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Olfaction and Schizophrenia Clinical Risk Status: Just the Facts

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Dear Editors,

The recent meta-analysis by Cohen et al. (2012) offered a review of the evidence regarding olfactory dysfunction in both schizophrenia patients and individuals at risk for the illness. Their analysis supported the presence of a robust olfactory identification deficit in patients. However, concerning the study of at-risk individuals, they concluded as follows: “Overall, the present findings failed to find evidence that olfaction identification deficits are a meaningful vulnerability marker of schizophrenia pathology..(We) believe that conducting further studies…is not a particularly promising endeavor.” It is our opinion that this assertion could have an unwarranted and unfortunate chilling effect on future research, as it does not accurately reflect the current status of the field. In reviewing 16 studies purported to examine schizophrenia risk status, the authors conflate three very different categories of risk. Five were studies of otherwise-healthy individuals who scored high on a psychometric scale of schizotypal features (e.g. Schizotypal Personality Questionnaire). Nine were studies of unaffected family members of schizophrenia patients. Only two were studies of “ultra-high risk” individuals in the sub-psychotic or prodromal state, as assessed by the Structured Interview for Prodromal Syndromes (SIPS). The incidence of future conversion to overt psychosis is very different in these sub-categories. Grouping them together presents a distorted picture that can lead to erroneous conclusions.

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Conversion rates among prodromal individuals with symptoms severe enough to prompt clinical referral have been reported as approximately 35% within 2.5 years (Cannon et al., 2008). Unaffected first-degree relatives of schizophrenia patients, in contrast, have a lifetime psychosis incidence of approximately 10% (Karlsson, 1982). Since most of the published family studies were of older adults (i.e., parents and siblings of schizophrenia probands), many of whom were already past the peak ages of illness onset, the actual incidence in this group was likely substantially lower. In the two existing large-scale longitudinal studies of individuals with psychometrically defined schizotypy, one reported zero cases of psychosis among 91 “at-risk” subjects after 5 years (Gooding et al., 2005). The other reported 10 cases of psychosis among 182 subjects (5.5%) after 10 years (Chapman et al., 1994). Clearly, the risk for psychosis among ultra-high risk subjects greatly exceeds the risk among individuals in the other two categories. A sensitive and specific marker of disease vulnerability should, ideally, reflect this heightened risk profile. Indeed, any vulnerability marker that cannot distinguish among these three groups has very little predictive utility. The results for odor identification, *as reported by Cohen*, are entirely consistent with these expectations regarding an ideal vulnerability marker. He determined the effect size for the ultra-high risk group to be −0.67 (a moderate to large effect), whereas the effect sizes for unaffected family members and psychometrically defined schizotypals were −0.21 and −0.14, respectively (small to insignificant effects).

The facts regarding olfaction and clinical high-risk status are the following. There have been a total of three published studies of olfactory deficits in clinical high-risk subjects relative to demographically comparably healthy individuals (Brewer et al., 2003; Kamath et al., 2012; Woodberry et al., 2010). The overall effect size in the Brewer study was −0.48 (Woods, S.J. Personal communication). The effect size, as listed in the Woodbury manuscript, was −0.89 (not −0.84 as reported by Cohen). The effect sizes in the Kamath study — which was not included in Cohen’s review due to its recent publication — were −1.26 for odor identification and −1.11 for odor discrimination. A meta-analysis of all available data from these three studies yields a composite effect size of −0.77, rather than −0.67.

Importantly, the Brewer and Woodberry studies also included longitudinal follow-ups of their clinical high-risk participants, which allowed them to examine separately the baseline data from those subjects who subsequently became psychotic. The effect sizes for these future-psychosis subsamples were substantially higher than for the high-risk groups as a whole, −0.68 and −1.32, respectively. Brewer’s future-psychosis sample was large enough to be further parsed into those who developed schizophrenia and those who developed other psychotic illnesses. The effect size for odor identification deficits in those who subsequently developed schizophrenia was −1.12; for those who developed other psychoses, it was −0.24.

So the facts, as opposed to the fiction, regarding olfaction and clinical high-risk status are these. There have been three independent studies to date, with three sets of positive findings, a large composite effect, and initial evidence to suggest that this impairment is indicative of a future schizophrenia-spectrum psychotic disorder. The magnitude, consistency and predictive potential of this deficit collectively establish olfactory impairment as one of the most viable biomarkers of the psychosis clinical high-risk state yet identified. Our confidence in making this assertion would, of course, be greater if it were based on a greater number of studies, and it may ultimately be proven false. But to conclude, based on current evidence, that further study is unwarranted would be a truly egregious error.

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