Computing cortical surface measures in schizophrenia

Harms et al\textsuperscript{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\textsuperscript{1}’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,\textsuperscript{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 covered with total cortical or hemispheric thickness, given the wide variability across the cortex. For analysing an \textit{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\textsuperscript{3} and the cortical measure collected.\textsuperscript{4} Familial trends in cortical thickness measurements in schizophrenia shown elsewhere\textsuperscript{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.\textsuperscript{6} Consequently, volume needs be treated as an ambiguous measure when exploring the cortical genetic variance.

\textit{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.\textsuperscript{7} 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\textsubscript{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 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,\textsuperscript{8,9} 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.\textsuperscript{1,4} Since the computation of a ‘rest of the brain’ thickness was not possible (see Method),\textsuperscript{5} the thickness covariate was the mean thickness of the whole cortex. Because prefrontal cortical thickness 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).\textsuperscript{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


Lena Palaniyappan, Division of Psychiatry, Newcastle University, Newcastle upon Tyne NE1 4LP, UK. Email: Lena.Palaniyappan@nottingham.ac.uk
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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.


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.


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
distress to disease and medicalise all depression.\textsuperscript{1} Our data argue that psychosocial stress and social isolation, rather than psychiatric morbidity, are risk factors for suicide in rural south India.\textsuperscript{2}


Fetal androgens and autism

In their comprehensive meta-analysis of the literature on prenatal risk factors for autism, Gardener et al\textsuperscript{1} examined and summarised more than 50 such antecedents. Under prenatal factors associated with an increased risk of later autism in the child, Gardener et al listed advanced parental age, maternal use of medication, maternal birth place abroad, bleeding, gestational diabetes, and sibling rank. The authors were rightly cautious to draw strong conclusions from these meta-analytic findings, as the evidence for a role of any of these prenatal risk factors in the aetiology of autism is not sufficient, although on the whole this set of findings suggests that complications during pregnancy in general might contribute to an increased risk for autism.

Fetal sex-hormone profiles might be added to the above list of identified prenatal antecedents of autism. The sex difference in the lifetime prevalence of autism-spectrum disorders, wherein boys and men exceed girls and women by a large margin, is well-known and has partly been attributed to possible influences of early (i.e. organisational) sex-hormone action which contributes to gender differences in neurocircuitry and neuroanatomy.\textsuperscript{2}

A role of fetal androgens for autism is suggested by recent research on the second-to-fourth digit ratio (2D:4D), a currently widely studied biomarker.\textsuperscript{3} Many researchers believe that 2D:4D might provide a useful retrospective window into the prenatal sex-hormonal milieu during critical neurodevelopmental phases of fetal life (i.e. the second trimester) and might be a biomarker for prenatal testosterone exposure and sensitivity specifically.\textsuperscript{4} Human 2D:4D is sexually differentiated (lower in the male than in the female gender), and gender and individual differences in 2D:4D emerge prenatally and are preserved during the growth phases of postnatal life.\textsuperscript{4} Among other supportive evidence for the validity of this anatomical marker, lower (i.e. more male-typical) 2D:4D has been found to be associated with higher sensitivity to testosterone (as effectuated through functional polymorphisms in the androgen receptor gene) and with a higher testosterone-to-oestradiol ratio, as assayed from the amniotic fluid.\textsuperscript{4}

Consistent with the above reasoning and background, Manning et al\textsuperscript{5} found that children with autism or high-functioning autism (Asperger syndrome), as well as their unaffected first-degree relatives (i.e. siblings, mothers, and fathers), have conspicuously lower (i.e. hypermasculinised) 2D:4D than healthy general population controls. Since then, the gist of this interesting evidence has been independently replicated by some ten further studies (reviewed elsewhere).\textsuperscript{6} Inter alia, the evidence base now includes successful replications across ethnicity (East Asians and Caucasians) and similar findings of a low (masculinised) 2D:4D among children with various subtypes of attention-deficit/hyperactivity disorder,\textsuperscript{7} all in all indicating that the effect is robust.

Of note, the initial study in this line of research (Manning et al),\textsuperscript{5} as well as subsequent related research reports, are found in PubMed when using the search terms Gardener et al\textsuperscript{8} used. So it may well be that Gardener et al did not include this literature in their meta-analysis on the grounds that they categorised it under ‘medical hypotheses’, one of their listed non-eligibility criteria. However, it is interesting that Gardener et al, in their discussion, also noted the following general limitations: (a) only few prenatal risk factors for autism have been examined in multiple studies; (b) generally, fewer than six studies for any of these factors could be included; and (c) when risk factors were examined across multiple studies, the evidence was, for the most part, inconsistent. A formal meta-analysis of the emerging literature on 2D:4D and autism is beyond the present scope, but it is evident from one review\textsuperscript{9} that the limitations noted by Gardener et al do not apply for this literature. All in all, the evidence points to a possible role of masculinised sex-hormone profiles, already arising in utero, as a further prenatal risk factor in the pathways leading to the neurodevelopmental disorder autism.


Authors’ reply: We note with interest the comments raised by Voracek. He suggests that sex-hormone exposures in utero may play a role in the aetiology of autism, and that the second-to-fourth digit (2D:4D) ratio may be a marker for fetal androgen exposure. This seems to be a plausible hypothesis, and we believe that the potential association between the 2D:4D ratio and autism risk deserves further exploration. More importantly, studies on the direct effect of fetal sex-hormone profiles on autism risk are warranted.

However, the 2D:4D ratio was not included in our meta-analysis of potential prenatal risk factors for autism because it was not considered to be a prenatal exposure variable itself, although it likely represents the effects of prenatal exposures, in particular sex steroid hormones. There are many characteristics that become evident after birth that are likely due to prenatal exposures, but in our meta-analysis of risk factors for autism we focused only on those variables that could be assessed during the prenatal period (e.g. maternal medication use, parental age). Voracek speculates ‘that Gardener et al did not include this
literature [2D:4D ratio] in their meta-analysis on the grounds that they categorised it under "medical hypotheses". This is not the case. Rather, we did not include the 2D:4D ratio because our article was limited to conditions assessed during the prenatal period, not their sequelae.

Corrections

Adverse reactions to antidepressants. BJP, 195, 202–210. The final paragraph of the appendix (p. 210) should read: This checklist was developed by Dr K. J. Aitchison, as part of the GENDEP research project (http://gendep.iop.kcl.ac.uk/results.php). Dr Aitchison created this on the basis of her own prior research work and that of other investigators, receiving comments from colleagues including Professor A. E. Farmer.

Early intervention in panic: pragmatic randomised controlled trial. BIP, 196, 326–331. In Fig. 1 (p. 328) PDSS–SR is in one instance spelled incorrectly as PDSS–SRY.

Correspondence

Hannah Gardener, University of Miami, Miller School of Medicine, Department of Neurology, Miami, Florida, USA. Email: hgardener@med.miami.edu; Stephen L. Buka, Brown University, Department of Community Health, Providence, Rhode Island, USA.

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Music Swims Back to Me

Anne Sexton

Wait Mister. Which way is home?
They turned the light out
and the dark is moving in the corner.
There are no sign posts in this room,
four ladies, over eighty,
in diapers every one of them.
La la la, Oh music swims back to me
and I can feel the tune they played
the night they left me
in this private institution on a hill.
Imagine it. A radio playing
and everyone here was crazy.
I liked it and danced in a circle.
Music pours over the sense
and in a funny way
music sees more than I.
I mean it remembers better;
remembers the first night here.
It was the strangled cold of November;
even the stars were strapped in the sky
and that moon too bright
forking through the bars to stick me
with a singing in the head.
I have forgotten all the rest.
They lock me in this chair at eight a.m.
and there are no signs to tell the way,
just the radio beating to itself
and the song that remembers
more than I. Oh, la la la,
this music swims back to me.
The night I came I danced a circle
and was not afraid.
Mister?


Anne Sexton (1928–1974) was an American poet of the Confessional school. Throughout her life she had severe depression and was hospitalised on several occasions. She began writing poetry while recovering after a suicide attempt in 1956, as suggested by her therapist, Dr Martin Orne, and almost instantly won great acclaim – her first book, To Bedlam and Part Way Back (1960), was critically praised and nominated for a National Book Award. Sexton’s poetry explored childhood guilt, mental illness, motherhood and female sexuality in a candid and unflinching way (she thought that poetry ‘should almost hurt’), and is characterised by musical rhythms and striking imagery. She died by asphyxiating herself.

Researchers: Kasia Krawczyk. Other poems by Anne Sexton have featured in the November 2008 and October 2009 issues of the Journal.
Authors' reply:
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References
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