

No association between psychometrically-determined schizotypy and olfactory identification ability in first-degree relatives of patients with schizophrenia and non-psychiatric controls

Michael T. Compton*, Victoria H. Chien

Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, Georgia, 30322 USA

Received 22 August 2007; received in revised form 12 November 2007; accepted 14 November 2007

Available online 20 February 2008

Abstract

Objective: This study examined potential associations between schizotypy—including positive, negative, and disorganized domains—and olfactory identification ability. Based on a prior report (Park, S., Schoppe, S., 1997. Olfactory identification deficit in relation to schizotypy. *Schizophr. Res.* 26, 191–197), it was hypothesized that positive and negative schizotypy would be associated with poorer olfactory identification ability, at least among male participants.

Method: As part of a larger study, the Schizotypal Personality Questionnaire (SPQ) and University of Pennsylvania Smell Identification Test (UPSIT) were administered to 98 participants, including 44 healthy first-degree relatives of individuals with schizophrenia and related disorders and 54 non-psychiatric controls. Potential associations between SPQ subscales and UPSIT score were examined while considering the effects of sociodemographic variables on these measures.

Results: SPQ and UPSIT scores were not significantly different in first-degree relatives and controls. There was no evidence of an association between SPQ domains and UPSIT score, even when controlling for possible confounding variables, including age and educational attainment.

Conclusions: The nascent literature on potential associations between schizotypy and olfactory identification ability has yielded mixed findings to date. The current study does not support a correlation between these two markers, and this lack of association—in addition to equal olfactory identification performance in relatives and controls—casts doubt on the utility of the UPSIT as a measure of an endophenotypic trait. Future research would benefit from larger, more diverse samples; the addition of objective, interviewer-based measures of schizotypy; and attention to potentially confounding sociodemographic variables.

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Keywords: Olfactory identification; Psychosis proneness; Schizotypal Personality Questionnaire; Schizotypy; University of Pennsylvania Smell Identification Test

1. Introduction

Schizotypy is a multidimensional construct encompassing a set of behavioral, perceptual, ideational, cognitive, and affective traits that exist along a continuum in the general population. Schizotypy and the categorical diagnosis of schizotypal personality disorder are thought

* Corresponding author. Emory University School of Medicine, 49 Jesse Hill Jr. Drive, S.E., Room #333, Atlanta, GA 30303, USA. Tel.: +1 404 778 1486; fax: +1 404 616 3241.

E-mail address: Michael.Compton@emory.edu (M.T. Compton).

to be genetically related to schizophrenia, given that relatives of individuals with schizophrenia are more likely to exhibit schizotypal traits compared to those without a family history of the illness (Kendler et al., 1995). A number of self-report instruments have been developed to measure schizotypy or psychosis proneness, and the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) provides subscales in positive, negative, and disorganized domains. Some evidence indicates that positive and negative symptoms in patients with schizophrenia predict corresponding positive and negative schizotypal traits in their relatives (Fanous et al., 2001).

Schizotypy is associated with a number of trait markers, or endophenotypes, of schizophrenia. Neurocognitive deficits (e.g., impairments in sustained attention and working memory) similar to, but less prominent than those found in schizophrenia are associated with schizotypy (Bergida and Lenzenweger, 2006; Gooding and Braun, 2004; Gooding et al., 2006; Park and McTigue, 1997). Additionally, schizotypy is associated with deficits in prepulse inhibition of the startle response (Evans et al., 2005), as well as abnormalities in smooth pursuit eye movements and antisaccade task performance (Holahan and O'Driscoll, 2005; Kelley and Bakan, 1999; O'Driscoll et al., 1998; Smyrnis et al., 2003). One increasingly studied phenotype identified in schizophrenia—olfactory identification impairments—has received very little research attention in the context of schizotypy.

Olfactory deficits in persons with schizophrenia appear to pertain primarily to odor identification rather than odor detection or olfactory acuity (Kopala et al., 1994; Striebel et al., 1999). Olfactory identification ability is most commonly measured with the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), and has been shown to be impaired in individuals with schizophrenia compared with controls (Moberg et al., 1999). Baseline UPSIT score may be predictive of remission of negative and cognitive/disorganized symptoms at one year (Good et al., 2006), and poorer odor identification scores are correlated with longer durations of illness, higher levels of negative and disorganized symptoms, as well as impairments in memory domains (Compton et al., 2006; Moberg et al., 2006).

Olfactory identification deficits have been documented in first-episode and neuroleptic-naïve patients (Kopala et al., 1993; Wu et al., 1993), as well as in ultra-high-risk adolescents and young adults who later develop psychotic disorders (Brewer et al., 2003), and olfactory identification impairment has been suggested as a potential vulnerability marker for psychosis (Brewer et al., 2006). Very few studies have examined UPSIT performance among relatives of patients with schizophrenia. Kopala

and colleagues (1998) studied olfactory identification in 12 pairs of monozygotic twins discordant for schizophrenia, finding that the combined twin group scored significantly lower on the UPSIT than a group of 12 healthy controls, and that scores from affected and unaffected twins did not differ. In a study of familial schizophrenia, the same group (Kopala et al., 2001) found that nonpsychotic first- and second-degree family members ($n=27$) scored midway between patients ($n=19$) and healthy controls ($n=43$). However, Compton et al. (2006) failed to replicate this step-wise pattern in patients, relatives, and controls.

Remarkably little research is available on olfaction in relation to schizotypy. Mohr et al., (2001) found elevated olfactory detection thresholds (diminished olfactory acuity) in healthy subjects at or above the median magical ideation score compared to those with low scores, though olfactory discrimination performance was unrelated to magical ideation. Olfactory identification, as measured by the UPSIT, was not tested. Park and Schoppe (1997) examined olfactory identification in relation to schizotypy among 87 undergraduates. Male and female participants were analyzed separately due to prior studies suggesting that sex hormones may have an effect on olfactory function. Among 44 males, UPSIT score was correlated with negative schizotypy (measured by the interpersonal subscale of the SPQ). Six “high schizotypy” males had poorer olfactory identification performance than the remaining 38 males; conversely, 10 “anosmic” males scored higher on the positive (cognitive-perceptual) and negative (interpersonal) SPQ subscales. The only significant association among the 43 females was contrary to expectations — those categorized as anosmic had lower positive schizotypy scores than normosmic females.

The current analysis examined potential associations between schizotypy—including positive, negative, and disorganized domains—and olfactory identification ability in a sample of healthy first-degree relatives of individuals with schizophrenia and related psychotic disorders, as well as non-psychiatric controls. Although research studying these potential associations is very limited, it was hypothesized that positive and negative schizotypy would be associated with poorer olfactory identification ability, at least among male participants, in accordance with the findings of Park and Schoppe (1997).

2. Methods

2.1. Setting and participants

This study was conducted at a large public-sector health system that serves a predominantly African

American population. The sample was comprised of 98 participants, including 44 (44.9%) first-degree relatives and 54 (55.1%) non-psychiatric controls. Among the first-degree relatives, 19 (43.2%) were mothers, 13 (29.5%) were sisters, 5 (11.4%) were daughters, 5 (11.4%) were fathers, and 2 (4.5%) were brothers. Of the controls, 25 (46.3%) were recruited from an ambulatory medicine clinic waiting room, 17 (31.5%) were recruited by researchers providing information on the project at a local farmer's market/food court, and 12 (22.2%) were enrolled after calling the project because they had heard of it (and the compensation of \$65) by word of mouth from other controls. In the clinic waiting room, controls were recruited by approaching individuals seated and waiting to be seen by their own physician or waiting for a family member who was being seen; at the farmer's market, researchers sat at a table with a poster advertising screening for the study. These sites were used in order to draw a sample with very similar sociodemographic characteristics to the group of first-degree relatives, though pair-wise matching was not conducted.

Exclusion criteria for all participants included: (1) inability to speak English, (2) active substance abuse or dependence, (3) mental retardation (assessed by asking participants about educational history, history of being in special classes, and history of diagnosed mental retardation, as well as by clinical observation based on interactions during the assessment), (4) history of neurological disease or clinically significant head injury, and (5) presence of any active medical condition that could affect olfactory identification (e.g., active allergic rhinitis or upper respiratory tract infection). Additionally, first-degree relatives were excluded if they endorsed any personal history of psychotic or mood disorders, and controls were excluded if there was evidence of any personal or family history, in first- or second-degree relatives, of psychotic or mood disorders. The presence of mood disorders served as an exclusion criterion due to the potential for psychotic mood disorders (psychotic depression or psychotic mania) to have some phenomenologic and diagnostic overlap with primary psychotic disorders, as well as the concern that participants may be unable to distinguish affective and nonaffective psychoses. Thus, to exclude the possibility of any personal (in relatives and controls) or family (in controls) history of psychosis broadly defined, histories of both psychotic and mood disorders were assessed. Psychiatric diagnoses in participants were excluded using the psychotic disorders, mood disorders, and substance use disorders modules of the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID; First et al., 1998). Family history was assessed

informally by participants' verbal responses to several questions during the first half of the study and by using the *Family Interview for Genetic Studies* (Maxwell, 1992) in the second half. None of the participants were taking psychotropic medications. The research was approved by the university's institutional review board, and all participants provided written informed consent. As mentioned above, participants were remunerated for their time and effort, given that participation in the larger project required approximately three hours.

2.2. Measures

The *Schizotypal Personality Questionnaire* (SPQ) is a self-report questionnaire used to screen for schizotypy or schizotypal personality disorder (Raine, 1991). Each of the 74 items presents a statement or question, about which the respondent circles "yes" or "no." Affirmatively-endorsed items count one point toward the total score (range: 0–74), with higher scores indicating higher levels of schizotypy. The instrument is comprised of cognitive-perceptual (positive schizotypy), interpersonal (negative schizotypy), and disorganized subscales. Internal consistency reliability, test-retest reliability, and criterion validity of the SPQ are acceptable (Raine, 1991).

The *University of Pennsylvania Smell Identification Test* (UPSIT) is a standardized, easy-to-administer measure of olfactory identification ability (Doty et al., 1984). The instrument is a scratch-and-sniff test consisting of four multiple-choice options for each of 40 items. For each item, a microencapsulated patch containing the odor is scratched with a pencil in a standardized fashion to release the fragrance. The number of correct items is summed to determine an overall score (possible range, 0–40), with higher scores indicating better olfactory identification ability. Adequate test-retest reliability and criterion-related validity have been demonstrated (Doty et al., 1984; Malaspina et al., 1994).

2.3. Data analysis

First-degree relatives and non-psychiatric controls were compared with regard to sociodemographic variables using chi-square tests, Fisher's exact tests, and independent samples Student's t-tests as appropriate. Mean SPQ subscale scores and mean UPSIT scores of the two subgroups were compared. Demographic correlates of SPQ subscale scores and UPSIT score were evaluated in bivariate analyses and then more comprehensively using multivariate analysis of covariance (MANCOVA) for SPQ subscale scores and analysis of covariance (ANCOVA) for UPSIT score.

To examine potential associations between SPQ subscales and UPSIT score, zero order correlations were followed by correlations in male and female participants separately, as done by Park and Schoppe (1997). Potential differences in UPSIT scores in low schizotypy *versus* high schizotypy participants were examined, and differences in SPQ subscale scores in normosmic *versus* anosmic participants were assessed, again in males and females separately. Low schizotypy and high schizotypy were defined by the first and fourth quartiles of the total SPQ score in the overall sample. As in prior studies, anosmia was defined as an UPSIT score of ≤ 34 in men and ≤ 35 in women (Doty et al., 1984; Park and Schoppe, 1997).

To control for potential confounding effects of socio-demographic variables, UPSIT score was added as an independent variable in the aforementioned MANCOVA, and SPQ total score was added as potential predictor in the ANCOVA in which UPSIT score was the dependent variable. All analyses were conducted using SPSS 14.0.

3. Results

3.1. Sample characteristics

Sociodemographic characteristics of the two subgroups are shown in Table 1. Mean age and mean years of educational attainment did not differ between first-degree relatives and controls. First-degree relatives were more likely to be female compared with controls, which was not unexpected due to the preponderance of mothers and sisters willing to participate in the former subgroup. Controls were characterized by a higher proportion of African American participants compared to the relatives. As shown in Table 2, first-degree relatives had scores very similar to controls on all three SPQ subscales and the UPSIT (no significant differences).

3.2. Demographic correlates of SPQ scores

Participants' age was inversely correlated with SPQ disorganized scores ($r = -.22$, $p = .03$). The magnitude

Table 1
Basic sociodemographic characteristics of the study sample

	First-degree relatives ($n = 44$)	Controls ($n = 54$)
Age, years	43.2 \pm 15.5	44.8 \pm 11.3
Educational attainment, years	13.1 \pm 2.7	12.3 \pm 2.1
Gender, female ^a	37 (84.1%)	27 (50.0%)
Race, African American ^b	36 (81.8%)	53 (98.1%)

^a $\chi^2 = 12.44$, $df = 1$, $p < .001$.

^b $\chi^2 = 7.75$, $df = 1$, Fisher's exact $p = .01$.

Table 2
Mean SPQ subscale scores and UPSIT total scores by group status

	First-degree relatives ($n = 44$)	Controls ($n = 54$)
SPQ cognitive perceptual	6.7 \pm 6.5	6.6 \pm 5.5
SPQ interpersonal	7.6 \pm 6.2	7.9 \pm 6.7
SPQ disorganized	3.5 \pm 3.9	2.7 \pm 3.1
UPSIT score	31.8 \pm 6.3	30.6 \pm 5.0

of the inverse correlations between age and the cognitive-perceptual and interpersonal domains were numerically similar, though not statistically significant ($r = -.18$, $p = .08$; $r = -.18$, $p = .09$). Correlations of similar strength were apparent in the two subgroups separately. Years of educational attainment was inversely correlated with all three SPQ domains ($r = -.26$, $p = .01$; $r = -.43$, $p < .001$; $r = -.21$, $p = .05$ for cognitive-perceptual, interpersonal, and disorganized subscales, respectively). In general these correlations appeared stronger among first-degree relatives ($r = -.27$ to $r = -.56$) than controls ($r = -.17$ to $r = -.32$).

Gender was not associated with scores on any of the three SPQ domains in the overall sample. There was no association among first-degree relatives in particular, though gender was associated with SPQ interpersonal scores in controls — female controls had lower interpersonal scores (5.9 \pm 6.4) than male controls (9.9 \pm 6.5). Race was associated with SPQ cognitive-perceptual and interpersonal scores in the overall sample. Specifically, African American participants had higher cognitive-perceptual scores (7.1 \pm 6.0) than Caucasian participants (2.7 \pm 3.8; $t = 2.13$, $df = 91$, $p = .04$). Similarly, African American participants had higher interpersonal scores (8.3 \pm 6.6) than Caucasian participants (3.2 \pm 2.2, $t = 2.28$, $df = 90$, $p = .03$). This association was not examined in the two subgroups individually due to the small number of Caucasian participants.

To further elucidate the effects of group status and demographic variables on SPQ scores, a MANCOVA was conducted, with group status (relative *versus* control), gender, and race as factors, and age and level of educational attainment as covariates. Two of the interaction terms (group status by gender and group status by race) were not significant and therefore were dropped from the model. A significant effect was found for gender ($\lambda(3,81) = 3.18$, $p = .03$), race ($\lambda(3,81) = 3.78$, $p = .01$), the gender by race interaction ($\lambda(3,81) = 2.95$, $p = .04$), and educational level ($\lambda(3,81) = 5.96$, $p = .001$). Follow-up univariate ANCOVAs indicated that gender and race and the gender by race interaction did not have statistically significant main effects on any of the three individual

SPQ domains. However, SPQ interpersonal scores were predicted by educational level, and SPQ disorganized scores were predicted by both age and educational level.

3.3. Demographic correlates of UPSIT score

Participants' age was inversely correlated with UPSIT score ($r = -.44, p < .001$). The correlation was stronger among first-degree relatives ($r = -.57, p < .001$) than controls ($r = -.25, p = .08$). Years of educational attainment was slightly correlated with UPSIT score ($r = .21, p = .05$), though in the two subgroups individually this correlation failed to reach statistical significance, likely due to the smaller sample sizes. Gender was not associated with UPSIT score, and this was true in the two subgroups individually, as well. Race was not associated with UPSIT score in the overall sample; as above, this association was not examined in the two subgroups due to the small number of Caucasian participants.

To further explore the effects of group status and demographic variables on UPSIT score, an ANCOVA was conducted (with group status, gender, and race as factors, and age and level of educational attainment as covariates). The three interaction terms were not significant and therefore were dropped from the model. Both age ($F(1,87) = 22.9, p < .001$) and educational level ($F(1,87) = 5.23, p = .03$) were statistically significant predictors of UPSIT score.

3.4. Lack of associations between SPQ scores and UPSIT score

An examination of zero-order correlations between SPQ domains and UPSIT score revealed no significant correlations ($r = -.01, r = .00, r = -.01$ for correlations between UPSIT and cognitive-perceptual, interpersonal, and disorganized SPQ domains, respectively).

In contrast to Park and Schoppe (1997), correlational analyses did not reveal a significant association between UPSIT score and the negative dimension of schizotypy (or the other two dimensions) in men in particular. As expected based on this lack of significant correlation, there also was no apparent associations between dichotomized low schizotypy *versus* high schizotypy status and UPSIT score, or between anosmic *versus* normosmic olfactory identification status and schizotypy scores. Similarly, correlational analyses did not reveal a significant association between UPSIT score and the three dimensions of schizotypy for females, and no association was found between dichotomized low schizotypy *versus* high schizotypy status and UPSIT

score, or between anosmic *versus* normosmic olfactory identification status and SPQ scores in females.

When UPSIT score was added as a covariate in the aforementioned MANCOVA, only educational level was a significant predictor of schizotypy (UPSIT score was not a significant predictor of schizotypy scores when controlling for the other factors and covariates). Similarly, when the SPQ total score was entered as a covariate in the above ANCOVA in which UPSIT score was the dependent variable, only age and educational level were predictive of UPSIT score, and SPQ total score was not a unique predictor.

4. Discussion

Several key findings emerged from this analysis. First, first-degree relatives had scores very similar to controls on all three SPQ subscales. There are several potential reasons for this lack of difference, which will be outlined briefly. (1) As suggested previously (Bollini et al., 2007), the fact that patients with schizophrenia and related psychotic disorders referred one first-degree relative to participate in the study may have resulted in a biased group of relatives with fewer schizotypal traits because relatives with suspiciousness, subtle thought disorganization, or interpersonal deficits may have been less likely to be referred or to participate if referred. (2) Some researchers explain the lack of difference between groups as resulting from defensive reporting in relatives (Calkins et al., 2004; Chang and Lenzenweger, 2005), given that relatives may have a heightened awareness of schizophrenia symptoms and associated sociocultural stigma, and as a result may present themselves as psychologically healthy, whereas controls do not feel as compelled to do so. (3) The SPQ may not have adequate sensitivity to detect differences between the two groups, though this can be argued against in light of previous research using this instrument. For example, Yaralian and colleagues (2000) found elevated cognitive-perceptual scores among relatives compared to controls, though scores in that report were generally much higher than in the present study. (4) Relatively small sample sizes may have resulted in insufficient power to detect small but meaningful differences between relatives and controls. This potential reason has been put forth by others to explain nonsignificant differences between the two groups (Schürhoff et al., 2007).

The second key finding is that, as reported previously in a subset of this sample (Compton et al., 2006), mean UPSIT scores were not significantly different in first-degree relatives and controls. This is contrary to the findings of Kopala and colleagues (2001), and does not

lend support to one criteria for an endophenotype—that the marker is found in unaffected family members at a higher rate than in the general population (Gottesman and Gould, 2003). Clearly, additional research on olfactory identification in relatives of patients with schizophrenia is warranted. Third, in general, UPSIT scores were relatively quite low in this sample. This may have been a function of particular sample characteristics (e.g., mean age and educational level), and future research should include larger, more diverse samples.

Fourth, and most importantly, in contrast to the findings of Park and Schoppe (1997), there was no evidence of an association between SPQ domains and UPSIT score. There are a number of potential explanations for the lack of association between schizotypy and olfactory identification ability. It could be argued that the SPQ failed to validly measure schizotypy. However, prior results from this sample demonstrated associations between schizotypy measured with the SPQ and cigarette smoking in first-degree relatives (Esterberg et al., *in press*), and past alcohol, cannabis, and cocaine use (Compton et al., *submitted for publication*), in the expected directions. On the other hand, it could be suggested that the UPSIT failed to validly assess olfactory identification ability. Yet, a prior report from a subset of the current participants demonstrated associations between UPSIT score and verbal memory performance (Compton et al., 2006) in the hypothesized direction. Given the particular characteristics of the current sample, the lack of association also could be sample-dependent and obscured by demographic correlates of either schizotypy or olfactory identification ability. However, even controlling for such potential confounders failed to reveal any significant correlations. Finally, and perhaps most convincing, is the possibility that schizotypy is indeed not correlated with olfactory identification ability, even though it is associated with other markers such as neurocognitive impairments, deficits in prepulse inhibition, and abnormalities in smooth pursuit eye movements and the antisaccade task.

Several methodological limitations should be recognized. First, sociodemographic characteristics of the sample limit generalizability to broader populations. Second, the measurement of schizotypy was based on self-report, and future studies also should examine potential correlations between olfactory identification performance and schizotypy using objective, interviewer-based measures of schizotypy. Given the possibility of defensive reporting in relatives mentioned above, clinician-administered interviews may provide a better assessment of schizotypy. Additionally, some domains of schizotypy, such as vague or circumstantial

thinking and speech, constricted affect, and odd or eccentric behavior, may be observable by interviewers but unrecognized by the individuals with these traits. Interestingly, in a previous study based on a subset of the current sample, both neurological soft signs and minor physical anomalies were associated with the level of interviewer-assessed schizotypal features in controls, but neither of these trait markers was associated with self-reported schizotypy (Bollini et al., 2007). Third, women's estradiol levels are believed to influence olfactory ability (Kopala et al., 1995), though the current study did not record menstrual stages or hormone levels of female participants. Fourth, unirhinal olfactory identification was not assessed, though several prior studies suggest that unirhinal measurement may be informative (Good et al., 1998; Good et al., 2002; Szeszko et al., 2004). Finally, though the largest feasible sample was recruited during the time- and resource-limited research period (aiming for a sample at least as large as the 87 participants assessed by Park and Schoppe (1997)), the potential for type II error cannot be excluded given the relatively small sample size.

Despite these limitations, the current study adds to the very nascent literature on potential associations between schizotypy and olfactory identification ability. The lack of association between these two variables in a sample of biological relatives of patients with schizophrenia and non-psychiatric controls points to the need for additional research. This lack of association, in addition to equivalence in olfactory identification performance between relatives and controls (though more research is needed on UPSIT performance in first-degree relatives, which has been limited to three reports to date: Compton et al., 2006; Kopala et al., 1998; and Kopala et al., 2001), casts doubt on the utility of the UPSIT as a measure of an endophenotypic trait. Given past findings of associations between olfactory identification ability and verbal memory domains (Compton et al., 2006), one possible explanation for the mixed findings on schizotypy and olfactory identification to date is that deficits in UPSIT performance are epiphenomenal, reflecting more generalized endophenotypic neurocognitive impairments, rather than representing a true endophenotype in itself. The UPSIT requires the matching of odors with a written label, a task that is more complex (i.e., tapping language-mediated processes) than mere olfactory perception (Mohr et al., 2001). The current findings also point to the need to carefully control for potential sociodemographic confounders; for example, increasing age is associated with lower SPQ scores and lower UPSIT scores, and increasing educational attainment is associated with lower SPQ scores and

higher UPSIT scores. Further research on these issues would be beneficial.

Role of the funding source

This research was supported by a “Young Minds in Psychiatry” award from the American Psychiatric Institute for Research and Education/AstraZeneca and a grant from the Emory Medical Care Foundation. These funding sources played no role in data collection, data analysis, or the preparation of this manuscript.

Contributors

Each of the below coauthors has made a substantial contribution to the research and the drafting of the manuscript and has approved the manuscript for submission.

Michael T. Compton, M.D., M.P.H.

Victoria H. Chien, B.A.

Conflicts of interest

The authors know of no conflicts of interest pertaining to this manuscript.

Acknowledgements

This research was supported by a “Young Minds in Psychiatry” award from the American Psychiatric Institute for Research and Education/AstraZeneca and a grant from the Emory Medical Care Foundation.

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