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- 4 Ueda K, Fujiwara H, Miyata J, Hirao K, Saze T, Kawada R, et al. Investigating association of brain volumes with intracranial capacity in schizophrenia. *NeuroImage* 2010; **49**: 2503–8.
- 5 Goghari VM, Rehm K, Carter CS, Macdonald AW. Sulcal thickness as a vulnerability indicator for schizophrenia. *Br J Psychiatry* 2007; **191**: 229–33.
- 6 Panizzon MS, Fennema-Notestine C, Eyer LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 2009; **19**: 2728–35.

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Computing cortical surface measures in schizophrenia

Harms *et al*¹ suggest that volume deficits in frontal regions of interest (ROI) represent a potential endophenotype worth investigating in schizophrenia. Cortical volume is a product of thickness and surface area. Harms *et al*'s finding that volume but not thickness or surface area show some degree of familial sharing merits a critical analysis of the study.

Their conclusion is based on examining manually parcellated frontal subregions that were compared across patients with schizophrenia, siblings and healthy controls, using global measures that exclude the ROI as covariate for volume and surface area. Whole brain average thickness has been included as a covariate for thickness calculations. Although methods similar to this have been reported elsewhere,² this approach seriously affects the conclusions one can draw from the results.

First, the hypothesis behind the study is based on the idea that region-specific grey matter deficits are present in schizophrenia. Let us assume that schizophrenia has a pathological mechanism that selectively affects certain brain regions but does not affect the remaining cortex to similar extent. In this case, using an ROI-subtracted measure of global volume as a covariate will incorrectly inflate the estimates. Total intracranial volume would have been a more appropriate variable.

Second, for thickness measures, the appropriateness of using global thickness as a covariate is questionable. It is difficult to construe the anatomical meaning of regional thickness covaried with total cortical or hemispheric thickness, given the wide variability across the cortex. For analysing an *a priori* hypothesis involving thickness of frontal regions, a global covariate of average thickness appears redundant.

Choosing global values for adjusting regional measures is influenced by various factors, including actual ROI, disease process investigated, developmental age³ and the cortical measure collected.⁴ Familial trends in cortical thickness measurements in schizophrenia shown elsewhere⁵ have not been replicated in this study. In healthy individuals, it has been shown that both total cortical surface area and average cortical thickness are highly heritable but not collinear.⁶ Consequently, volume needs to be treated as an ambiguous measure when exploring the cortical genetic variance.

1 Harms MP, Wang L, Campanella C, Aldridge K, Moffitt AJ, Kuelper J, et al. Structural abnormalities in gyri of the prefrontal cortex in individuals with schizophrenia and their unaffected siblings. *Br J Psychiatry* 2010; **196**: 150–7.

2 Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 2003; **60**: 878–88.

Authors' reply: We fully agree with Dr Palaniyappan that the manner in which regional measures are controlled for possible global changes has important implications for the interpretation of a study. In our study of prefrontal regions in individuals with schizophrenia and their siblings, we used global brain covariates matched in type (volume, surface area or thickness) to the structural measure being analysed.¹ Regardless of the type of measure, the inclusion of an appropriate matched covariate is justified, so that the resulting statistical analysis can address the question of whether any regional differences between groups were in excess of possible global brain changes. We did not use intracranial volume as the covariate in our volume analyses because: (a) it is difficult to estimate accurately from T_1 -weighted magnetic resonance images; and (b) it does not actually control for decreases in overall brain volume that may occur following the completion of skull growth. Rather, we used an estimate of non-prefrontal cortical grey matter volume as the covariate for the volume analyses, obtained by subtracting the sum of our estimates of prefrontal grey matter from a measure of overall cortical grey matter. The use of a 'rest of the brain' covariate of this sort is common,^{2,3} so as to avoid using a covariate which itself includes a substantial contribution from the dependent variable of interest. In our study, non-prefrontal cortical grey matter volume itself differed between groups. Yet, even with the inclusion of this covariate the volumes of the inferior and middle frontal gyri differed between groups, indicating that the differences present in these gyri were in excess of differences that would be predicted based on the grey matter volume differences present in the rest of the brain.

Similarly, inclusion of a global thickness covariate was appropriate and necessary so that we could address whether any regional thickness differences were in excess of global cortical thickness differences between groups.^{1,4} Since the computation of a 'rest of the brain' thickness was not possible (see Method),⁵ the thickness covariate was the mean thickness of the whole cortex. Because prefrontal cortex was included in this overall measure, our thickness analyses should be viewed as conservative (i.e. biased towards finding a null result).

We agree that measures of cortical volume combine two distinct sources of genetic effects (thickness and surface area).⁶ As mentioned in our results, in the absence of covarying for overall brain changes we found statistically significant group differences for thickness and area of the inferior and middle frontal gyri. Further, the pattern of the thickness and area changes across groups was qualitatively similar to the pattern of the volume differences within these two gyri. Thus, we believe that

changes in thickness and area both contributed to the volume differences across groups in these gyri, even if the thickness and area results did not themselves reach statistical significance after rigorously controlling for overall brain changes.

- 1 Goghari VM, Rehm K, Carter CS, MacDonald 3rd AW. Regionally specific cortical thinning and gray matter abnormalities in the healthy relatives of schizophrenia patients. *Cereb Cortex* 2007; **17**: 415–24.
- 2 Barton RA, Harvey PH. Mosaic evolution of brain structure in mammals. *Nature* 2000; **405**: 1055–8.
- 3 Rilling JK, Seligman RA. A quantitative morphometric comparative analysis of the primate temporal lobe. *J Hum Evol* 2002; **42**: 505–33.
- 4 Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 2003; **60**: 878–88.
- 5 Harms MP, Wang L, Campanella C, Aldridge K, Moffitt AJ, Kuelper J, et al. Structural abnormalities in gyri of the prefrontal cortex in individuals with schizophrenia and their unaffected siblings. *Br J Psychiatry* 2010; **196**: 150–7.
- 6 Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 2009; **19**: 2728–35.

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Risk factors for suicide

The article by Manoranjitham *et al*¹ provides a great deal of insight into the risk factors for suicide in rural India. The study was conducted with the best possible methodology, using the surveillance system method carried out by a community health worker who is part of the same community. The authors employed verbal autopsy, pair matched the suicide case and control groups, used more than one informant to obtain the information, used the Structured Clinical Interview for DSM–III–R (SCID) to establish the psychiatric diagnosis and their study was adequately powered to investigate the desired outcome. The authors were very humble in acknowledging the limitations of the study which cannot be avoided in any set up. However, some of the issues need to be addressed before accepting the fact that it is not the psychiatric diagnosis but ongoing stress and chronic pain that are the most important predictors of suicide.

The results showed that 37% of the suicide group had a psychiatric diagnosis. However, the authors did not mention whether it was the current diagnosis or lifetime diagnosis. It is possible that the surveillance system which has been operational for so many years is also helpful in picking up psychiatric diagnosis early and arranging treatment, leading to lower rates of current psychiatric diagnosis in the suicide cases. The authors also did not provide any information about the relatives, as the information obtained about the person who completed suicide was collected by the health team and their accuracy can vary depending on the relationship, closeness and duration of stay of the informant with the person who died.

Further, although there was significant difference in some of the variables (living alone, break in steady relationship) between the two groups in the bivariate analysis, data presented in Table 3 suggest that these variables have not been included in the multivariate analysis. The arbitrary definition of ‘ongoing stress’ and ‘chronic pain’ is also not very clear. Studies in the past have reported that many physical illnesses are also risk factors for suicide,² but the authors did not provide any information with respect to this, nor did they use the same data in the analysis. Another important issue which needs to be considered is that the authors subsumed pain symptoms of 1 year duration under the risk factor of ‘chronic pain’. It is well known that individuals with depression in primary care manifest their depression with somatic symptoms, especially painful symptoms.^{3,4} This underlying depression was not picked up by SCID, resulting in such low prevalence of affective disorders in both groups. Previous studies⁵ have used life events as a single variable while trying to find the association of risk factors with suicide. Here, the authors have possibly analysed them as individual risk factors and therefore acute stress has not emerged as an important predictor. Similarly, the issue of comorbidity (presence of more than one psychiatric diagnosis or presence of psychiatric and physical illness together) has not been addressed.

- 1 Manoranjitham SD, Rajkumar AP, Thangadurai P, Prasad J, Jayakaran R, Jacob KS. Risk factors for suicide in rural south India. *Br J Psychiatry* 2010; **196**: 26–30.
- 2 Quan H, Arboleda-Flórez J, Fick GH, Stuart HL, Love EJ. Association between physical illness and suicide among the elderly. *Soc Psychiatry Psychiatr Epidemiol* 2002; **37**: 190–7.
- 3 Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain co morbidity: a literature review. *Arch Intern Med* 2003; **163**: 2433–45.
- 4 Caballero L, Aragonès E, García-Campayo J, Rodríguez-Artalejo F, Ayuso-Mateos JL, Polavieja P. Prevalence, characteristics, and attribution of somatic symptoms in Spanish patients with major depressive disorder seeking primary health care. *Psychosomatics* 2008; **49**: 520–9.
- 5 Vijayakumar L, Rajkumar S. Are risk factors for suicide universal? A case-control study in India. *Acta Psychiatr Scand* 1999; **99**: 407–11.

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Authors’ reply: We would like to clarify the points raised by Holikatti & Grover. We presented the current psychiatric diagnoses within the past month as assessed by the interview. The therapeutic effects of the surveillance system and the variance due to interviewing first-degree relatives are in common to both cases and controls, and hence we believe that these factors did not affect the results of our study. We could not include the variables ‘living alone’ and ‘break in steady relationship’, which were significant in the bivariate analyses, in the multivariate procedure as these variables were absent among the controls and hence it is not possible to calculate odds ratios and to include them in logistic regression.

Our study had *a priori* definitions for ‘chronic pain’ and ‘ongoing stress’ described in the paper, which also provides the details of psychiatric diagnoses. Holikatti & Grover suggest that chronic pain symptoms can be attributed to underlying depressive disorders. However, the contemporary classificatory systems in psychiatry have not approved the concept of ‘masked depression’ and they have not included pain symptoms in their diagnostic criteria for depression. Pain is a subjective experience, which has a psychological component. Psychiatrists tend to attribute human