Mentalising impairment as a trait marker of schizophrenia?

One of the most controversial issues in ‘theory of mind’ research in schizophrenia in recent years has been whether theory of mind impairment may be seen as a trait marker or rather linked to particular symptoms. Sprong et al1 conclude that evidence to date seems to favour the notion that mentalising impairment represents a possible trait marker. We believe that their meta-analysis is an excellent piece of scientific work but that this conclusion should remain tentative.

First, the existing evidence on theory of mind abilities in remitted patients is limited and difficult to interpret because of methodological shortcomings, such as non-explicit criteria for remission and poor control of cognitive abilities in the experimental design. A recent study by our group revealed that as a whole, stable patients did not show theory of mind impairment compared with carefully matched non-psychiatric controls. When standard consensus criteria for remission were applied to the sample, half failed to meet criteria for remission and showed a significantly worse theory of mind performance than remitted patients and controls. Specific theory of mind deficits in this group were associated with delusions. Thus, specific theory of mind impairment could go hand-in-hand with the presence of symptoms.2

Second, findings of theory of mind impairment in schizophrenia high-risk groups seem to support the assumption that theory of mind deficits represent a trait marker of the disorder. However, since these studies are mostly correlational, it is possible that the continuity of theory of mind deficits among ‘at risk’ groups may in fact derive from an intrinsic relationship between a psychotic symptoms continuum and theory of mind impairment. A review of the literature of theory of mind and schizotypal personality traits reveals that studies finding a positive significant relationship do so mainly with respect to schizotypal positive traits such as the cognitive-perceptual and unusual experiences dimensions of the schizotypy instruments.3 Regarding investigations of first-degree relatives, evidence is controversial,1 with findings of impaired performance on the more common types of theory of mind tasks but not on the ‘eyes’ test. However, it should be noted from these studies that those controlling for subclinical symptoms or schizotypal traits conclude that the association may be linked exclusively to the presence of subclinical positive symptoms.4,5

In our opinion, the existing evidence in theory of mind research is still limited but the possibility of a state-like association should not be ruled out. The most methodologically sound means to explore this would be to carry out longitudinal studies comparing theory of mind abilities in different phases of the illness, defined by explicit criteria. Future studies also need to differentiate between the affective and cognitive aspects of theory of mind, since it is possible that these show a different pattern of relationship with symptom clusters or schizophrenia profiles. Furthermore, it is possible that future research reveals that state–trait interactions may be occurring.

Authors’ reply: Pousa et al comment that our conclusion that theory of mind impairment represents a possible trait marker for schizophrenia should remain tentative for two reasons. Regarding their first argument, data on remitted patients are indeed limited and have methodological shortcomings. Only five studies in remitted patients were available, and the number of remitted patients in each of these studies was small. We also remarked that the criteria for remission used may have varied across studies, and that other factors may have influenced the results. Thus, we agree that the conclusion that theory of mind impairment represents a trait marker for schizophrenia should be tentative. In fact, we did describe it as a ‘possible’ trait marker. It is important to note that meta-analyses are about effect sizes rather than significance levels. By synthesising data of multiple studies there is more statistical power to detect smaller group differences. Thus, although in three out of five studies the theory of mind impairment in remitted patients was not statistically significant, when the studies were combined, the overall effect was significant (mean $d = -0.692$, $P < 0.01$). So when Pousa et al do not find theory of mind impairment in stable remitted patients, we are not only interested in the $P$-levels, but also in the effect size. We also agree with the second point that there is evidence of an association between psychotic symptoms and theory of mind impairment, but do not see why this would argue against our conclusion. Frith1 already proposed associations between specific schizophrenia symptoms (e.g. paranoid delusions) and mentalising impairment, and in their upcoming paper Pousa et al apparently also find significant associations between theory of mind impairment and psychotic symptoms. Perhaps we should have stated that theory of mind impairment is a possible trait marker for psychosis rather than schizophrenia. We believe that theory of mind probably does not represent an ‘all or nothing’ skill, and that schizophrenia should perhaps be studied using a dimensional instead of a categorical approach.

Month of birth in relation to suicide

Salib & Cortina-Borja\(^1\) find that persons born during the spring–summer season of April, May and June were significantly more likely to die by suicide than those born during other months: they find a peak for May and a trough for October.

However, they misreport our earlier results in this field when they state in the introduction that ‘Chotai et al’\(^2\) reported that people born in winter in Sweden were significantly more likely than those with other birth seasons to have used hanging as a suicide method. They further misreport earlier findings of ours when they state in the discussion that: ‘...winter variations in serotonin reported by Chotai & Åsberg\(^3\) are inconsistent with the findings of this study, essentially the opposite of the Swedish findings.’\(^4\)

Our earlier findings are in fact similar to and consistent with the results of Salib & Cortina-Borja. In Chotai et al\(^5\) we clearly show that those who preferred hanging rather than poisoning or petrol gases were significantly more likely to be born during February–April. In Chotai & Åsberg\(^6\) we demonstrate that those born during February–April had significantly lower levels of 5-hydroxyindoleacetic acid (5-HIAA).

We have also published cosine analyses of our data,\(^4\) in which we found that the minimum of the month-of-birth curve for 5-HIAA was obtained for the birth month April (\(t\)-min 3.4, Table I, where the interval 3–4 depicts April) and the maximum was obtained for October (\(t\)-max 9.4). We also reported that the maximum of the month-of-birth curve for preferring hanging was for March–April and the minimum was for September–October.

Low serotonin turnover has been implicated as a risk factor for suicidal behaviour, particularly with violent or lethal methods of suicide, as discussed by Salib & Cortina-Borja.\(^1\) Thus, our findings are in line with those of Salib & Cortina-Borja regarding suicidality, since we obtained a peak for the birth month April comparable to their peak for May, and found a trough for 5-HIAA for the birth month April.

In another epidemiological study,\(^5\) we report that season of birth association with suicide methods is found in those without a history of psychiatric contacts, but not in those with such a history. We have argued that season of birth associations for suicide methods are likely to be mediated to a large extent by a suicidality trait independently of specific major psychiatric disorders, with serotonin as the likely underlying neurotransmitter.

In our studies, the season of birth variation was found for hanging as the suicide method, but not for other methods often denoted as violent, for example firearms or drowning. Hanging is a more universal method of suicide, and gender differences in the proportion of hanging are much lower than for other methods. In this light, it would be of interest to analyse the data of Salib & Cortina-Borja, specifically with regard to whether there is a month of birth variation in suicide by hanging.

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Authors’ reply: Jongbloet provides an alternative explanation of our findings about the effect of month of birth on suicide that is based on the oocyte origins hypothesis as opposed to the maternal–foetal origin hypothesis. The oocyte hypothesis (also referred to in literature as ‘conception hypothesis’) may have significant implications in psychiatry. The intricate interplay between non-optimal oocyte maturation and genes results in a complex pathogenesis of the resultant foetuses or individuals. This occurs in well-timed menstrual cycles, but more so in instances of distorted hormonal tuning, not only in deprived socio-economic conditions but also at the extremes of maternal reproductive life, among endocrinologically unbalanced mothers, after very short pregnancy intervals during the seasonal transitions of the ‘ovulatory’ seasons, etc. A similar broad spectrum of male-biased developmental anomalies – low birth weight and length, small stature at school age or adulthood, morbidity, and mortality – is present in all these circumstances.2

To illustrate the oocyte or conception hypothesis in practical terms: mothers with low socio-economic status are known to suffer from more menstrual disorders,1 low standards of nutrition and abnormal body mass index. They also are more likely to be smokers or to misuse drugs4 and to employ less safe methods of contraception resulting in unplanned and unwanted pregnancies, particularly at the extremes of maternal reproductive age and during the postpartum restoration of the ovulatory pattern (i.e. after very short inter-pregnancy intervals). They are likely to have non-optimal oocyte maturation, thus rendering the offspring vulnerable to low birth weight and certain psychiatric disorders. However, we are not clear as to how this hypothesis actually differs from the maternal–foetal origin hypothesis used to explain our findings.1

The geographical latitude effect in incidence rates of suicide in England, Wales and elsewhere is assumed by Jongbloet to be a consequence of the stronger seasonal ovulatory pattern the further away from the equator, just as in animals, and, in turn, stronger transitional stages between the ovulatory seasons and, thus, more poor-quality oocytes. However, the only way to accept or reject this concept is by demonstrating the same increase of suicide incidence rate – and of other disease entities or behaviour of complex origin.

We are also grateful to Chotai for his comments. Although we did not look at hanging in relation to month of birth in our study, we did in fact examine the relationship between month of birth and violent suicide (including hanging) as opposed to non-violent suicide, but found no significant association. However, a previous study,6 in an attempt to replicate the findings of Chotai et al,1 showed that those born during the season January–April were more likely to prefer hanging than poisoning: data from North Cheshire (n=502) appeared to suggest that suicide by hanging was significantly more frequent in those born in the summer months compared with those who used other methods such as poisoning by solids or gases. The findings were not in keeping with reports by Chotai et al. However, methodological limitations of the North Cheshire study, including a relatively small sample size, have significantly limited its inferential value. Studies with sufficient power to detect the association between month of birth and risk of hanging are required to show whether one truly exists.

Seasonality of birth studies in relation to suicide may enhance our understanding of some biological aspects in the aetiology of suicide such as the oocyte origins hypothesis proposed by Jongbloet.

are always moderate’ due to the differences in levels of emotional and physical stress. The subgroup of patients with low emotional stress before treatment might have experienced deterioration in outcome measures after reattribution because of the consequent opening up and admittance of their problems. Although this is a clinically valuable change process, by reporting the overall treatment effects, this profit might be concealed.

In short, we think that some of the questions surrounding the treatment of patients with medically unexplained symptoms has been clarified by this high-quality trial, but there remain many others.


Authors’ reply: Thank you for the interest in our paper; we would like to clarify some points.

First, we conducted a 6-hour training intervention in reattribution because, on the basis of a series of studies of training in primary care, this is the length of training that most general practitioners (GPs) are prepared to attend in the UK and also in many other healthcare systems in the world. The 6-hour training produced the changes in communication that have been reported with 20-hour training in reattribution. Moreover, more extensive training in reattribution for more than 20 hours by GPs does not necessarily improve patient outcome. We used nurses and a psychologist because in practice these trainers would carry out this training in the workplace if the intervention was ever implemented in routine practice in the UK. We received systematic feedback from the GPs about training via feedback forms at the time of practice and GP level, age and gender of patient using generalised linear latent and mixed models. The data suggest that patients perceived GPs trained in reattribution to be no less empathic than GPs delivering treatment as usual. Therefore, there may be other features of the reattribution intervention delivered by GPs in this way that may explain its lack of effectiveness. We have explored this in a qualitative interview study with patients in the trial that will be submitted for publication. Finally, we agree that certain subgroups of patients with medically unexplained symptoms may benefit from reattribution. However, our trial was not powered to examine this issue.

Second, the paper describing the reattribution model, which was written by one of our team (L.G.) and subsequent descriptions of reattribution written by members of our team, have always promoted a model in which doctors provide the ‘making the link’ explanation although they should do this through negotiation with the patient. In our trial, the intervention group of GPs gave the ‘making the link’ explanation in a negotiatory manner much more frequently than the treatment as usual group. We agree that reattribution may be more effective on patient outcome if patients made the link themselves between their physical symptoms and a psychosocial cause. However, GPs may need to spend much longer with patients to achieve this.

Third, we agree that an instrumental task-oriented consultation such as reattribution might be perceived as less empathic by patients with medically unexplained symptoms than treatment as usual. However, in our trial the data from the patient satisfaction questionnaire suggests that compared with treatment as usual, after reattribution training twice as many patients were very satisfied with how well the GP understood the nature of their problems and their worries (reattribution training (n=57) v. treatment as usual (n=68); nature of the problem 34 (60%) v. 23 (34%); worry 34 (60%) v. 20 (29%); P<0.10 for both items, intention-to-treat analysis allowing for missing data, clustering at practice and GP level, age and gender of patient using generalised linear latent and mixed models). The data suggest that patients perceived GPs trained in reattribution to be no less empathic than GPs delivering treatment as usual. Therefore, there may be other features of the reattribution intervention delivered by GPs in this way that may explain its lack of effectiveness. We have explored this in a qualitative interview study with patients in the trial that will be submitted for publication. Finally, we agree that certain subgroups of patients with medically unexplained symptoms may benefit from reattribution. However, our trial was not powered to examine this issue.
Reattribution for medically unexplained symptoms
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Access the most recent version at DOI: 10.1192/bjp.192.4.314a