Published in final edited form as:

Psychiatry Res. 2013 August 30; 209(1): 27–31. doi:10.1016/j.psychres.2013.03.028.

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^{a,*†}, Dawn Flosnik Ionescu^a, Beth Broussard^{a,*}, Sarah L. Cristofaro^b, Stephanie Johnson^b, Patrick J. Haggard^b, Amy A. Potts^b, Claire Ramsay Wan^b, and Elaine F. Walker^c

^aThe George Washington University School of Medicine and Health Sciences, Department of Psychiatry and Behavioral Sciences, Washington, DC, USA 20037

^bEmory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, GA, USA 30322

^cEmory University Graduate School of Arts and Sciences, Department of Psychology, Atlanta, GA, USA 30322

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 χ^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.

© 2013 Elsevier Ireland Ltd. All rights reserved.

[†]Corresponding author: Michael T. Compton, M.D., M.P.H., The George Washington University School of Medicine and Health Sciences, Department of Psychiatry and Behavioral Sciences, 2120 L Street, N.W., Suite 600, Washington, DC 20037. Tel: 202-741-3554. Fax: 202-741-2891. mcompton@mfa.gwu.edu.

^{*}When data for this analysis were collected, Dr. Compton and Ms. Broussard were with the Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, GA.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: The authors know of no financial involvements that would appear to be a conflict of interest in connection with this manuscript.

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* (BVM-T-R) was used to measure visual learning and memory (visuoconstructional 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 χ^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., .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

Funding for this project was made possible through a grant from the National Institute of Mental Health, R01 MH081011. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

References

- Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test—Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*. 1998; 12:43–55.
- Benedict RHB, Schretlen D, Groninger L, Dobraski M. Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. *Psychological Assessment*. 1996; 8:145–153.

- Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): A structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Research*. 1989; 27:335–350. [PubMed: 2710870]
- Chan RC, Gottesman II. Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a Northern star? *Neuroscience and Biobehavioral Reviews*. 2008; 32:957–971. [PubMed: 18462797]
- Chkonia E, Tsverava L. Investigation of explicit verbal memory in patient with paranoid schizophrenia and their first degree relatives. *Georgian Medical News*. 2007; 1:14–17. [PubMed: 17984556]
- Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacology Bulletin*. 1988; 24:689–692. [PubMed: 3249771]
- Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
- Compton MT, Chien VH, Bollini AM, Walker EF. Lack of support for the inability to taste phenylthiocarbamide as an endophenotypic marker in patients with schizophrenia and their first-degree relatives. *Schizophrenia Research*. 2007; 95:65–69. [PubMed: 17689053]
- Constantinidis J. Les marqueurs de chromosomes chez les schizophrènes et la recherche du linkage entre ces caractères et la schizophrénie par la méthode de Penrose. *Journal de Génétique Humaine*. 1958; 7:189–242.
- Drayna D. Human taste genetics. *Annual Review of Genomics and Human Genetics*. 2005; 6:217–235.
- Drayna D, Coon H, Kim UK, Elsner T, Cromer K, Otterud B, Baird L, Peiffer AP, Leppert M. Genetic analysis of a complex trait in the Utah Genetic Reference Project: A major locus for PTC taste ability on chromosome 7q and secondary locus on chromosome 16p. *Human Genetics*. 2003; 112:567–572. [PubMed: 12624758]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: New York State Psychiatric Institute, Biometrics Research Department; 1998.
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12:189–198. [PubMed: 1202204]
- Freire-Maia N, Karam E Jr, Mehl H. PTC sensitivity among psychiatric patients. *Acta Genetica et Statistica Medica*. 1968; 18:31–37. [PubMed: 5694808]
- Gasperoni TL, Ekelund J, Huttunen M, Palmer CG, Tuulio-Henriksson A, Lonnqvist J, Kaprio J, Peltonen L, Cannon TD. Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2003; 116B:8–16.
- Gershon ES, Goldin LR. Clinical methods in psychiatric genetics, I: Robustness of genetic marker investigative strategies. *Acta Psychiatrica Scandinavica*. 1986; 74:113–118.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Gottesman II, Shields J. Genetic theorizing and schizophrenia. *British Journal of Psychiatry*. 1973; 122:15–30. [PubMed: 4683020]
- Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: The consortium on the genetics of schizophrenia. *Archives of General Psychiatry*. 2007; 64:1242–1250. [PubMed: 17984393]
- Groth-Marnat, G. *Handbook of Psychological Assessment*. Hoboken, NJ: John Wiley & Sons, Inc.; 2009.
- Guo SW, Reed DR. The genetics of phenylthiocarbamide perception. *Annals of Human Biology*. 2001; 28:111–142. [PubMed: 11293722]
- Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, Kanes S, Blangero J, Gur RC. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *American Journal of Psychiatry*. 2007; 164:813–819. [PubMed: 17475741]

- Hilsenroth MJ, Ackerman SJ, Blagys MD, Baumann BD, Baity MR, Smith SR, Price JL, Smith CL, Heindselman TL, Mount MK, Holdwick DJ. Reliability and validity of DSM-IV Axis V. *American Journal of Psychiatry*. 2000; 157:1858–1863. [PubMed: 11058486]
- Hoelzle JB, Nelson NW, Smith CA. Comparison of Wechsler Memory Scale-Fourth Edition (WMS-IV) and Third Edition (WMS-III) dimensional structures: Improved ability to evaluate auditory and visual constructs. *Journal of Clinical and Experimental Neuropsychology*. 2010; 33:283–291. [PubMed: 20924914]
- Hui CL, Wong GH, Chiu CP, Lam MM, Chen EY. Potential endophenotypes for schizophrenia: Neurological soft signs. *Annals of the Academy of Medicine, Singapore*. 2009; 38:408–413.
- Joiner TE Jr, Perez M. Phenylthiocarbamide tasting and family history of depression, revisited: Low rates of depression in families of supertasters. *Psychiatry Research*. 2004; 126:83–87. [PubMed: 15081630]
- Kalkstein S, Hurford I, Gur RC. Neurocognition in schizophrenia. *Current Topics in Behavioral Neurosciences*. 2010; 4:373–390. [PubMed: 21312407]
- Kay S, Fiszbein A, Opler L. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*. 1987; 13:261–276. [PubMed: 3616518]
- Keshavan MS, Kulkarni S, Bhojraj T, Francis A, Diwadkar V, Montrose DM, Seidman LJ, Sweeney J. Premorbid cognitive deficits in young relatives of schizophrenia patients. *Frontiers in Human Neuroscience*. 2010; 3:1–14.
- Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science*. 2003; 299:1221–1225. [PubMed: 12595690]
- Maxwell, E. Manual for the Family Interview for Genetic Studies. Bethesda, Maryland: National Institute of Mental Health, Clinical Neurogenetics Branch, Intramural Research Program; 1992.
- Moberg PJ, McGue C, Kanes SJ, Roalf DR, Balderston CC, Gur RE, Kohler CG, Turetsky BI. Phenylthiocarbamide (PTC) perception in patients with schizophrenia and first-degree family members: Relationship to clinical symptomatology and psychophysical olfactory performance. *Schizophrenia Research*. 2007; 90:221–228. [PubMed: 17208411]
- Moberg PJ, Roalf DR, Balderston CC, Kanes SJ, Gur RE, Turetsky BI. Phenylthiocarbamide perception in patients with schizophrenia and first-degree family members. *American Journal of Psychiatry*. 2005; 162:788–790. [PubMed: 15800154]
- Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewy R, O'Brien M, Nuechterlein KH, Green MF, Cannon TD. Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia Research*. 2006; 84:100–111. [PubMed: 16563699]
- Niendam TA, Bearden CE, Rosso IM, Sanchez LE, Hadley T, Nuechterlein KH, Cannon TD. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *American Journal of Psychiatry*. 2003; 160:2060–2062. [PubMed: 14594759]
- Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ 3rd, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR. The MATRICS Consensus Cognitive Battery, Part 1: Test selection, reliability, and validity. *American Journal of Psychiatry*. 2008; 165:203–213. [PubMed: 18172019]
- Perkins DO, Leserman J, Jarskog LF, Graham K, Kazmer J, Lieberman JA. Characterizing and dating the onset of symptoms in psychotic illness: The Symptom Onset in Schizophrenia (SOS) inventory. *Schizophrenia Research*. 2000; 44:1–10. [PubMed: 10867307]
- Schlosberg A, Baruch I. Phenylthiocarbamide (PTC) tasting in paranoid and nonparanoid schizophrenic patients. *Perceptual and Motor Skills*. 1992; 74:383–386. [PubMed: 1594398]
- Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*. 1979; 86:420–428. [PubMed: 18839484]
- Strauss, E.; Sherman, EMS.; Spreen, O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. New York: Oxford University Press; 2006.
- Wechsler, D. WAIS-III Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation; 1997.

Whittemore PB. Phenylthiocarbamide (PTC) tasting, genetics, and depression. *Journal of Clinical Psychology*. 1990; 46:262–272. [PubMed: 2347929]

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

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

Table 1

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

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