justification for the study, could cast new light on these questions if the authors are able to adopt a hypothesis-testing approach to the data they are accumulating. Relevant to these issues is the nature of the speech and communication difficulties that are described in the Structural Interview for Schizotypy assessments.

The 'Discussion' considers methodological problems that are specific to this study, but also touches on the theoretical issues. Neither has a significant impact on the guarded conclusion in the summary.

There may be a case for interim publication on the progress of this study, but if so it seems that much of the introduction and some of the discussions which relate to theoretical issues that are not addressed at all in the conclusions of the study could be omitted. More importantly, it seems that this interim report provides an opportunity for the authors to review their study in the light of the questions concerning the nature of psychosis that have now come into focus and towards which they are moving. What is the nature of the genetic predisposition? To what function do these genes relate (Crow, 1997)? What is the relationship between brain change and genetic predisposition? Can the early or precursor symptoms be interpreted as language-related and how do these change with onset of frank psychosis?

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AUTHOR'S RESPONSE

We are sorry that Professors Farmer and Jablensky do not think that this paper warrants publication at the present time. It is perfectly true that there is no clear message from the paper; it describes case identification and very preliminary findings in a study which one of the other commentators is kind enough to describe as unique. The sample is certainly unusual and the fact that these subjects, although not complaining or seeing themselves as unwell, have been able to be recruited in such numbers to a complex and ongoing study, could be considered as worthy of report. The purposes of the presentation and the study as a whole are both briefly described. The purposes of the study as a whole will be discussed in full detail when it is complete.

Power calculations have been conducted and a detailed account of these was given in the proposal for funding. We did not think it appropriate to present them here, as they relate to the numbers of subjects who may be expected to develop psychosis over the period of the study, and this issue cannot yet be addressed.

We entirely agree that a 10-year follow-up would be more useful, and we very much hope that those who fund us will share this view. Funding agencies like to see evidence of the diligence of those they support, and for this reason, as well as because of other pressures such as the Research Assessment Exercise, young investigators are encouraged by older ones to get their findings in print if they can.

Professor Kendler is correct in drawing attention to the difficulty of selecting appropriate controls. 'Screened controls' would probably be a good term, as he suggests, although 'supernormal' seems a little excessive.

Potential controls were only excluded if they had first-degree relatives with functional psychotic illness. Alcohol misuse, minor depression, neurotic illness, or dementia in old age did not lead to exclusion. In fact, disorders such as alcohol misuse and neurotic illness were widely described in the families of both the high-risk subjects and the controls. We would have liked to meet the criterion that the control group should be identical to the index group in all characteristics except the presence of the initial diagnosis, but we did not achieve this. Controls were excluded if they said that they had relatives with bipolar affective disorder, and high-risk cases were included if they had relatives with bipolar affective disorder (in addition to sufficient relatives with schizophrenia). This situation arises because we were not in a position to obtain the case notes of the relatives of the control subjects and we wanted to be as sure as we could be that the controls did not have relatives with schizophrenia.

We are very well aware of the fact that age of onset of schizophrenia varies from family to family. The power calculations of the proposal for the study depend upon the actual ages of onset in the initial families identified. We are aware that some of the subjects are at much greater risk than others. We are developing a complex statistical model based upon detailed knowledge of the health of individual members of all the extended families involved in the study. This will allow us to take this variable risk into account, but for the central purpose of the main study it is probably not important. What we are trying to do is to look at possible precursors of schizophrenia and to see how they evolve towards the onset of psychotic illness. In order to do this, we have to be able to examine in detail adequate numbers of people who are destined to develop schizophrenia, before they have complaints suggestive of the condition or features that would indicate to others that such a diagnosis would be appropriate. For that purpose, all we require is a sufficiently large sample of individuals who, on average, have a risk that is increased enough beyond that of the general population for interpretable numbers to reach set criteria for the diagnosis of schizophrenia during the period of the study, in order that they may be contrasted with those who do not meet such criteria.

We have defined what we mean by 'well' in our protocol and should have noted it in the paper. The criteria are that the subjects do not complain of features suggestive of current psychiatric disorder and that they have no history that would suggest that they have had a psychotic illness, no history that any doctor has ever considered that they may have had features of such an illness, and no history of ever having been prescribed antipsychotic medication.

Professor Jablensky sets out specific questions and makes specific suggestions:

(a) Sometimes the SIS interviews were conducted blind to high-risk/control status and sometimes they were not. Recruitment throughout the country meant that our raters were sometimes involved in case ascertainment/identification, although it had not originally been intended that this would happen.

(b) No individuals met the DSM–IV or ICD criteria for schizotypal disorder at the time of first assessment.

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Meanwhile, a "breakdown of the sample by number of affected family members and degree of relatedness", which will be developed into a quantitative measure of degree of risk, and the neuropsychological testing and magnetic resonance imaging results will be presented in subsequent papers.

The questions raised by Dr Crow are of interest but we cannot address them at this stage of the study: as we have mentioned, we make no assumptions about the nature of the genetic transmission at present. It is the enhanced risk that is important to this study. Our definition for including a case as having developed schizophrenia will be an operational one, based upon Present State Examination criteria as used in many of our Northwick Park studies. Data collected will be sufficient for other definitions to be applied later. It is anticipated that issues of the extent to which the aspects of genetic predisposition relate to the development of illness *per se* (as we operationally are defining it, or by other definitions) or to abnormalities of function on various tests which are not associated with manifest illness will be able to be addressed although we cannot address them at this stage. Many assessments of neuropsychological functions are being undertaken – the test battery takes about one working day to conduct in each case.

It has been gratifying to us that many people who hear about this study express interest in it and make suggestions about assessments that might be made. Often these are helpful but they cannot all be included. The essential features of this study are to acquire the sample (and we have now identified 228 high-risk subjects) and to keep their cooperation during a prolonged study. My young co-authors have been extremely skilled in these areas. They may well not have the pleasure of presenting the full results in due course, as by the time these are available they may have moved on from the study. I am pleased to have the chance of recording now my appreciation of their considerable achievement so far. I hope our critics will not think me impertinent if I ask how they think they would themselves have fared had they tried to acquire (and keep) such a sample?

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