Facial emotion recognition deficits in relatives of children with autism are not associated with 5HTTLPR

Prejuízos no reconhecimento de emoções faciais em parentes de primeiro grau de portadores de autismo não são associados com o polimorfismo 5HTTLPR

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Abstract

Objective: A large body of evidence suggests that several aspects of face processing are impaired in autism and that this impairment might be hereditary. This study was aimed at assessing facial emotion recognition in parents of children with autism and its associations with a functional polymorphism of the serotonin transporter (5HTTLPR). **Method**: We evaluated 40 parents of children with autism and 41 healthy controls. All participants were administered the Penn Emotion Recognition Test (ER40) and were genotyped for 5HTTLPR. **Results**: Our study showed that parents of children with autism performed worse in the facial emotion recognition test than controls. Analyses of error patterns showed that parents of children with autism over-attributed neutral to emotional faces. We found evidence that 5HTTLPR polymorphism did not influence the performance in the Penn Emotion Recognition Test, but that it may determine different error patterns. **Conclusion:** Facial emotion recognition deficits are more common in first-degree relatives of autistic patients than in the general population, suggesting that facial emotion recognition is a candidate endophenotype for autism.

Descriptors: Autistic disorder; Emotion; Neurosciences; Genetics; Family

Resumo

Objetivo*: Diversos estudos sugerem que o processamento de emoções faciais está prejudicado em portadores de autismo e que tal prejuízo possa ser hereditário. Nós estudamos o reconhecimento de emoções faciais em parentes de primeiro grau de portadores de autismo e suas associações com o polimorfismo funcional de transportador de serotonina (5HTTLPR).* ***Método:*** *Foram avaliados 40 parentes de primeiro grau de portadores de autismo e 41 controles saudáveis. Todos os participantes foram submetidos ao Teste de Reconhecimento de Emoções (ER40) da Bateria Neuropsicológica Computadorizada da Universidade da Pensilvânia (PENNCNP) e genotipados para o 5HTTLPR.* ***Resultados:*** *Os parentes de primeiro grau de portadores de autismo apresentaram pior reconhecimento de emoções faciais comparados aos controles. A análise do padrão de erros mostrou que eles tendiam a reconhecer faces demonstrando emoções como neutras. O genótipo para o 5HTTLPR não influenciou a acurácia no Teste de Reconhecimento de Emoções, mas os homozigotos para o alelo L apresentaram padrão de erros diferente. Nossos resultados sugerem que prejuízos no reconhecimento de emoções faciais possam ser encontrados em maiores taxas em parentes de primeiro grau de autistas do que na população em geral.* ***Conclusão:*** *Nossos resultados sugerem que o reconhecimento de emoções faciais seja um candidato a endofenótipo no estudo do autismo.*

Descritores: *Transtorno autístico; Emoções; Neurociências; Genética; Família*

Introduction

Autism is a pervasive neurodevelopmental disorder with an early onset in childhood characterized by qualitative alterations in many domains including social reciprocity, communication, restricted interests and by the presence of repetitive and stereotyped behaviors.[1] The etiology of autism is not yet well understood, but there is much evidence showing that genetics possibly accounts for an important part of it.[2,3] Such evidence comes from epidemiologic genetic studies, mainly twin studies, which showed an autism heritability of about 90%, one of the highest among all neuropsychiatric disorders.[1,2]

Despite this high heritability, the identification of genes linked to autism has been a difficult endeavor: genome scans have not been

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able to find regions of genome-wide significance, and association studies still are, at best, inconclusive.[4] This can be explained by the complex model of inheritance of neuropsychiatric disorders like autism, where multiple alleles, generally displaying small effects, interact with one another and with the environment to cause diseases. In fact, the number of genes estimated to contribute to autism can be over 100,[2] and possibly any individual gene makes only a small contribution to the entire autism phenotype. In addition, we can speculate that the most-used phenotype, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis, may not be adequate for molecular studies and that a new approach might be required to better identify autism vulnerability genes.

An interesting approach to circumvent some of those difficulties comes from the endophenotype concept proposed by Gottesman and Shield (1972), which has been a matter of renewed interest in recent years. Endophenotypes are quantitative, heritable, trait-related deficits typically assessed by laboratory-based methods rather than clinical observation.[5] Endophenotypes are seen as lying more closely to genetic variations than to complete phenotypes.[6,7] In this context, the endophenotype strategy offers opportunities to understand the genetic basis of mental disorders. The reasonable criteria for a viable and generative endophenotype are as follows: (1) the deficits in the endophenotype are associated with psychiatric disorders; (2) the deficits are heritable; (3) the endophenotype deficits are stable; (4) the endophenotype and disorder show co-segregation; and (5) any specific endophenotype deficit is found at higher rates among patients' relatives than in the general population.[5-7]

Since the initial description of autism by Kanner (1943), problems in social and emotional reciprocity are considered a hallmark of the illness.[8,9] An important component of both social interaction and emotional reciprocity is face processing. In fact, the face is probably the most important conveyor of emotional information, and many components of face processing seem impaired in autism, such as gaze processing,[8] face recognition memory[8] and recognition of facial emotion expressions.[8-15] Interestingly, some studies found a high prevalence of deficits in social and communicative behaviors in relatives of individuals with autism.[13,16,17] Bolte and Poutska found a tendency for subjects from multiplex families with autistic loading to score lower on the test of facial emotion recognition than individuals from simplex families with autistic loading.[13] Adolphs investigated face processing by using a method known as the "bubbles", which measures how viewers make use of information from specific facial features in order to judge emotions. They described that parents of autistic children showed a remarkable reduction in processing the eye region in faces, together with enhanced processing of the mouth, compared to a control group of parents of healthy children. This pattern of face processing was previously reported to occur in autism and in siblings of autistic children.[16,17] These findings provide a window into the endophenotype that may result from a subset of the genes that contribute to social cognition.[16,18,19]

A widely studied functional polymorphism in the promoter region of the serotonin transporter (5HTTLPR), exhibiting two different alleles (one long, L, and one short, S), emerges as a strong candidate to be associated with facial emotion recognition in autistic subjects and their relatives. Serotonin plays a central role in the processing of emotion, as evidenced by brain serotonergic abnormalities in emotional disorders and the therapeutic efficacy of drugs targeting this system.[20] Moreover, 5HTTLPR genotypes impair the functional connectivity of the amygdala and ventromedial prefrontal cortex (VMPFC) circuitry, which is essential for the expression and regulation of emotion.[20-23] Second, some studies have shown an association between 5HTTLPR and neuroticism, anxiety, and stress reactivity, suggesting that this can be an important genetic variation in human behavior.[21] Third, some studies reported an association of 5HTTLPR with autism.[4] However, which allele (short or long) was associated with autism varied across studies, possibly due to the great heterogeneity of autism itself,[1] as well as to the ethnic heterogeneity seen in some studies.[24] Finally, 5HTTLPR has also been studied in association with emotion processing in autism. Tordjman found an increased severity in the Autism Diagnostic Interview - Revised combining the social/communication domain and the conversation subdomain in subjects with the short 5HTTLPR allele.[25] Brune found that nonverbal communication was more severely affected in the short allele group and that the long allele was associated with increased difficulties to direct facial expressions in the Autism Diagnostic Observation Schedule Scale. The heterogeneity of these results points to the necessity of more research to elucidate the influence of 5HTTLPR in emotional processing.

This study investigates the recognition of facial emotion in relatives of autistic patients compared with healthy controls, using the Penn Computerized Neuropsychological Battery, and more specifically the Penn Emotion Recognition Test (ER40).[7] Furthermore, we investigated the association between the allelic polymorphism 5HTTLPR and the recognition of facial emotion. We hypothesized that the recognition of facial emotion could be used as an endophenotype for autism, that the recognition of facial emotion would be impaired in first-degree relatives of patients with autism, and that the short allele (S) might be associated with such deficits.

Method

1. Participants

Forty parents (30 mothers and 10 fathers) of 30 children with autism, and forty-one non-patient control participants (28 women and 13 men), all self-reported Caucasian-Brazilian, were enrolled in the study. The diagnosis of autism in children was made by a psychiatrist following DSM-IV criteria. After a full explanation of the study, all participants provided written informed consent to participate. The study was approved by our local ethics committee in Universidade Federal de Minas Gerais (ETIC 0028/06).

To be enrolled, subjects had to be between 18 and 65 years old and to have at least six years of formal education. Subjects in

the percentile below 25 on the Raven Progressive Matrices and illiterate subjects were not enrolled.

All participants were further evaluated by a psychiatrist using a structured diagnostic instrument, the Mini International Neuropsychiatry,[26] based on DSM-IV criteria. Participants with an axis I diagnosis were not enrolled (n = 7). The study took place at Raul Soares Hospital, Minas Gerais, Brazil, from March to December of 2009.

2. Facial emotion recognition assessment

Participants were tested in a silent room, and facial stimuli were presented on a computer screen.

The ER40 is a computerized test that assesses categorical identification of facial expressions of emotion[27] and lasts about 15 minutes. Subjects are asked to choose, using the computer mouse, the most appropriate emotion label from a list of five (happiness, sadness, anger, fear, or no emotion). Forty square photographs with eight actors with hair were used: eight neutral expressions, four emotional expressions of low intensity, and four emotional expressions of high intensity for each of the four emotions. Across emotional categories, stimuli were balanced for posers' gender and ethnicity, with 21 white and 19 non-white faces. The test measures the subject's response time. The validity of the test has been previously evaluated[28] in an English population.

3. Face memory assessment

The Penn Facial Memory Test (PFMT) was used to measure memory to facial displays. The test lasts about 10 minutes. In the first part of the test, the participants were shown 20 faces, which they were asked to memorize. Later, participants were shown these 20 faces and 20 new faces, presented in a random order. The participants had to decide whether they had seen the faces presented immediately before. They had to choose, using the computer mouse, among four options: "definitely yes", "probably yes", "probably no", and "definitely no." For this memory task, all facial stimuli were black and white photographs of faces rated as having neutral expressions, balanced for gender and age.[28]

4. Genotyping

All participants were genotyped. DNA was extracted from whole blood. 5HTTLPR genotyping was performed using previously described methods.[29] S allele carriers were assigned to the same group (LS + SS genotypes) since it has been proposed that this allele acts in a nearly dominant way and, functionally, the uptake of serotonin (5-HT) is approximately twofold higher in cells containing the homozygous LL form of 5HTTLPR than either the LS or SS forms.[29]

5. Data analysis

ER40 scores were compared between groups. First, we evaluated whether the scores followed a normal distribution with the Shapiro-Wilk test. The answers and median response time for correct answers in the ER40 and PFMT were used as response variables for the analyses. Since the response variable in the ER40 and PFMT had no normal distribution, we used the Mann-Whitney test to compare emotion recognition between the relatives of autistic patients and controls. We named accuracy the total of correct responses in the test. A chi-square test was used to compare genotype frequencies among the parents of children with autism and control participants.

First, we evaluated the effect of genotype for 5HTTLPR in facial emotion recognition within the two groups. Next, we evaluated the effect of genotype for 5HTTLPR in the ER40 scores of all participants using the ordinal logistic regression model. This analysis was performed to adjust for potentially confounding variables (age, education, family history for autism). Regression models were used to predict the probability of occurrence of an event by fitting data into a logistic curve, the event in question being the probability of 5HTTLPR influencing facial emotional recognition. The ordinal logistic regression was applied because we have an ordinal response variable (answers in the ER40 and PFMT). All tests were two-tailed, and the significance level was 5%.

Results

The sample of first-degree relatives of autistic children comprised 30 women (75%) and 10 men (25%). The participants' age ranged from 21 to 61 years, with a mean of 41.5 and standard deviation of 10. The average education was 16 years of study.

The control sample consisted of 41 participants, 28 women (68.3%) and 13 men (31.7%), with an average education of 16 years. The age in this group ranged between 22 and 63 years, with a mean of 38.4 and standard deviation of 12.1.

We used the chi-square test to analyze the association between family history of autism in first-degree relatives and gender, age, and education. There were no statistically significant differences regarding gender ($p = 0.503$), age ($p = 0.146$) or education ($p = 0.182$) between the two groups.

The statistical power was calculated using the software G*Power, The analysis yielded a statistical power of 0.756 to compare the two groups, with alpha = 0.05 and a moderate magnitude of effect according to Cohen's classification = 0.5.

1. Facial memory

Diagnosis groups (parents of children with autism versus control participants) and genotype groups (LL versus LS + SS) did not significantly differ in terms of accuracy and median response time to correct answers in the PFMT.

2. Facial emotion recognition

We used univariate analysis to compare the performance in the ER40 between diagnosis groups because autistic patients' relatives and controls were statistically similar in regard to age, sex, education, and genotype distribution. We observed that the group of relatives performed worse in facial emotion recognition than controls. Emotions were not well recognized in female faces ($p = 0.0009$), male faces ($p = 0.0019$), and in faces expressing mild ($p = 0.0032$) and extreme emotions ($p = 0.0022$).

Happiness was the most well recognized emotion in both groups, and accuracy improved with the intensity of emotion. In addition, age and gender were considered important co-factors in the ER40. The same pattern was previously described by other authors using the same test.[30,31]

In the recognition of specific emotions, the relatives of autistic patients showed impaired recognition of anger (p = 0.0217), fear (p = 0.0063), and happiness (p = 0.0235), but not of sad and neutral facial displays (Table 1). Examining error patterns, we found that the parents of children with autism over-attributed neutral to emotional faces (p = 0.0033). Furthermore, the response time for correct answers was slower than the controls' (p < 0.001) - Table 1.

Some patterns of facial emotion recognition were identified in the two groups. Both were more accurate in recognizing emotion displayed by female posers. Recognition was better for high-intensity than low-intensity expressions for all emotions, and accuracy was better for happy faces when compared with the other emotions.

3. Genotypes

In the group of relatives of autistic patients, 14 individuals were L homozygotes, 14 had an LS genotype, and 12 were S homozygotes. Within the control group, 9 participants were LL homozygotes, 22 had an LS genotype, and 10 were S homozygotes. The genotypic distribution was also comparable between the parents of children with autism, with $X^2 = 2.51$ and p = 0.28. The genotypic distribution followed the Hardy-Weinberg equilibrium in parents of children with autism (p = 0.059) and healthy controls (p = 0.636).

To study the influence of genotype on the ER40 we compared the S allele carriers (SS and LS genotypes) and subjects with the LL genotype. No effects of 5HTTLPR in the ER40 scores were found in the group of relatives of children with autism or in controls.

Moreover, the univariate analysis of the data of all the participants together showed that some variables influenced responses in the ER40, like sex and age. Thus, we grouped all the participants (n = 81) and performed a multivariate analysis to test the effect of genotypes in the ER40 scores, adjusting for possible confounding variables (age, years of education, and family history of autism in the first degree). We found no accuracy differences in the ER40 between the genotype groups, but we found that L homozygotes (LL genotype) had different error patterns. LL individuals tended to misrecognize some emotions, such as fear (p = 0.030) and happiness (p = 0.011) - Table 2.

Discussion

We studied facial emotion recognition in parents of children with autism and in healthy parents of non-ill children, and found that parents of children with autism performed worse than the control group. Furthermore, our findings suggest that the 5HTTLPR polymorphism may influence facial emotional processing.

In order to avoid confounding factors, subjects presenting a psychiatric axis I diagnosis were excluded from the sample because impaired facial processing abilities have been described in relation with other neuropsychiatric disturbances, like schizophrenia,[27] depression,[30] social phobia,[31] obsessive compulsive disorder, and

Table 1 - Facial emotion recognition in relatives of children with autism (n = 40) and healthy controls (n = 41)

ER40 measures	Autism relatives		Controls		Significance level	
	Mean (standard deviation)	Median	Mean (standard deviation)	Median	Univariate analysis	Adjusted analysis
Time for correct answers	3182,3 (1005.7)	2954	2321.4 (468.5)	2303	**p < 0.001**	**p < 0.001**
Correct responses (0-40)	31.2 (3.4)	32.5	33.8 (3.4)	35	**p < 0.001**	**p < 0.001**
Correct identifications in female posers (0-20)	16.1 (2.0)	17	17.4 (1.9)	18	**p < 0.001**	**p < 0.001**
Correct identifications in male posers (0-20)	15.1 (2.1)	15.5	16.4 (2.0)	17	**p < 0.001**	**0.03**
Correct identifications in faces with low intensity of emotion	11.3 (1.3)	11	12.3 (1,9)	12	**0.02**	**0.02**
Correct identifications in faces with extreme intensity of emotion	13.7 (1.7)	14	14.6 (1.6)	15	**p < 0.001**	**0.02**
Correct identifications of anger (0-8)	4.3 (1.3)	4	5.0 (1.5)	5	**0.02**	**0.07**
Correct identifications of fear (0-8)	6.4 (1.3)	7	7.1 (1.1)	8	**p < 0.001**	**0.03**
Correct identifications of happiness (0-8)	7.8 (0.46)	8	7.9 (0.15)	8	**0.02**	**0.04**
Correct identifications of sadness (0-8)	6.4 (1.3)	7	6.8 (1.2)	7	0.13	0.38
Correct identifications of neutral (0-8)	6.2 (1.6)	7	6.8 (1.2)	7	0.09	0.30
False positive - anger responses	0.65 (0.97)	0	0.51(0.87)	0	0.47	0.72
False positive - fear Responses	1.62 (1.70)	1	1.39 (1.26)	1	0.82	0.93
False positive - happiness responses	0.92 (1.25)	0	0.58 (0.8)	0	0.34	0.45
False positive - neutral responses	3.05 (2.0)	3	1.75 (2.0)	1	**p < 0.001**	**0.02**
False positive - sadness responses	2.5 (1.8)	2	1.9 (1.9)	1	0.07	0.27

Table 2 - Comparison of the performance in the facial emotion recognition task in all study participants (n = 81) divided by the genotype of the functional polymorphism of the serotonin transporter 5HTTLPR (LL versus LS + SS).

ER40 measures	LS/SS genotype		LL genotype		Significance level (Univariate analysis)	Significance level (Adjusted analysis)
	Mean (standard deviation)	Median	Mean (standard deviation)	Median		
1- Correct responses (0-40)	32.9 (3.7)	34	31.7 (3.2)	33	0.09	0.27
2- Correct identifications in female posers (0-20)	16.8 (2.1)	17	16.6 (2.0)	17	0.53	0.99
3- Correct identifications in male posers (0-20)	16.0 (2.1)	17	15.1 (1.9)	15	0.02	0.05
4- Correct identifications of anger (0-8)	4.8 (1.5)	5	4.3 (1.3)	4	0.16	0.24
5- Correct identifications of fear (0-8)	6.8 (1.2)	7	6.7 (1.4)	7	0.90	0.56
6- Correct identifications of happiness (0-8)	7.8 (0.37)	8	7.9 (0.28)	8	0.80	0.48
7- Correct identifications of neutral (0-8)	6.6 (1.4)	7	6.3 (1.5)	7	0.57	0.63
8- Correct identifications of ssadness (0-8)	6.7 (1.3)	7	6.3 (1.2)	7	0.11	0.20
9- False positive - anger responses	0.55 (0.88)	0	0.65 (1.0)	0	0.66	0.73
10- False positive - fear responses	1.3 (1.5)	1	1.9 (1.3)	2	0.04	**0.03**
11- False positive - happy responses	0.60 (1.0)	0	1.3 (1.0)	1	0.01	**0.01**
12- False positive - neutral responses	2.4 (2.2)	1	2.3 (1.8)	3	0.91	0.58
13- False positive - sad responses	2.1 (1.8)	2	2.2 (2.0)	2	0.95	0.64
14- Correct identifications in faces with low intensity of emotion	11.8 (1.7)	12	11.7 (1.6)	12	0.87	0.69
15- Correct identifications in faces with extreme intensity of emotion	14.4 (1.7)	15	13.6 (1.6)	14	0.01	0.05

Huntington's disease.[31] We did not assess axis II diagnoses with a structured scale, and therefore we cannot exclude the possible influence of such diagnoses in our results. Nevertheless, according to our findings, the relatives of children with autism had impaired facial emotion recognition, but unaffected memory to faces, suggesting that this impairment could be more specific and not a part of a global cognitive deficit.

The parents of children with autism showed impairments in the recognition of high arousal emotions (fear, anger, and happiness). The neural basis of facial emotion processing comprises a network of cortical and subcortical structures that includes the amygdala, which is particularly activated by high arousal emotions,[31,32] and there is evidence indicating that amygdala dysfunction contributes to face processing abnormalities in autism.[8,9,11,33-35] Consequently, we may speculate that the impairments in emotion recognition seen in parents of children with autism reflect impaired amygdala connectivity. Specifically during emotion recognition, fathers of autistic children show reduced fusiform gyrus activation.[36] Neural activity in the fusiform gyrus was reported to be inversely correlated with social deficits in autistic subjects,[36] perhaps as the result of a compensatory mechanism. More neuroimaging studies are necessary to elucidate the brain network underlying the impairments in facial emotion recognition observed in autism.

Emotion recognition and Theory of Mind (ToM) are two core components of social cognition.[37] There are few studies on the relation between emotion recognition and ToM. Most, but not all, of these studies show a correlation between the performance in emotion recognition tasks and ToM in children and in adults.[37] Furthermore, both processes share a common network including areas assumed to be involved in embodied simulation and perception processes as core regions: the amygdala and areas belonging to the mirror neuron system.[37] However, more studies are necessary to elucidate the link between ToM and facial emotion recognition, maybe using autism and focusing in amygdala connectivity.

We found evidence that facial emotion recognition is impaired in relatives of children with autism when compared with healthy controls. Our results are in agreement with previous studies[8,10,13,16,17] that also showed emotional impairment in relatives of children with autism, even considering that different methodologies were employed. Our results fulfill one of the criteria for an endophenotype - "specific endophenotype deficit is

found at higher rates in the probands' relatives than in the general population" - and we suggest that facial emotion recognition should be tested as an endophenotype for autism. The search for endophenotypes is challenging and complex because there are no prior criteria for deciding if a particular element of any psychiatric illness reflects the effect of a single gene. We propose that neuroimaging could be used as an extended endophenotype connecting the pathophysiology of a given disorder and particular loci or sets of loci.[19]

We found evidence that 5HTTLPR did not influence accuracy in the ER40, but apparently determined different error patterns. Harmer described that 10 micrograms of citalopram improved the recognition of fear, and that the acute depletion of tryptophan worsened the recognition of fear,[38] while dietary tryptophan supplementation seems to improve facial emotion recognition.[39] Battaglia showed that children who have one or two copies of the short allele of 5HTTLPR appear to have a different pattern for the processing of happy, neutral, and angry expressions.[31] Those data suggest an important role of the serotonergic system in facial emotion recognition. Since 5HTTLPR can have a pivotal role in the serotonergic function, it emerges as a natural candidate gene, and our results support this view. Nonetheless, our results do not allow for conclusive statements concerning the role of 5HTTLPR in the recognition of facial emotion in relatives of autistic children, especially due to the small sample size.

Limitations of our study include the fact that we did not test the patients themselves. This can be explained by the difficulties to test emotion recognition in patients with autism, since mental retardation and behavioral disturbances are frequently present. Nevertheless, impaired facial emotion recognition in autism, as well as in Asperger Syndrome, has been previously described.[11] Furthermore, the study of non-ill relatives of patients with autism may be a better approach to characterize the endophenotype than the study of the patients themselves, whose multiple deficits may obscure a unique endophenotype.[19] Another limitation is the lack of further cognitive assessment in our study, including the domain of attention, to analyze the effects of general cognition on facial emotion recognition, as well as those of laterality. Finally, as in all case-control genetic studies, we must be aware of false-positive and false-negative findings due to ethnic stratification. Our sample comprised only participants who were self-designated as Caucasian-Brazilian; however, as recently demonstrated, race as determined by self and/or clinical evaluation is a poor predictor of ancestry in Brazil and an ethnic stratification bias cannot be ruled out in this case.[40]

Conclusion

We showed that parents of children with autism performed worse in a facial emotion recognition test than parents of non-ill children. To our knowledge this is the first study to describe the patterns of emotional recognition in relatives of children with autism and their correlations with 5HTTLPR using the ER40. Although future research is warranted to elucidate and replicate these data, our findings suggest that impaired facial emotion recognition is a candidate endophenotype for autism.

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Disclosures

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For more information, see Instructions for Authors.

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