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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 age[3] and the cortical measure collected.[4] Familial trends in cortical thickness measurements in schizophrenia shown elsewhere[5] 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 be treated as an ambiguous measure when exploring the cortical genetic variance.

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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.

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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