Serotonin transporter gene polymorphisms and auditory hallucinations in psychosis

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Introduction. To study the role of the serotonin transporter gene (*SLC6A4*) in the emotional processing of auditory hallucinations it can be particularly important to better understand the pathophysiology of auditory hallucinations. Moreover, a polymorphism located in this gene (5-HTTLPR) has been previously associated with different disorders related to altered emotional responses. The aim of this study was to evaluate the relationship between different polymorphisms of the *SLC6A4* gene and different aspects of auditory hallucinations in schizophrenic patients, with a special consideration toward the emotional response to auditory hallucinations.

Subjects and methods. Two samples of 224 patients with auditory hallucinations and 346 healthy subjects were studied. AH were assessed in patients through the PSYRATS scale for auditory hallucinations. Several polymorphisms located within the *SLC6A4* gene were analysed through case-control comparisons as well as association analyses with different parameters of auditory hallucinations.

Results. No differences were found between patients and controls for any of the analysed polymorphisms ($p > 0.05$). However, the evaluation of auditory hallucinations parameters showed that the low expressing alleles of the 5-HTTLPR polymorphism were associated with higher levels of intensity of the distress caused by auditory hallucinations ($p = 0.049$ corrected for the item 'intensity of distress'). There was also a trend with the parameter 'disruption' ($p = 0.06$ corrected). These two items of the PSYRATS scale are directly related to the emotional dimension of auditory hallucinations. In contrast, we did not observe any association with items related to other dimensions of auditory hallucinations.

Conclusions. Our results support a possible role of the serotonin transporter in the emotional response to auditory hallucinations.

Key words. Auditory hallucinations. Emotional response. Genetic polymorphisms. Psychosis. Serotonin transporter. *SLC6A4*.

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Introduction

The lack of consistent findings in the molecular genetics of schizophrenia has led to propose the deconstruction of this syndrome into more specific endophenotypes [1]. But before selecting the best possible endophenotype, we need to decide how we are going to select the patients, and this decision must be clinically based. The problem is [2] that there are 69 different possible combinations of symptoms that fulfil the criterion 'A' from DSM-IV for schizophrenia [3]. Thus, we consider that, to understand the pathophysiology of schizophrenia, we need to understand the neurobiology of its most frequent symptoms.

Although auditory hallucinations (AH) can appear in other mental disorders, they remain as the hallmark of psychosis and especially of schizophrenia [4]. The present study is part of an integrated phenomenological [5], genetic [6,7] and neuroimaging approach [8] searching for the specific neurobiological basis of AH in psychosis. Surprisingly, most of the genetic studies of hallucinations have been done in neurological patients [9,10]. However, it is worth remembering that in almost all conditions in which hallucinations occur, visual hallucinations predominate. The exception is schizophrenia, in which auditory hallucinations, and especially voices, predominate [11]. Furthermore, these voices usually have a disturbing content that induces an intense emotional response in these patients [12,13].

For years, many investigators have been studying the genetic basis of emotionality, and the serotonergic system appears to be especially interesting. Serotonin plays an important role in neural development, adult morphogenesis and plasticity and this neurotransmitter also controls several complex processes. Serotonergic neurotransmission is mainly regulated by the serotonin transporter,

encoded by the *SLC6A4* gene. Many studies have related this gene to several neuropsychiatric disorders, especially anxiety-spectrum and mood disorders, such as obsessive-compulsive disorder, impulsivity, major depression and higher neuroticism [14-16]. Furthermore, the relationship between the *SLC6A4* gene and schizophrenia has been analysed, although in these cases the results are less clear and more contradictory [17].

Recently, we have investigated whether the functional promoter polymorphism of *SLC6A4*, 5-HTTLPR, is associated with any form of AH in psychotic patients [6]. This polymorphism, situated in a repetitive region that modulates transcriptional activity, leads to a long variant (*l*) and a short variant (*s*), being the s allele of lower transcriptional activity [18]. In our preliminary report [6], we concluded that patients carrying the *s* allele showed a higher emotional response to AH. These results are coincident with previous studies [19,20]. Very recently, SNP rs25531, an A/G substitution immediately upstream of 5-HTTLPR that changes the consensus sequence for the transcription factor AP2β [21], was discovered. The combination of this SNP with the functional promoter polymorphism generates four main alleles: the L_A allele with high activity, and the L_G, S_A and S_G alleles, which have lower transcriptional levels and less serotonergic activity [21,22].

In addition to 5-HTTLPR, other polymorphisms in the *SLC6A4* gene have been explored, such as a variable number of tandem repeats located in intron 2 (STin2 VNTR), which seems to act as an enhancer during embryonic development. Moreover, the relationship between several SNP variants and different diseases, such as autism [23], and affective disorders [24,25], has also been studied.

Taken together, all these results led us to investigate more deeply the effect of the *SLC6A4* gene on the vulnerability to auditory hallucinations in psychotic patients. In this study, we examine the existence of association between several polymorphisms of *SLC6A4* and schizophrenia with AH, as well as with different parameters that evaluate, among others, the emotional dimension of auditory hallucinations.

Methods

Subjects

224 patients with AH and 346 unrelated controls of similar characteristics were included. All subjects were Caucasians from Valencia (Spain) with a similar age and sex distribution among groups. Exclusion criteria considered in this study were: incoherence of speech and/or incapability for basic comprehension of the questions, with regard to patients; and, for control subjects, history or familiar background of mental disorders. Patients came from the Valencia University Hospital and gave their written informed consent to participate in this study, approved by the Ethical Committee of the Medicine Faculty, University of Valencia.

The retrospective clinical data collected from each patient were compared with the information obtained from clinical reports and family members. According to DSM-IV criteria, 188 patients suffered schizophrenia, 12 subjects had schizoaffective disorders, one suffered a delusional disorder, 11 presented other psychoses, three suffered depression and nine were affected by bipolar disorder. All patients had a minimum one-year evolution of the illness and were on antipsychotic treatment at evaluation time.

Auditory hallucinations were assessed using the Psychotic Symptom Rating Scale (PSYRATS) [26,27]. This standardized scale rates 11 parameters of AH on a five-point scale: frequency, duration, location, loudness, beliefs about the origin of voices, amount of negative content, degree of negative content, amount of distress, intensity of distress, disruption to life and controllability of voices.

Genotyping

Genomic DNA was extracted from the peripheral blood of each subject according to standard procedures.

Polymorphisms (Table I) were selected from the Single Nucleotide Polymorphism database (dbSNP) according to previous reports, localization, frequency data and a probable functional implication. In detail, 5-HTTLPR and STin2 affected gene functionality. Moreover, SNP rs2228673 is a nonsynonymous change with a possible functional implication. rs3813034 is located in a polyadenilation site [28], while rs1042173 seems to affect a predicted exonic splicing enhancer. The remaining SNPs were included due to previous studies in relation to autism [23,29].

SNPs were genotyped through restriction assays, whereas genotypes for STin2 and 5-HTTLPR were determined by PCR as previously described (Table I).

A subsample of patients and controls was re-genotyped to confirm the quality and reliability of the genotyping process, and the coincidence was 99%.

Statistical methods

QUANTO software v. 1.2.3 was used to calculate the statistical power of our study [30]. This power was found to be between 0.4 and 0.99, depending on the risk assumed for each polymorphism.

Prior to the statistical analyses, 5-HTTLPR genotypes were grouped according to the level of activity detected in previous reports [21-22]: 'high expression' (L_A/L_A), 'medium expression' (L_A/L_G, L_A/S_A and L_A/S_G) and 'low expression' (L_G/L_G, L_G/S_A, L_G/S_G, S_A/S_G, S_A/S_A and S_G/S_G).

All polymorphisms were assessed for Hardy-Weinberg Equilibrium (HWE) in both patient and control samples by applying a χ^2 test implemented in Haploview Program version 3.4 [31].

Allelic differences between patients and control subjects were assessed via Unphased program v. 3.0.12 [32]. The application SNPStats [33] was used to compare the genotypic frequencies between groups and to study the likely relationship between the polymorphisms and PSYRATS scale items. This software uses a logistic regression approach for the case-control comparisons. By contrast, linear regression analysis was used to evaluate the associations with AH parameters. Different inheritance models were considered and tested during the logistic and linear regression analyses. In all cases, the Bonferroni sequential test for multiple comparisons [34] was applied to correct all the reported *p*-values. Furthermore, Haploview program was used to estimate D' and r^2 values as measures of pair wise linkage disequilibrium (LD) [31]. Haplotype block structure was determined according to the criteria described elsewhere [35]. Haplotype analysis (frequency estimation and comparison among groups) was performed with the Unphased Package [32].

It should be noted that all association analyses were carried out considering the original sample of 224 hallucinatory patients, but were also conducted on a smaller sample, which only included 188 patients who were diagnosed as schizophrenics.

Results

PSYRATS scale scores

Table II shows the mean values obtained by the hallucinatory patients for each item of the PSYRATS scale. Thirteen patients could not be evaluated for the PSYRATS scale.

Table I. *SLC6A4* polymorphisms analysed in this study.

Polymorphism	Location	RFLP	Primers [a]
5-HTTLPR (44 bp VNTR + rs25531 A/G)	Promoter	*Hpa*II (for rs25531)	F 5'TCCTCCGCTTTGGCGCCTCTTCC3' R 5' TGGGGGTTGCAGGGGAGATCCTG3'
rs2066713 C/T	Exon 1A	*Bfm*I	F 5'CTCCTGAGAACACACGTTGCC 3' R 5'CACAGGTGTGAGACACCATGC 3'
rs2020936 T/C	Exon 1A	*Eco*31I	F 5'ACCACTGACTACCAAGTTCAG3' R 5'CACCAGGCAATGTCAGTCAC 3'
STin2 17 bp VNTR (9, 10, 12 repeats)	Intron 2	–	F 5'GTCAGTATCACAGGCTGCGAG3' R 5'TGTTCCTAGTCTTACGCCAGTG 3'
rs2020942 A/G	Intron 2	*Hpa*II	F 5'ATCTCCTGCTCCAGAGGACTC3' R 5'TGGTGTCTCCTGGATCTTGTG3'
rs2228673 C(Asp)/G(Lys)	Exon 4	*Sac*I	F 5'GGCCTGGAGTCCTTGGAATGG3' R 5'GTTGCCAGTGTTCCAGGAGCT3'
rs1042173 T/G	3'UTR	*Acs*I	F 5'CATGGTAGACTGTGACACAGC3' R 5'CTCACAAGCTTGCATGGACAC3'
rs3813034 G/T	3'UTR	*Tru*1I	F 5'TGCTGGAATCTACTAGAACCTTC3' R 5'TCCAATAATAACCTCCATACACA3'

RFLP: restriction fragment length polymorphism; VNTR: variable number tandem repeats; UTR: untranslated region; F: forward primer; R: reverse primer. [a] Amplification of 5-HTTLPR, STin2 and rs3813034 was performed using primers designed previously by other authors [28,48,49].

Linkage disequilibrium analysis

The SNP rs2228673 was monomorphic in our samples, so we performed the statistical analyses with the other polymorphisms. Moreover, the low frequency of the nine repeat allele of STin2 (0.009 in control subjects) led us to exclude all the carriers of this allele from all the analyses. Moreover, SNP rs2020936 was out of HWE in controls (p = 0.043 uncorrected).

Two LD blocks were observed. One of them included the four polymorphisms located in introns 1A and 2 (r^2 between rs2066713 and rs2020942 ranged between 0.96 and 0.91), whereas the two SNPs located in the 3'UTR region formed a second block (r^2 = 0.95 in both patients and controls). Polymorphism 5-HTTLPR showed the lowest LD values (both r^2 and D') when compared with the rest of the SNPs.

Case-control association analysis

No significant differences in the allelic frequencies between cases and controls were detected in our samples. Regarding the genotypic frequencies, only

Table II. Mean scores for the PSYRATS scale for auditory hallucinations. We show the results for the whole sample of hallucinatory patients, as well as for the subsample, which included those patients diagnosed as schizophrenics according to DSM-IV criteria.

	PSYRATS scale scores (mean ± standard error of the mean)											
	Total score	Frequency	Duration	Location	Loudness	Belief about origin	Frequency of negative content	Degree of negative content	Amount of distress	Intensity of distress	Disruption	Grade of control
Psychotic patients with AH (*n* = 211)	17.51 ± 1.08	1.75 ± 0.12	1.71 ± 0.12	1.53 ± 0.11	1.30 ± 0.09	1.77 ± 0.12	1.64 ± 0.11	1.61 ± 0.11	1.41 ± 0.11	1.42 ± 0.11	1.49 ± 0.10	1.89 ± 0.12
Schizophrenic patients with AH (*n* = 176)	18.41 ± 1.18	1.88 ± 0.13	1.80 ± 0.13	1.59 ± 0.12	1.35 ± 0.10	1.86 ± 0.13	1.70 ± 0.13	1.66 ± 0.13	1.49 ± 0.12	1.48 ± 0.12	1.60 ± 0.11	2.00 ± 0.14

AH: auditory hallucinations; DSM-IV: *Diagnostic and statistical manual of mental disorders, 4 ed.*; PSYRATS: Psychotic Symptom Rating Scale.

SNP rs2020936 showed slight differences when taking into account the entire sample of hallucinatory patients and the control group (p = 0.019), and also when comparing the subsample of hallucinatory schizophrenic patients with healthy subjects (p = 0.026). These differences disappeared when correction for multiple testing was applied.

Haplotype analysis in both patients and controls revealed seven common 7-marker haplotypes (frequency > 0.03), which represented about 90% of all possible combinations. However, no significant differences were found between groups.

Association analysis of *SLC6A4* polymorphisms with PSYRATS scale parameters

Table III shows the results of association tests with the clinical parameters of the PSYRATS scale when the complete sample of hallucinatory patients was considered. Briefly, patients with low expression 5-HTTLPR genotypes scored significantly higher in two PSYRATS items: 'intensity of distress' and 'disruption'. Polymorphisms rs2066713 and rs2020942 were also associated with the parameter 'location'. Regarding the subsample of 188 schizophrenic cases, subjects with low expression 5-HTTLPR genotypes scored significantly higher in the total PSYRATS evaluation (p = 0.032), 'intensity of distress' (p = 0.006), 'disruption' (p = 0.0092), 'amount of distress' (p = 0.013), 'frequency' (p = 0.033) and 'duration' (p = 0.036).

After multiple-testing correction, only the association of 5-HTTLPR with the 'intensity of distress' to AH remained significant. Table IV shows the results of the association analysis between the functional 5-HTTLPR polymorphism and AH emotional dimensions in the whole sample of hallucinatory patients.

Discussion

In this study, we analysed several polymorphisms in the *SLC6A4* gene and the most interesting result was the association of the 5-HTTLPR polymorphism with the 'intensity of distress' to auditory hallucinations. We also found a trend toward association with two other parameters related to the emotional response to AH ('frequency of distress' to AH and 'disruption' to life). As a consequence of our results in this field, we have developed a model [4] that allows us to provide an explanation for the aetiopathogenesis of AH (Figure). In this model, two different pathways were considered, the first of which is a vulnerability to language disorders, which could be due to changes in the *FOXP2* gene, among others [7]. *FOXP2* is the first gene that has been related to a language disorder [36]. Second, cultural aspects can influence the content and social adjustment of voices. Finally, the last considered dimension in the neurobiology of AH is the central aspect of our present work: the vulnerability to abnormal emotional responses. This emotional dysfunction has a crucial role in schizophrenia, as shown in previous studies that have related the AH with negative emotional states [37]. We have reasons to support the role of emotional processing in the pathophysiology of AH. We previously designed an auditory emotional functional magnetic resonance imaging (fMRI) paradigm to elicit

Table III. Uncorrected p-values obtained from association analyses between the seven polymorphisms and PSYRATS scale items when the sample of 224 hallucinatory patients was analyzed.

	Total score	Frequency	Duration	Location	Loudness	Belief about origin	Frequency of negative content	Degree of negative content	Amount of distress	Intensity of distress	Disruption	Grade of control
5-HTTLPR	0.058 (D)	ns	ns	ns	ns	ns	ns	ns	0.014 (D)	0.007 (D)	0.009 (D)	ns
rs2066713	ns	ns	ns	0,046 (A)	ns	ns	ns	ns	ns	ns	ns	ns
rs2020936	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
STin2	ns	ns	ns	0,051 (A)	ns	ns	ns	ns	ns	ns	ns	ns
rs2020942	ns	ns	ns	0,039 (A)	ns	ns	ns	ns	ns	ns	ns	ns
rs1042173	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
rs3813034	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

The best fitting model is shown in brackets. A: additive, which considers that each copy of the less frequent allele modifies the risk; D: dominant, which groups the heterozygote with the homozygote for the less frequent allele; ns: not significant ($p > 0.05$); PSYRATS: Psychotic Symptom Rating Scale.

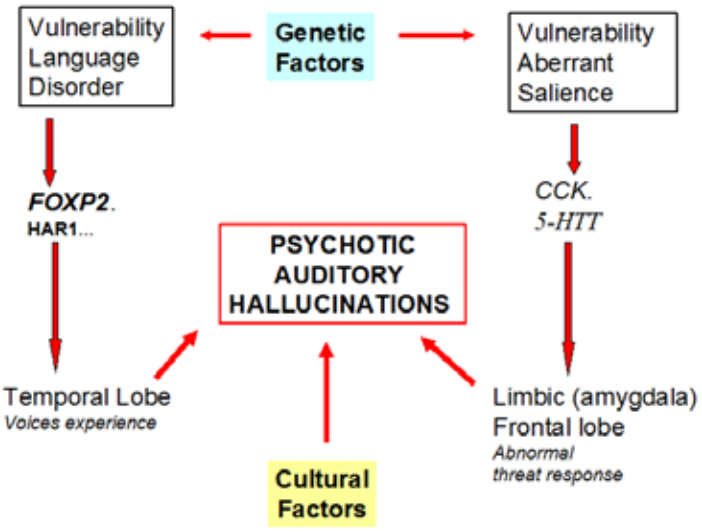
Table IV. Association analysis between the 5-HTTLPR and PSYRATS scores in the whole sample of patients with auditory hallucinations. The results for PSYRATS total score and emotional items are indicated.

Genotipo 5-HTTLPR	PSYRATS scale scores (mean ± standard error of the mean)			
	PSYRATS total score	Amount of distress to AH	Intensity of distress to AH	Disruption of voices to life
High expression genotypes [a] (*n* = 43)	15.49 ± 2.47	1.26 ± 0.23	1.33 ± 0.24	1.30 ± 0.24
Medium expression genotypes [a] (*n* = 99)	16.34 ± 1.54	1.22 ± 0.16	1.15 ± 0.15	1.30 ± 0.24
Low expression genotypes [a] (*n* = 69)	20.43 ± 1.88	1.81 ± 0.20	1.83 ± 0.20	1.87 ± 0.18
p	0.058 (ns corrected)	0.014 (ns corrected)	0.007 [b] (0.049 corrected)	0.009 [b] (0.06 corrected)

AH: auditory hallucinations; ns: not significant ($p > 0.05$); PSYRATS: Psychotic Symptom Rating Scale. [a] Genotypes are grouped depending on the number of high expression (L_A) and low expression (L_G, S_A, S_G) alleles; [b] The given p-values correspond to an inheritance model that compares the low expression genotypes against the two other groups (SNPStats software found this model to be the most likely). Corrected *p*-values are given in brackets.

the emotional states experienced when suffering from AH [13]. In that work, we obtained an enhanced activation of limbic and frontal brain areas in our group of persistent hallucinatory patients in response to emotional words. But it is also necessary to study the genetics of AH. As far as we know, there are only a few studies that have examined the genetics of hallucinations in psychotic patients [38-40]. Moreover, until now, there was only one previous report [38] that had analyzed the association between *SLC6A4* and AH in psychosis. In this case, the long allele of the 5-HTTLPR polymorphism was found to be associated with the intensity of hallucinations in schizophrenic patients. However, in our study we did not find an association with any of the items of the PSYRATS scale directly related to the physical dimension of AH. Our hypothesis is that the serotonin transporter gene may control the emotional response to auditory hallucinations but not other dimensions. Supporting this hypothesis,

Figure. A possible model to explain the vulnerability to AH. Firstly, we have a vulnerability to language disorders related to *FOXP2* linking with temporal lobe, raising the possibility of hearing voices. Secondly, we have the vulnerability to aberrant emotional responses related to the serotonin transporter promoter polymorphism (among others) and frontal and limbic areas, raising the possibility of an abnormal emotional response to voices. Finally, cultural factors are also important in the content and social adjustment of voices.



we have found a significant association between the low expression alleles of 5-HTTLPR and the 'intensity of distress' to AH, as well as a trend towards an association with the parameter 'disruption'. It must be remarked that the items 'intensity of distress' and 'disruption' are directly related to the emotional response to AH. Remarkably, our findings were similar for the whole sample of hallucinatory patients and for the subsample of schizophrenics with hallucinations, suggesting that the *SLC6A4* gene is involved in the hallucinatory phenomenon independently of the type of psychosis suffered by each individual.

The short allele of the 5-HTTLPR has been described before as a risk allele for the development of affective disorders [25,41]. Furthermore, our finding is in agreement with our preliminary work [6], where we found significant associations between the *s* allele of 5-HTTLPR and the items of the PSYRATS scale evaluating the emotional response. fMRI approaches are also of strong interest. It has been shown that the *s* allele of 5-HTTLPR produced an increased amygdala response to fearful stimuli in a sample of healthy controls [19], as well as higher amygdala activation in patients with social phobia [42] and panic disorders [43], as well as in phobic-prone healthy subjects [44]. Moreover, in a preliminary work we found an association between the short allele of the serotonin transporter gene and higher amygdala activation in response to emotional words [45]. There are also clear evidences relating vulnerability to environmental stress with variations in the *SLC6A4* gene. Caspi and colleagues [20] found that the short allele of 5-HTTLPR predisposed individuals to depression in response to life events. Since then, these results have been replicated and studies with animal models also support this hypothesis [46,47]. In the light of all these findings, we can hypothesize that 5-HTTLPR polymorphism, together with other factors, could be regulating the development and function of those neurobiological circuits related to the processing of emotional stimuli, and therefore producing a differential emotional response dependent on 5-HTTLPR.

Although there are several limitations in the present study, such as the reduced sample size and the existence of many other genes related the emotional response, it is worth mentioning that this study contributes to the vulnerability to psychosis with a new approach, named 'deconstructing the symptom', which allows the study of the neurobiological systems implicated in the most specific symptoms of psychosis.

To summarize, we can conclude that the genetic variation in the *SLC6A4* locus modulates the emotional dimension of AH. Our model has relevance not only for the aetiology but also for the therapeutic treatment of AH. It would be very interesting to perform new integrative studies of neuroimaging and genetics that could allow us to support more robustly the role of the serotonin transporter gene in the aetiology of AH in psychosis.

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Variación en el gen del transportador de serotonina y alucinaciones auditivas en la psicosis

Introducción. Estudiar el papel del gen del transportador de serotonina (*SLC6A4*) en el procesado emocional de las alucinaciones auditivas podría ser muy importante para entender mejor su fisiopatología. Además, este gen ya se ha relacionado previamente con trastornos emocionales. El objetivo fue evaluar la relación entre polimorfismos del gen *SLC6A4* y diferentes aspectos de las alucinaciones auditivas en la esquizofrenia, con una especial consideración hacia la respuesta emocional frente a las alucinaciones auditivas.

Sujetos y métodos. Se compararon dos muestras de 224 pacientes con alucinaciones auditivas y 346 sujetos sanos. La evaluación de las alucinaciones auditivas en los pacientes psicóticos se realizó mediante la escala para la valoración de los síntomas psicóticos (PSYRATS). Varios polimorfismos situados en el gen *SLC6A4* se genotiparon y analizaron a través de comparaciones de casos y controles y análisis de asociación con diferentes parámetros clínicos de las alucinaciones auditivas.

Resultados. No se encontraron diferencias entre pacientes y controles para ninguno de los polimorfismos analizados ($p > 0,05$). Sin embargo, la evaluación de los ítems de la escala PSYRATS mostró que los alelos de baja expresión del polimorfismo 5-HTTLPR se asociaban con niveles más altos de ansiedad ($p = 0,049$, corregido para el ítem 'intensidad de la ansiedad'). Además, se observó una tendencia a asociación con el parámetro 'repercusión' ($p = 0,06$, corregido). Estos ítems se relacionan con la dimensión emocional de las alucinaciones auditivas. No se observó, en cambio, asociación con parámetros relacionados con otras dimensiones de dichas alucinaciones.

Conclusiones. Nuestros resultados apoyan el posible papel del transportador de serotonina en la respuesta emocional de los pacientes con alucinaciones auditivas.

Palabras clave. Alucinaciones auditivas. Polimorfismos genéticos. Psicosis. Respuesta emocional. *SLC6A4*. Transportador de serotonina.