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An examination of associations between the inability to taste phenylthiocarbamide (PTC) and clinical characteristics and trait markers in first-episode, nonaffective psychotic disorders

Michael T. Compton, Dawn Flosnik Ionescu, Beth Broussard, Sarah L. Cristofaro, Stephanie Johnson, Patrick J. Haggard, Amy A. Potts, Claire Ramsay Wani, and Elaine F. Walker

Abstract

Research findings are mixed as to whether or not the inability to taste phenylthiocarbamide (PTC) might represent an endophenotypic trait marker for schizophrenia. We hypothesized associations between PTC-tasting status and select clinical characteristics and trait markers in patients with psychotic disorders that, if present, would provide support for the inability to taste PTC as a trait marker. In a first-episode psychosis sample (n=93), we measured PTC tasting, family history of psychosis, age at onset of prodrome and psychosis, severity of positive and negative symptoms, global impairment in functioning, neurological soft signs, and four neurocognitive domains (verbal learning/memory, visual learning/memory, verbal working memory, and spatial working memory). Associations between PTC-non-tasting and clinical/neurocognitive variables were examined with \( \chi^2 \) tests and independent samples \( t \) tests. Among participants, 67.7% tasted PTC in comparison to a strip of control paper, and 25.8% were non-tasters. Tasters and non-tasters did not statistically significantly differ with respect to family history, age at onset, severity of symptoms, neurological soft signs, or the four neurocognitive domains. In conjunction with other findings, it is unlikely that PTC-non-tasting is a trait marker of schizophrenia, though a conclusive study is warranted.

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Keywords
Endophenotype; First-episode psychosis; Phenylthiocarbamide; Psychosis; PTC; Schizophrenia

1. Introduction

The inability to taste the bitter chemical phenylthiocarbamide (PTC) has a strong genetic basis; specifically, PTC taste ability is almost completely attributable to the TAS2R38 gene (in the TAS2R bitter taste receptor family of genes) on chromosome 7q (Kim et al., 2003). Thought to be the simplest and best understood taste variation in humans (Drayna et al., 2003), approximately 70% of the U.S. population is able to taste PTC, with the other roughly 30% being non-tasters (Drayna, 2005; Guo and Reed, 2001). Several studies have proposed that inability to taste PTC is more prevalent in patients with schizophrenia (Constantinidis, 1958; Freire-Maia et al., 1968; Moberg et al., 2005; Moberg et al., 2007; Schlosberg and Baruch, 1992); this may even be true among unaffected first-degree relatives (Moberg et al., 2005; Moberg et al., 2007). If proven, this finding could have implications for understanding the genetics of schizophrenia. Most recently, Moberg et al. (2007) found a significantly higher rate of PTC-non-tasting among 67 patients with schizophrenia (57%) compared to 30 controls (23% of whom were non-tasters). Additionally, 30 unaffected first-degree relatives of the patients also showed a higher prevalence of PTC-non-tasting (60%) compared to the healthy volunteers. Yet, Compton et al. (2007) did not find a difference in PTC-tasting status among 48 patients with schizophrenia and schizoaffective disorder, 28 first-degree relatives, and 32 controls (30%, 26%, and 23% were non-tasters, respectively). Furthermore, Brewer et al. (2012) very recently reported no differences in PTC taster status in ultra-high risk participants based on transition to psychosis status, schizophrenia diagnosis, or family history of schizophrenia. In contradistinction to the limited positive findings pertaining to schizophrenia, some prior studies indicate that PTC tasters have a higher likelihood of personal and family history of depression (Joiner and Perez, 2004; Whittemore, 1990).

In light of some positive findings, it has been hypothesized that PTC-non-tasting may represent an endophenotypic marker of inherited neuronal dysfunction that elevates vulnerability for developing schizophrenia (Moberg et al., 2007). Endophenotypes, or trait markers, were described by Gottesman and Shields (1973) as internal phenotypes discoverable by a biochemical test or physiological marker. Using criteria from previous work with identifying genetic markers in psychiatry (Gershon and Goldin, 1986), five criteria have been suggested for establishing a marker as endophenotypic (Gottesman and Gould, 2003): (1) the marker is associated with the illness in the population, (2) it is heritable, (3) it is primarily state-independent (i.e., being present regardless of whether or not there is active disease), (4) it cosegregates with the illness within families, and (5) it is found in unaffected family members at a higher rate than in the general population.

Multiple schizophrenia endophenotypes have been proposed, such as impairments in working memory (Gasperoni et al., 2003; Niendam et al., 2003). Greenwood and colleagues (2007) reported a propensity for endophenotypes to be genetically related to each other—exemplified by associations between verbal memory and working memory deficits—suggesting an overlapping genetic architecture between various endophenotypes. Additionally, endophenotypes tend to be associated with select clinical variables. For example, impairments in verbal declarative (long-term) memory, working memory, and attention have been associated with earlier age at onset of schizophrenia, family history, and/or a greater severity of negative symptoms (Chkonia and Tsverava, 2007; Keshavan et al., 2010; Niendam et al., 2006).
Despite the original negative finding from our site (that patients, first-degree relatives, and controls did not differ in terms of PTC-tasting status; Compton et al., 2007), we hypothesized that—in an independent, case-only, first-episode psychosis sample—we would find associations between PTC-tasting status and select clinical characteristics and trait markers. Such associations would provide further support for PTC-non-tasting as a potential trait marker. Thus, in a first-episode sample, uncomplicated by chronicity and long-term medication use, we tested the hypothesis that inability to taste PTC would be associated with: family history of a psychotic disorder and earlier age at onset; severity of negative symptoms, positive symptoms, and global impairment in functioning (but especially negative symptoms); and five widely accepted endophenotypes (Chan and Gottesman, 2008; Gottesman and Gould, 2003; Gur et al., 2007; Hui et al., 2009; Kalkstein et al., 2010) that were measured as part of the overarching first-episode psychosis study: neurological soft signs, verbal learning and memory, visual learning and memory, verbal working memory, and visuospatial working memory. While not a direct test of the aforementioned five criteria for an endophenotype, this was deemed a reasonable approach in a case-only sample and in light of the general characteristics of other proven endophenotypic traits (e.g., associations with a family history and an earlier onset, inter-correlations amongst markers).

2. Methods

2.1. Setting and sample

Consecutively admitted first-episode patients were recruited from the inpatient psychiatric units (n=70) or psychiatric emergency service (n=5) of a large, urban, teaching hospital, or from a crisis stabilization unit in a neighboring suburban county (n=18). Both facilities serve a predominately African American, low-income, and uninsured/underinsured population. Individuals who were 18–40 years of age and were receiving or recently had undergone a first evaluation or hospitalization for a nonaffective primary psychotic disorder were eligible to participate. Exclusion criteria included having a prior hospitalization for psychosis >3 months before the index hospitalization, having taken antipsychotic medications for >3 months (though the large majority were treatment-naïve at initial hospitalization), known or suspected mental retardation, a significant medical condition that could interfere with ability to participate, and a Mini-Mental State Examination (Cockrell and Folstein, 1988; Folstein et al., 1975) score of <24. An in-depth clinical research evaluation, which included the PTC-tasting assessment described below, was conducted after the patient was stabilized and gave written informed consent, at a mean hospital day of 5.1±3.7 (median=4.5).

Participants were predominately male (66, 71.0%) and African American (83, 89.2%). The mean age was 23.6±4.8 years. Although the eligible age range was 18–40 years, 80.5% of participants were 18–26 years of age. Psychotic disorder diagnoses of the 93 participants, obtained using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1998) were: schizophrenia, paranoid type (43, 46.2%), other schizophrenia subtypes (13, 14.0%), schizoaffective disorder (13, 14.0%), psychotic disorder not otherwise specified (12, 12.9%), schizophreniform disorder (9, 9.7%), brief psychotic disorder (2, 2.2%), and delusional disorder (1, 1.1%). The typical duration of untreated psychosis was more than a year long (median=71 weeks). Participants’ overall functioning was generally low, as reflected by a mean Global Assessment of Functioning (GAF; Hilsenroth et al., 2000) score of 38.8±12.7.

2.2. Procedures and measures

Participants were recruited between August 2008 and February 2011. Following admission and initial stabilization, eligible and interested participants provided written informed consent. Trained research interviewers conducted the in-depth clinical research assessment.
for the overarching study, which lasted approximately six hours, typically divided over 2–3 days. The study was approved by the university’s Institutional Review Board and the health system’s Research Oversight Committee.

Consistent with prior methods (Compton et al., 2007), PTC-tasting status was determined by asking the participant to place for 1–2 seconds a control strip of filter paper on his/her tongue and press the strip of paper against the roof of the mouth. This was followed by placing a PTC-saturated strip of filter paper manufactured by the same supplier on the tongue using the same instructions. The assessor asked the participant if he/she tasted anything different from the first piece of filter paper. Difference was examined using the response choices of “no,” “possibly,” or “yes.” The participant also rated taste intensity of the second strip on a 100mm visual analog line, which ranged from 0mm (no taste) to 100mm (extremely strong taste), as in our prior study (Compton et al., 2007). Odorless filter paper saturated with 0.007mg of PTC, measuring approximately 40mm by 14mm (Carolina Biological Supply Company, Burlington, N.C.) allowed for standardized test administrations, consistent with those of Moberg and colleagues (2005; 2007).

Family history was defined as a history of either narrowly defined schizophrenia or broadly defined psychosis in a first-degree family member. This dichotomization was done after detailed information was collected from the patient and, when available, 1–3 family member “informant” interviews—23 (24.7%) had no participating informants, 38 (40.9%) had one, 30 (32.3%) had two, and two (2.2%) had three participating informants—using an adapted version of the Family Interview for Genetic Studies (Maxwell, 1992).

The Symptom Onset in Schizophrenia (SOS; Perkins et al., 2000) inventory was used to determine age at onset of prodrome and age at onset of psychosis. Fourteen well-defined symptoms commonly observed during the prodrome were rated on a 4-point scale based on frequency and duration of disturbance. The date of the first prodromal symptom(s), as identified by the SOS, was operationalized as the onset of the prodrome. The SOS also allowed for dating the onset of positive symptoms. Using all available data from the clinical treatment team, a chart review, the SOS inventory with the patient, and the SOS inventory rated after in-depth interviews with 1–3 informants when available (as above), consensus-based best estimates for date (and thus age) of onset of prodrome and psychosis were derived.

Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The researcher conducted a chart review and an in-depth interview focused on participants’ current and past-month symptoms. The widely used, original positive and negative symptom subscale scores were computed. Inter-rater reliability of the PANSS positive and negative subscale scores were assessed across the study’s trained raters using a two-way mixed (judges fixed) effects intraclass correlation (ICC) coefficient analysis of variance model (Shrout and Fleiss, 1979). Both ICC coefficients were .92.

The Neurological Evaluation Scale (NES; Buchanon and Heinrichs, 1989) is a structured, approximately 30-minute examination consisting of 26 items designed specifically to measure neurological soft signs in schizophrenia. The total NES score was calculated, which had an inter-rater ICC coefficient of .96 amongst the raters.

Verbal learning and memory, visual learning and memory, verbal working memory, and visuospatial working memory, all of which have been posited as neurocognitive endophenotypes of schizophrenia, were assessed. Four reliable and valid neurocognitive tests were selected from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al., 2008), the best available measures of neurocognition in schizophrenia. The first three trials of Form 1
of the Hopkins Verbal Learning Test–Revised (HVLT-R) were administered to assess verbal learning and memory, by requiring the participant to learn a list of nouns over three trials and reproduce them without time given for rehearsal (Benedict et al., 1998; Strauss et al., 2006). The Brief Visuospatial Memory Test–Revised (BVMT-R) was used to measure visual learning and memory (visuoconstructual ability and visuospatial memory). This task, particularly sensitive to assessing fine motor coordination within the context of an individual’s spatial planning/organization ability, involves a 10-second presentation and then reproduction of six figures over three trials. Visual learning is determined by calculating a total score based on accuracy and correct location of the figures (Benedict et al., 1996).

Verbal working memory was evaluated with the Letter-Number Span (LNS) subtest of the Wechsler Memory Scale–Third Edition (WMS-III). In this non-timed task, different combinations of letters and numbers are read to the participant, who is required to first recite the numbers in ascending order and then recite the letters in alphabetical order; for example, the correct response to an examiner’s inquiry of “2-G-9-B” would be “2–9–B–G.” The task relies heavily on executive functioning and attention to actively hold and manipulate auditory/verbal information (Groth-Marnat, 2009; Strauss et al., 2006). Visuospatial working memory was assessed with the Spatial Span (SS) subtest of the WMS-III, which requires the participant to touch a sequence of blocks in the same order as the examiner, and subsequently, touch the blocks the examiner touched, but in reverse order. The task assesses an individual’s ability to store and manipulate visuospatial information in short-term memory while being faced with contextual distracters (Hoelzle et al., 2010; Strauss et al., 2006; Wechsler, 1997). Participants’ raw scores were used in analyses involving both verbal and visuospatial working memory.

2.3. Data analyses

Distributional properties of all variables were examined. Associations between inability to taste PTC and nominal variables were examined using \( \chi^2 \) tests of association, and associations with continuous variables were assessed with independent samples Student’s \( t \) tests. Regarding the latter, to assess practical meaningfulness beyond statistical significance, we computed Cohen’s \( d \) (Cohen, 1988) as a standardized effect size, considering .2 as a small effect, .5 as a medium effect, and .8 as a large effect. After the main analyses, sensitivity analyses were conducted by combining the small group who responded as “possibly” tasting PTC with the “non-tasters,” and then with the “tasters.” Finally, sub-analyses were run restricting the dataset to more homogeneous groups; specifically the younger first-episode patients (ages 18–26 years) and then participants with a diagnosis of schizophrenia.

3. Results

Among 93 first-episode patients with available data on PTC tasting, 63 (67.7%) indicated that they tasted the chemical in comparison to the strip of control paper, and 24 (25.8%) were non-tasters. The remaining six (6.5%) endorsed “possibly” tasting the chemical and were excluded from the main analyses (though included in subsequent sensitivity analyses described below). As in the previous study (Compton et al., 2007), we compared categorical responses (yes/no) to the ratings obtained using the 100mm visual analog line, as a means of validating the categorical response approach. The distribution of intensity ratings is shown in the histogram in Figure 1. Participants responding “no” to a difference in taste endorsed a significantly lower intensity rating (16.4±28.2) compared to participants responding “yes” (60.6±26.0; \( t = 6.47, df=80, p<.001 \)), similar to findings from the prior study (11.0±16.3 and 69.0±25.8; \( p<.001 \); Compton et al., 2007).
Tasters and non-tasters did not differ in terms of mean age or gender composition. Among 83 patients with available data on family history, seven of 24 patients (29.2%) who reported an inability to taste PTC had a first-degree family history of psychosis, compared to nine of 59 (15.3%) who tasted it ($\chi^2=2.12, df=1$, Fisher’s exact $p=.218$). As shown in Table 1, age at onset of prodrome and age at onset of psychosis were not significantly associated with PTC-tasting status. Furthermore, positive symptom severity, negative symptom severity, and global functioning at initial hospitalization were not associated with PTC-tasting status. PTC-non-tasting was not associated with any psychiatric trait markers, including the level of neurological soft signs or degree of impairment in the four domains of neurocognition. Effect sizes generally ranged from negligible (e.g., positive symptom severity and global functioning) to small (i.e., $\leq .38$). In examining the single PANSS depression item, tasters and non-tasters did not differ (3.2±1.8 and 3.5±1.6, respectively, $p=.44$).

As in the prior report (Compton et al., 2007), to provide a sensitivity analysis given that six participants responded as “possibly” tasting PTC, this small group was combined with non-tasters, which resulted in no meaningful changes to the lack of statistically significant associations noted above (all $p>.1$). Similarly, when these six participants were combined with the taster group, re-analysis again revealed no significant differences (again, all $p>.1$). A sub-analysis restricting the sample to younger patients (ages 18–26 years) revealed no meaningful differences from those given in Table 1 (again, all $p>.1$). The same was true in a sub-analysis involving only those participants with a diagnosis of schizophrenia.

4. Discussion

Several findings are noteworthy. First, the prevalence of PTC-non-tasting in this sample of 93 first-episode psychosis patients (26%) was consistent with previously published population norms of about 30%—and with the prevalence of 30% reported among 48 chronic patients with schizophrenia and schizoaffective disorder from this site (Compton et al., 2007)—but quite dissimilar from the prevalence (57%) reported by Moberg and colleagues (2005; 2007) in samples of 42 and 67 patients with chronic schizophrenia. Thus, the proposition that PTC-non-tasting is more common in patients with psychotic disorders (the first criterion for an endophenotype) is not supported here; results are thus mixed. Second, assuming that an endophenotype would be associated with select clinical features (e.g., family history, age at onset, severity of negative symptoms) and other known trait markers (e.g., neurological soft signs and neurocognitive deficits), the present findings do not support such associations. Specifically, we failed to find evidence that inability to taste PTC is associated with presence of any clinical or neurocognitive features. We concede, however, that although no differences were statistically significant, several modest effect sizes were in the hypothesized direction. For example, family history was numerically more common, age at onset numerically lower, neurological soft signs numerically higher, and working memory numerically poorer, among the 24 non-tasters compared to the 63 who could taste the chemical. The potential for type II error is discussed further below.

Discovery and confirmation of endophenotypes for schizophrenia and other mental illnesses is important in identifying specific susceptibility genes (Gur et al., 2007), and these may also improve overall understandings of the neurobiology of psychopathology (Gottesman and Gould, 2003). This may ultimately lead to improved diagnostic criteria, earlier identification of disease states, and enhanced treatment and preventive approaches. The prospect of a very easy-to-assess endophenotype, such as PTC-non-tasting, is exciting. However, given these findings showing no significant support for PTC-tasting status as an endophenotypic marker for schizophrenia, the hope of using this test as a viable trait marker for schizophrenia appears limited at present. Given the mixed findings to date, a larger-scale, conclusive study is needed.
A noteworthy, puzzling observation is a small literature suggesting that females with major
depression (n=23) who tasted PTC experienced a greater severity of depression, longer
depressive episodes, symptoms resembling endogenous depression, and a greater likelihood
of a family history of depression (Whittemore, 1990). Furthermore, among 42 volunteers,
PTC “supertasters” (those who are very sensitive to the chemical’s taste) were significantly
less likely to report first-degree relatives with a history of depression relative to tasters and
non-tasters (Joiner and Perez, 2004). It is interesting that the limited literature pertaining to
schizophrenia suggests, in some studies, a higher proportion of non-tasters among both
patients and their relatives, yet the literature relating to depression indicates that PTC tasters
are more likely to be depressed and to have a family history of depression. Given the high
rate of comorbidity between mood and psychotic disorders—and the evidence of shared
genetic risk factors—these findings are difficult to reconcile. It seems unlikely that both sets
of findings would be valid (though it is possible that neither set of findings is valid).

Several methodological limitations must be acknowledged. Most importantly, as noted
above, though no statistically significant differences emerged, findings were numerically in
the hypothesized direction. This raises the possibility of Type II error, or insufficient power.
Larger sample sizes may indeed detect differences, though effect sizes suggest that clinical
meaningfulness (and thus, utility as an endophenotype) must be seriously considered.
Second, participants were demographically relatively homogeneous (from a predominantly
African American, socially disadvantaged population), which enhances internal validity, but
limits generalizability.

Additional research is necessary before the potential association between PTC-tasting status
and schizophrenia can be definitively stated or disproven. Further research is warranted
primarily because of the relative ease of administration of this test, as compared to many
other endophenotypes (e.g., smooth-pursuit eye tracking, electrophysiologic indices). These
findings indicate, however, that a clear and consistent signal is lacking.

5. Conclusions

Within this case-only, first-episode psychosis sample, PTC tasters and non-tasters did not
statistically significantly differ with respect to family history, age at onset, severity of
symptoms, degree of neurological soft signs, or level of impairment on the four
neurocognitive domains. This suggests that it is unlikely that PTC-non-tasting clearly
represents a trait marker of schizophrenia, given that most other trait markers associate with
one or more of these features.

Acknowledgments

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Figure 1.
Histogram showing the distribution of PTC intensity ratings among first-episode psychosis patients (n=93)
Table 1

Associations between PTC-tasting status and clinical characteristics and trait markers in patients with first-episode, nonaffective psychotic disorders

<table>
<thead>
<tr>
<th></th>
<th>Tasters (n=63)</th>
<th>Non-Tasters (n=24)</th>
<th>t</th>
<th>df</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of prodrome</td>
<td>18.5±4.8</td>
<td>16.4±7.5</td>
<td>1.22</td>
<td>28.0*</td>
<td>.23</td>
<td>.38</td>
</tr>
<tr>
<td>Age at onset of psychosis</td>
<td>20.8±4.4</td>
<td>19.0±7.4</td>
<td>1.11</td>
<td>28.4*</td>
<td>.28</td>
<td>.34</td>
</tr>
<tr>
<td>PANSS positive symptoms</td>
<td>23.4±5.6</td>
<td>23.5±4.3</td>
<td>0.14</td>
<td>85</td>
<td>.89</td>
<td>−.02</td>
</tr>
<tr>
<td>PANSS negative symptoms</td>
<td>21.6±5.4</td>
<td>20.5±6.6</td>
<td>−0.81</td>
<td>85</td>
<td>.42</td>
<td>.19</td>
</tr>
<tr>
<td>GAF global functioning</td>
<td>38.3±12.2</td>
<td>38.9±13.5</td>
<td>0.21</td>
<td>82</td>
<td>.83</td>
<td>−.05</td>
</tr>
<tr>
<td>NES neurological soft signs</td>
<td>13.3±8.3</td>
<td>16.5±9.4</td>
<td>1.52</td>
<td>82</td>
<td>.13</td>
<td>−.38</td>
</tr>
<tr>
<td>HVLT-R verbal learning and memory</td>
<td>5.5±1.8</td>
<td>5.7±1.3</td>
<td>0.49</td>
<td>55.9*</td>
<td>.63</td>
<td>−.12</td>
</tr>
<tr>
<td>BVMT-R visual learning and memory</td>
<td>4.6±2.1</td>
<td>4.0±2.0</td>
<td>−1.15</td>
<td>74</td>
<td>.25</td>
<td>.29</td>
</tr>
<tr>
<td>WMS-III LNS verbal working memory</td>
<td>12.1±4.3</td>
<td>10.8±4.3</td>
<td>−1.33</td>
<td>79</td>
<td>.19</td>
<td>.31</td>
</tr>
<tr>
<td>WMS-III SS spatial working memory</td>
<td>13.0±4.0</td>
<td>11.8±3.9</td>
<td>−1.22</td>
<td>79</td>
<td>.23</td>
<td>.31</td>
</tr>
</tbody>
</table>

* Adjusted df based on a significant Levene’s test for equality of variances.