12/12 ($n=33$)	12/10 ($n=36$)	10/10 ($n=14$)	10/9 ($n=3$)	
	N (%)	*N* (%)	*N* (%)	*N* (%)	$P_{(Chi\text{-}sq)}$	*N* (%)	*N* (%)	$P_{(Chi\text{-}sq)}$	*N* (%)	*N* (%)	*N* (%)	*N* (%)	$P_{(Chi\text{-}sq)}$
Females	44 (51.2)	9 (60.0)	25 (53.2)	10 (41.7)	0.49	41 (52.6)	3 (37.5)	0.74	18 (55.5)	16 (44.4)	8 (57.1)	2 (66.7)	0.73
Diagnosys													
BP-I	39 (45.3)	8 (53.3)	22 (46.8)	9 (37.5)	0.81	34 (43.6)	5 (62.5)	0.43	16 (48.5)	13 (36.1)	8 (57.1)	2 (66.7)	0.27
BP-II	21 (24.4)	4 (26.7)	11 (23.4)	6 (25.0)		19 (24.4)	2 (25.0)		5 (15.1)	12 (33.3)	4 (28.6)	0 (0)	
CtD	26 (30.2)	3 (20.0)	14 (29.8%)	9 (37.5)		25 (32.0)	1 (12.5)		12 (36.4)	11 (30.6)	2 (14.3)	1 (33.3)	
Axis II	31 (36.1)	5 (33.3)	17 (36.2)	9 (37.5)	0.97	26 (33.3)	5 (62.5)	0.11	13 (39.4)	13 (36.1)	4 (28.6)	1 (33.3)	0.73
Lifetime SUD	43 (50.0%)	7 (46.7)	23 (48.9)	13 (54.2)	0.88	38 (48.7)	5 (62.5)	0.46	17 (51.5)	18 (50.0)	7 (50.0)	1 (33.3)	0.75
Relapse in SUD during follow-up	11 (25.6)	1 (14.3)	4 (17.4)	6 (46.1)	0.14	11 (28.9)	0 (0)	0.076	7 (41.2)	3 (16.7)	1 (14.3)	0 (0)	0.95
Treatments													
Antidepressants	47 (54.7)	8 (53.3)	24 (51.1)	15 (62.5)	0.65	43 (55.1)	4 (50.0)	0.78	24 (72.7)	15 (41.7)	6 (42.9)	2 (66.7)	0.047
Mood stabilizers	70 (81.4)	12 (80.0)	39 (83.0)	19 (79.2)	0.92	63 (88.8)	7 (87.5)	0.63	29 (87.9)	29 (80.6)	11 (78.6)	1 (33.3)	0.22
Antipsychotics	50 (58.1)	10 (66.7)	26 (55.3)	14 (58.3)	0.74	46 (59.0)	4 (50.0)	0.63	20 (60.6)	20 (55.6)	9 (64.3)	1 (33.3)	0.76
Sedative	38 (44.2)	7 (46.7)	16 (34.0)	15 (62.5)	0.071	35 (44.9)	3 (37.5)	0.69	19 (57.6)	14 (38.9)	4 (28.6)	1 (33.3)	0.22
Drop-out	30 (34.9)	3 (20.0)	18 (38.3)	9 (37.5)	0.38	28 (35.9)	2 (25.0)	0.53	10 (30.3)	14 (38.9)	4 (28.6)	2 (66.7)	0.56
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	$P_{(ANOVA)}$	Mean (SD)	Mean (SD)	$P_{(t\text{-}test)}$	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	$P_{(ANOVA)}$
Age (years)	45.7 (11.4)	47.1 (11.0)	47.0 (12.0)	42.3 (10.3)	0.23	45.3 (11.8)	49.0 (6.0)	0.39	45.1 (11.9)	46.4 (11.6)	46.6 (10.9)	39.3 (9.0)	0.75
Educational level	2.8 (0.8)	2.9 (0.7)	2.7 (0.8)	3.0 (0.7)	0.29	2.8 (0.8)	2.6 (0.7)	0.47	2.8 (0.8)	2.7 (0.7)	3.0 (0.9)	2.7 (0.6)	0.75
Age of onset (years)	29.9 (7.2)	29.7 (6.8)	30.8 (7.8)	28.4 (6.3)	0.41	29.4 (6.9)	34.7 (8.7)	0.047	29.7 (7.8)	29.2 (6.5)	32.6 (8.0)	29.0 (6.2)	0.51
Duration of current episode prior to intake (days)	65.3 (144.4)	42.2 (36.5)	85.8 (191.8)	39.6 (28.2)	0.36	56.9 (117.1)	147.2 (306.2)	0.09	92.8 (196.1)	57.0 (117.8)	31.0 (21.3)	22.7 (7.0)	0.51
Antidepressant treatment equivalents[§]	1.5 (0.9)	1.6 (1.1)	1.4 (0.8)	1.7 (0.9)	0.59	1.6 (0.9)	1.3 (0.7)	0.51	1.6 (0.9)	1.5 (0.8)	1.5 (1.1)	1.7 (1.1)	0.85
Baseline HAMD scores	18.4 (4.5)	19.7 (6.7)	18.5 (4.2)	17.4 (3.1)	0.29	18.7 (4.5)	15.9 (3.7)	0.09	18.2 (4.2)	18.2 (5.1)	19.9 (3.7)	16.0 (2.0)	0.50
HA score	104.4 (18.8)	102.9 (25.5)	104.9 (18.9)	104.5 (13.1)	0.95	105.2 (18.8)	97.2 (18.6)	0.32	107.1 (16.4)	101.9 (20.5)	103.4 (19.8)	115.0 (18.4)	0.67
HA groups													
	Mean (SD)	N (%)	N (%)	N (%)	$P_{(ANOVA)}$	N (%)	N (%)	$P_{(t\text{-}test)}$	N (%)	N (%)	N (%)	N (%)	$P_{(ANOVA)}$
High ($n=25$)	122.9 (10.6)	6 (50.0)	12 (34.3)	7 (43.7)	0.59	24 (42.1)	1 (16.7)	0.20	11 (50.0)	9 (32.1)	4 (36.4)	1 (50.0)	
Low ($n=38$)	92.2 (11.6)	6 (50.0)	23 (65.7)	9 (56.2)		33 (57.9%)	5 (83.3)		11 (50.0)	19 (67.9)	7 (63.6)	1 (50.0)	

Legend: BP-I, Bipolar disorder I; BP-II, Bipolar disorder II; CtD, Cyclotymic disorder; SUD, substance use disorder; HAMD, Hamilton rating scale for depression; HA, Harm avoidance.
[§] see Methods for details.