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Integration of Mental Health Care and Supported Employment

TO THE EDITOR: Judith A. Cook, Ph.D., et al. (1) presented an illuminating reanalysis of data from the Employment Implementation Demonstration Program, perhaps the largest study of supportive employment ever conducted. In their article, the authors shifted the analytic focus from a comparison of supported employment and control interventions (2) to a comparison of programs with greater integration of psychiatric and employment services and those with less integration. This is evidently a crucial shift because the difference in employment rates in the original analysis (55% for those with supported employment and 34% for comparison subjects—a 1.6-fold difference) was almost double in the newer analysis (58% employed in the high-integration programs versus 21% in the low-integration programs—a 2.8-fold difference).

Unfortunately, the explanation of the measure of integration was somewhat ambiguous. On p. 1950, a clearly defined four-level measure of integration was presented. It was subsequently explained that the measure was dichotomized at 50% or more, with integrated sites defined as those that met two or more of the four criteria. Given the hierarchical nature of the four-level measure (the higher levels seem to encompass the lower levels), the threshold for integration would seem to have been met if 1) common charts were used and 2) both types of service were provided by the same agency. This modest level of structural integration seems to have had a substantial impact on employment outcomes, and if replicable in other studies, it could be implemented widely. However, in footnote c to Table 2 and in the first paragraph of the discussion, all four integration criteria are listed, suggesting that perhaps all four had to be met for a program to be considered highly integrated. I inferred from the fact that two-thirds of the programs met the threshold for high integration that the looser criteria had been applied. Could the authors clarify what is the correct definition of the integration variable used in their analysis and whether they believe that such modest structural characteristics can, indeed, improve employment outcomes? If so, what is the role of the quality of supported employment itself? The importance of integration would have received stronger support if the authors had demonstrated a monotonal progressive improvement in employment outcomes as one moves up the five levels of integration on this measure. Was this observed?

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Dr. Cook and Colleagues Reply

To the Editor: We thank Dr. Rosenheck for his careful reading of our article, and in response to his question, we clarify that the definition of services integration that appears in the text of our article (p. 1950) is correct. The definition that appears in the footnote to Table 2 (p. 1954) lacks the detail that appears in the text. We apologize for any confusion this may have caused. Further, we agree with the excellent points that Dr. Rosenheck raises regarding the measurement of integrated mental health care and supported employment services. The analyses he suggests, including an examination of the effect of modest incremental change in the level of services integration on employment outcomes, would be of great interest to the field. Unfortunately, the measure of services integration that we used is not appropriate for such tests because it was created post hoc as a means of characterizing the variety of interventions included in the demonstration program based on available information. As such, we did not test its reliability or validity. The distribution of services integration with this measure was nonnormal, with modes at 0% and 100%. We feel that although the measure was able to differentiate high and low levels of integration of services in the Employment Implementation Demonstration Program multisite study, we cannot be sure that it taps the latent construct of integrated clinical and vocational services. Following Dr. Rosenheck's line of reasoning, we agree that development of a more rigorous measure of services integration would be of great value to our field.

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Are High-Risk Haplotypes in *DTNBP1* and *NRG1* Resistance Genes for Schizophrenia?

TO THE EDITOR: Recently, several candidate susceptibility genes of small effects for schizophrenia have been replicated in association studies. However, their possible roles in the manifestation of the disease remain obscure (1). Therefore,

we read with great interest the article by Ayman H. Fanous, M.D., and colleagues (2), which described the relationship between a high-risk haplotype in the *DTNBP1* gene and clinical features of schizophrenia. The conclusion—that the etiologically relevant variation in *DTNBP1* in presumptive linkage disequilibrium with the high-risk haplotype might be associated with high levels of negative symptoms—was derived from the observation that the high-risk haplotype frequency was higher in the subjects in the upper 40th percentile for the negative symptom factor.

However, the data in their Table 2 might suggest the opposite possibility. First, the frequency of the high-risk haplotype was higher in the upper 20%–40% subgroup for the negative symptom factor than in the upper 0%–20% subgroup (0.098 and 0.075, respectively). In addition, the high-risk haplotype frequencies in the upper 40% subgroup for four factors (negative, hallucinations, delusions, and manic) were higher in the broad-definition group than in the narrow-definition group. These results suggest that the high-risk haplotype in *DTNBP1* was overtransmitted to the milder cases with schizophrenia, which is just the opposite of their interpretation.

This might be the same with *NRG1*, another best-replicated positional candidate gene for schizophrenia. The high-risk haplotypes were associated with nondeficit schizophrenia but not with deficit schizophrenia (3).

A significant p value in an association study tells us nothing about the nature of the causal relationship between the gene and the disease (1). Therefore, it should be noted that a significant positive association with a disease does not necessarily imply susceptibility but rather may indicate resistance to the disease.

According to Kendler (4), one of the most perplexing problems concerned with the schizophrenia-*DTNBP1* connection is that although reduced levels of *DTNBP1* were seen in the hippocampus of nearly all affected cases, only a subset of individuals with schizophrenia carries the high-risk *DTNBP1* haplotypes that reduce *DTNBP1* expression in the brain (5). However, if the high-risk haplotypes in *DTNBP1* were resistance genes and a reduced *DTNBP1* level in the brain was a resistance response to the pathogenesis of the disease, the brains of most patients would show such a change and a subset of patients who carry apparent high-risk *DTNBP1* haplotypes should have a genetically determined resistance that makes the disease milder.

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Dr. Fanous and Colleagues Reply

TO THE EDITOR: We read with interest the letter submitted by Drs. Doi and Usui regarding our article. Several points are made in their letter. First of all, the authors state that our main finding, that subjects inheriting the high-risk haplotype in *DTNBP1* had higher levels of negative symptoms than expected by chance, "was derived from the observation that the high-risk haplotype frequency was higher in the subjects in the upper 40th percentile for the negative symptom factor." Actually, our results were not derived from analyses of the frequency of the high-risk haplotype in the various clinical subgroups, although frequencies were provided in our table. Rather, we employed the Transmission-Disequilibrium Test (1). This is a popular family-based association method that tests for excess transmission of alleles (or haplotypes) from heterozygotic parents to affected offspring. This transmission information, moreover, is not present in allele frequencies, which are derived from examining the entire group as a whole. In our experience, employing case-control methods, which are based on allele frequencies, in our group of 270 high-density schizophrenia families is less powerful than family-based tests such as the Transmission-Disequilibrium Test.

Second, they state that the "frequency of the high-risk haplotype was higher in the upper 20%–40% subgroup for the negative symptom factor than in the upper 0%–20% subgroup." Actually, the two groups that we tested were 1) the upper 0%–20% subgroup and 2) the 0%–40% subgroup. Therefore, the former was a subset of the latter group, comprising approximately half of it. Although we saw no preferential transmission to the 0%–20% group, we interpreted this as being due to insufficient power to detect association, which was recovered when we broadened our definition of affection to additionally include subjects in the upper 21%–40%. We believe that the interpretation of Drs. Doi and Usui, i.e., that these results suggest a protective effect of the *DTNBP1* high-risk haplotype, would therefore not follow. As an additional check, we went back to analyze the 21%–40% group. We found that the ratio of observed-to-expected transmissions was basically the same as that in the 0%–20% group.

Our interpretation of the results is that the *DTNBP1* high-risk haplotype preferentially increases risk for a more or less specific clinical form of illness, namely, one that is associated with higher levels of negative symptoms. It is not clear to us that this has implications for a protective effect of the *DTNBP1* genotype on the illness. A protective effect requires that one or more haplotypes be less likely to be transmitted to affected offspring than would be expected by chance. In the case of *DTNBP1*, if the high-risk haplotype were truly protective against negative symptoms, then it should be transmitted to all groups defined by high levels of negative symptoms (i.e., 0%–20%, 0%–40%, and 21%–40%) *less*—not more—as we observed, than would be expected by chance. In furthering their argument, Drs. Doi and Usui adduce results indicating that