obstruction, and severe weight gain, confidence that antipsychotics with fewer risks would not be effective is necessary before a trial of clozapine should be recommended. In clinical practice, it would be valuable to know whether treatment with a long-acting injectable antipsychotic should be offered to patients with first-episode schizophrenia before recommending clozapine, given the evidence that poor treatment response might result from non-adherence.[8] Given recent evidence that second-generation, long-acting injectable antipsychotics might substantially reduce the proportion who relapse in this patient group,[9] and might also be associated with reduced mortality,[10] it would be of particular interest to know how many patients benefit from these medications before being offered a trial of clozapine.

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Shared genetic factors, fetal programming, and the transmission of depression

Interest in prenatal exposures shaping later life has increased considerably in the past two decades. Set forth by Barker in the 1980s, the fetal programing hypothesis posits that in-utero exposures affect the early development of organs and tissues in ways that persist into adulthood.[1] The study of fetal programming has extended to neurodevelopment, with a growing amount of scientific literature of human and animal studies suggesting that prenatal maternal depression places offspring at increased risk for mental disorders.[2,3] Although the need to account for genetic and shared environmental confounding has been previously argued,[4] the field has not consistently obliged. The study by Laurie Hannigan and colleagues[5] will most certainly change that.

Hannigan and colleagues leverage an impressive cohort of twin (178 monozygotic and 104 dizygotic), sibling, and singleton mothers (n=21 913), and their offspring (n=35 229) to examine transmission mechanisms of familial depression, including shared genetic factors and exposure to prenatal and postnatal maternal depression. Using a children-of-twins study design and structural equation modelling, the authors test mechanisms of transmission accounting for associations between self-reported maternal prenatal depression (weeks 17 and 30) and offspring internalising and externalising problems (maternal report at 18, 36, and 60 months, when maternal depression was also assessed). Shared genetic factors accounted for the largest portion of offspring internalising (41%, 95% CI 36–46) and externalising (37%, 30–44) problems. Postnatal exposure to maternal depression had a smaller, but significant role for internalising disorders. Surprisingly, no support was found for fetal programming effects for either internalising or externalising disorders. This study reinforces the importance of shared genetic influences, providing a cautionary note with respect to the recent enthusiasm


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that the fetal programming hypothesis has garnered. In addition to its sample size, the study findings based on prospectively collected data allow the authors to make a compelling argument in support of genetic transmission. Also worth commending is the authors' consideration of the clinical implications of their work: even if intergenerational transmission is largely genetic, there are still substantial benefits to the mother and offspring in reducing exposure to maternal postnatal depression.

Despite the study's significant strengths, methodological limitations should be considered in the interpretation of the results. The field could also benefit from contextualising study findings within a broader theoretical understanding of the original fetal programming hypothesis.

Whereas the study sample is no doubt large, the levels of depressive symptoms are very low. Many mothers—quantification of data is difficult to ascertain but data were noted to be "excessively skewed"[5] and transformed mean was 0—report an absence of symptoms, and there is significant attrition of the most depressed mothers. This finding raises two concerns. First, low scores in mother and child will inherently correlate to each other which, given the assumptions underlying the study design, as well as potential differential selection or attrition of monozygotic versus dizygotic twins, risks overestimating the impact of genetic factors. Second, fetal programming might arise primarily in the context of more severe depression: the putative biochemical or hormonal in-utero exposures proposed to underlie fetal programming might occur only in mothers with considerable distress.

It also is worthwhile to review how fetal programming is being conceptualised and tested. As proposed by Barker,[1] in response to prenatal exposures, the fetus (and placenta) makes iterative adaptations, preparing the fetus for the postnatal environment and fostering survival and procreation. Thus, broad assessments of psychopathology starting as late as at 18 months might not capture subtle, evolving developmental divergences that might only loosely correspond to internalising or externalising problems. For example, 5-week-old infants of prenatally depressed mothers show alterations in brain structure and function that suggest accelerated maturation of limbic substrates.[6] In this example, the hypothesised adaptation could serve to prepare the child to monitor effectively a less responsive postnatal environment but would not necessarily translate to frank behavioural disturbances at 18 months.[7] Adaptations are probably not static but instead interact with both genes and subsequent environmental exposures, requiring longitudinal, in-depth evaluation of risk trajectories. Finally, Hannigan and colleagues did not examine offspring sex differences. Extensive literature documents sex differences in risk for childhood disorders, and more specifically, in fetal programming.[8–10] It is thus possible that by examining male and female offspring together, some effects went undetected.[11,12]

In summary, Hannigan and colleagues' work marks an important moment in developmental neuroscience research, reinforcing the need for rigour in accounting for genetic transmission when investigating fetal programming hypotheses. However, a coda is necessary: discarding the possibility of fetal programming effects in future work is not yet warranted. Polarising opinions (eg, nature *vs* nurture) are unlikely to do justice to the complexity of human development and historically have not served our field well.

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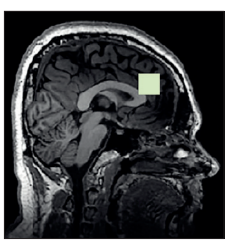
Glutamate–dopamine matters in psychosis



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In *The Lancet Psychiatry*, Sameer Jauhar and colleagues[1] present a formal investigation into the association between cortical glutamate and striatal presynaptic dopamine function in first-episode psychosis. This study was motivated by the notion that increased striatal dopamine function, as well as perturbed cortical glutamate function, possibly mediated via *N*-methyl-D-aspartate (NMDA) receptor hypofunction, have long been thought to be two principal neurochemical abnormalities associated with psychotic symptoms.

Using a commendable multimodal approach in a cohort (first-episode psychosis n=28, controls n=20), Jauhar and colleagues[1] compared assessments of striatal dopamine synthesis capacity and anterior cingulate cortex glutamate in patients with first-episode psychosis for the first time. Crucially, they observed that increased striatal dopamine synthesis capacity correlated with lower anterior cingulate cortex glutamate concentrations in patients with first-episode psychosis (β $-1{\cdot}71\times10^{-4}$, SE $7{\cdot}63\times10^{-5}$, $r=-0{\cdot}40$, $p=0{\cdot}03$). This correlation was absent in controls ($r=0{\cdot}20$, $p=0{\cdot}39$; group difference in correlation strength $Z=-2{\cdot}01$, $p=0{\cdot}04$). The authors hypothesise, while acknowledging methodological limitations, that the negative association between striatal dopamine synthesis capacity and anterior cingulate cortex glutamate concentration might suggest a deficit in an indirect pathway, by which hypofunction of NMDA receptors preferentially expressed on inhibitory γ-aminobutyric acid (GABA) interneurons could drive increased striatal dopamine synthesis capacity. This interpretation is consistent with the observations that cortical GABAergic interneurons control striatal dopamine release[2] and that hypofunction of NMDA receptors on GABAergic interneurons leads to increased amphetamine-induced striatal dopamine release.[3] Thus, in this respect, the work of Jauhar and colleagues[1] might have provided new mechanistic insights into the origin of psychotic symptoms.

One intriguing observation was the absence of a group difference in the striatal influx constant (K_i^{cer}, a well-established measure of dopamine synthesis capacity) between patients with first-episode psychosis (K_i^{cer}approximately 0·0128) and controls, which had numerically even greater dopamine synthesis capacity (K_i^{cer}approximately 0·013). Although this is in contrast to previous work, striatal dopamine synthesis capacity did correlate with positive symptom severity in first-episode psychosis. The authors suggested that the absence of a group difference in striatal dopamine synthesis capacity might be explained by the presence of treatment non-responders, who might have normative striatal dopamine synthesis capacity.[4]

In our view, this scenario would have crucial implications for the interpretation of the negative association between striatal dopamine synthesis capacity and glutamate concentration in the anterior cingulate cortex. The presence of treatment non-responders—suggested by lower striatal dopamine synthesis capacity in first-episode psychosis—introduces the possibility that the observed association might not bespeak a neurochemical mechanism. Rather, the association might be interpreted as a recapitulation of previous findings in two discrete patient subgroups: people who respond to treatment with antipsychotics, characterised by increased striatal dopamine synthesis capacity and unchanged anterior cingulate cortex glutamate concentration, and people who did not respond to antipsychotic treatment, who might have unaffected striatal dopamine synthesis capacity and increased anterior cingulate cortex glutamate concentration.[4]

One observation that would argue in favour of a mechanistic explanation (eg, low anterior cingulate cortex glutamate concentration driving increased striatal dopamine synthesis capacity) is the negative association between anterior cingulate cortex glutamate concentration and positive symptom severity. However,