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•Commentary•

Bridging the gap between research into biological and psychosocial models of psychosis

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Summary: Paul Bebbington's recent Special Article provides an excellent synthesis of recent advances in psychosocial research on psychosis. However, we doubt that a model based solely on social epidemiology and cognitive theory can totally describe psychosis, and to be fair, Bebbington does not suggest that it does. A complete model must also incorporate what we have learned from non-social epidemiology, neuroscience, and genetics. Evidence indicates that both the social risk factors that interest Bebbington and biological risk factors, such as abuse of stimulants and cannabis, can provoke psychotic symptoms by dysregulating striatal dopamine. The role of neurodevelopmental deviance also needs to be considered in the etiology of schizophrenia-like psychosis. Moreover, the striking advances in our understanding of the genetic architecture of psychosis open an exciting door into studies examining gene-environment correlation and gene-environment interaction. In short, Bebbington demonstrates the value of cognitive and social researchers talking to each other, but the occasional chat with the more biologically inclined could produce a more comprehensive model.

Keywords: psychosis; schizophrenia; genetics; neurodevelopment; dopamine; social factors.

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1. Bebbington's thesis

Paul Bebbington's recent Special Article[1] provides a thought-provoking review with many valuable suggestions for future studies aimed at understanding the psychological processes through which social risk factors contribute to the onset and persistence of psychotic disorders. He emphasizes the role of mood, sleep, and cognitive processes as mediating variables between psychosocial stress and psychotic symptoms. This fits well with a dimensional model of psychotic disorders that accepts that non-psychotic symptoms such as anxiety and depression have no diagnostic specificity, but emphasizes their role in precipitating the onset or exacerbating the course of a psychotic illness.[2] This acknowledgement is important as it implies that treating such symptoms may have beneficial effects in the treatment of psychosis. Indeed, this view directly contrasts with the traditional neo-Kraepelinian disease model of schizophrenia (still alive and kicking in North America) which considers such non-psychotic symptoms epiphenomena of an as yet to be discovered schizophrenic process, that will improve only when the underlying 'disease process' is satisfactorily treated. Sadly, this latter view often condemns psychotic patients to continuing psychotic and non-psychotic symptoms while their treating psychiatrists chop and change antipsychotics ineffectively but fail to address the anxiety or depression which drives the psychosis.

Bebbington rejoices in the idea of an extended psychosis phenotype including not only those affected

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by persistent and impairing psychotic disorders but also individuals with subclinical and transient psychotic symptoms who do not present to the psychiatric services. This view, popularized by Van Os and colleagues,[3] has had a hugely beneficial influence on research. Findings from population studies indicate that transition to a full psychotic syndrome and likelihood of need for care are determined not only by the severity and persistence of psychotic symptoms but also by developmental and psychological characteristics, such as premorbid functioning, affective dysregulation, cognitive functioning, and coping styles.[4] Within this framework, Bebbington describes his research strategy of multiple triangulation, in which the same hypothesis is tested across different clinical and non-clinical populations using both discrete and continuous outcomes. He makes a convincing case that this strategy can not only overcome the difficulties of epidemiological investigation of relatively rare adult-onset disorders such as schizophrenia, but it can also identify developmental, cognitive, and social variables predicting transition to psychosis in people showing the extended psychotic phenotype. We agree wholeheartedly that such an approach has potential to develop psychological interventions aimed at improving symptoms and functioning.

2. What is missing?

However, while not diminishing the achievements of social psychiatrists and cognitive theorists, we note that Paul Bebbington has not attempted to place these lines of work in the context of recent advances in non-social epidemiology, or in the context of biological understandings of psychosis. It is interesting that the word 'brain' does not appear anywhere in this otherwise impressive review! It is our contention that a comprehensive view of psychosis demands that recent knowledge derived from genetics and neuroscience be integrated with the findings from psychological and social research.

3. Dramatic developments in molecular genetics

Importantly, there have been major advances in our understanding of the genetics of psychosis. Pre-eminent are the findings from the huge PGC2 collaborative molecular genetic study of almost 37,000 patients with schizophrenia and 113,000 healthy controls which demonstrated that 108 loci are significantly associated with schizophrenia,[4] and that risk is influenced by a much greater number of genes (polygenes) of even smaller effect. The study pointed particularly to genes involved in neurodevelopment, genes involved in the immune and stress response, glutamate genes (which influence the dopamine system), and the dopamine D2 receptor gene itself. Interestingly, many of the susceptibility genes also increase risk of bipolar disorder and, to a lesser extent, major depression, providing support for the dimensional view that schizophrenia and these other two disorders are not categorically discrete but merge into each other. In addition to these polygenes, a small proportion of schizophrenia, perhaps 3%, has been found to be associated with the occurrence of copy number variants (CNVs), affecting mainly genes crucial to neurodevelopment; the effect size of these CNVs is much greater than that of the polygenes. Some of these CNVs have also been implicated in the etiology of autism and learning disability, but, interestingly, not of bipolar disorder.[5] Thus while many of the risk genes of small effect for schizophrenia are shared with bipolar disorder and major depression, the findings concerning CNVs suggest a continuum of developmental impairment across learning disability, autism, and a proportion of schizophrenia, a neurodevelopmental continuum to which bipolar disorder does not belong.[6]

4. The relationship between genetic and environmental risk

The above findings concerning genes of small effect enable the calculation of a polygenic risk score estimating an individual's genetic liability to schizophrenia and similar psychoses.[4] This should be of great interest to social researchers in at least two ways. Firstly, there has always been a question over whether social factors associated with psychosis are independent risk factors; for example, some biological reductionists argue that the association between child abuse or bullying and psychosis simply reflects the increased likelihood of children with a genetic loading for schizophrenias being abused or bullied. Such questions can now be examined by asking whether there is gene-environmental correlation. Similarly, sceptics, who doubt that cannabis use increases risk of psychosis, often ask "do those who use cannabis heavily do so because they themselves carry an increased loading for schizophrenia?" In support of this, one Australian study of the normal population reported that the polygenic risk score for schizophrenia weakly predicted cannabis use.[7] However, a second study failed to replicate this finding in a mixed population of controls and psychotic patients, suggesting that if the polygenic risk for schizophrenia does predict cannabis use, it accounts for only a very small proportion of the variance in cannabis consumption and does *not* explain the association between adolescent cannabis use and later psychosis.[8]

Even more interesting is the question of gene-environmental interaction. None of the known environmental risk factors for psychosis are sufficient in themselves to cause psychosis. So, are some individuals especially vulnerable to certain environmental factors? Preliminary research suggests that child abuse is more likely to result in serious psychiatric disturbance including post-traumatic stress disorder (PTSD) and psychosis (conditions Bebbington considers linked) if the child also carries a particular variant of the *FKBP5* gene.[9,10] Similarly, there is evidence that those who

carry particular risk variants of the dopamine *DRD2* gene[11] and *AKT1*[12] (a gene involved in determining post-synaptic dopamine signaling) are especially vulnerable to psychosis if they use cannabis heavily.

5. Risk factors and dopamine dysregulation

The second area of noteworthy advance has arisen from the demonstration that acute psychosis is associated with increased synthesis of dopamine in the striatum. Interestingly, childhood adversity, migration, and social stress have also been associated with increased dopamine synthesis in the striatum; and drugs such as cannabis and amphetamine have been shown to dysregulate striatal dopamine. After such exposures, the occurrence of further stressors, such as life events or even daily life challenges around the time of the onset of psychosis, could further stimulate the sensitized dopaminergic system, producing an aberrant attribution of salience to neutral stimuli. These findings were reviewed by Di Forti and colleagues[13] in an article entitled 'Risk factors for schizophrenia: all roads lead to dopamine'.

The evidence that increased striatal dopamine results in excessive salience and anomalous sensory experiences provides a mechanism whereby social factors may impact the neurochemical system which underlies psychotic experiences. Furthermore, as Bebbington points out, childhood adversity affects the cognitive schemas that individuals employ to understand daily life experiences, promoting negative representations of self and a tendency to interpret experiences as caused by malevolent external forces ('attribution bias'). As a result of such dysfunctional cognitive schemas of self and the world, the anomalous stimuli given excessive salience are interpreted as especially threatening, generating psychotic symptoms such as paranoid delusions, which, in turn, further amplify perceived stress. Moreover, the tendency of psychotic patients to jump to conclusions exacerbates and perpetuates these abnormal beliefs. In this way, a vicious cycle develops: psychosocial stress fuels the dopamine dysregulation that, when combined with altered cognitive schemas, produces psychotic symptoms, which, in turn, increase stress levels and stimulate further dopamine striatal release.

6. An integrated sociodevelopmental-cognitive model

One of us (RMM) has jointly authored a recent paper which attempts to link neurodevelopmental, dopaminergic, and cognitive hypotheses of schizophrenia.[14] According to this integrated model, genetic liability (including an excess of copy number variants and risk polymorphisms in genes involved in neurodevelopmental processes) contributes to neurodevelopmental abnormalities such as subtle motor, cognitive, or social impairment. These genetic liabilities interact with social environmental risk factors (such as early childhood adversities, migration, and social stress) to impact on the dopamine system, increasing its response to environmental stressors and to the abuse of certain illicit drugs such as stimulants and cannabis.

This model attempts to integrate Bebbington's psychosocial model of psychosis with the neurodevelopmental and dopamine hypotheses of schizophrenia. This integrated model is supported by preclinical evidence suggesting that early neurodevelopmental hazards – such as obstetric events, hypoxia, and early social deprivation – are associated with increased subcortical dopamine concentrations.[15] Furthermore, the sociodevelopmental-cognitive model points to the key role of social adversities not only as antecedents of abnormal cognitive style but also as contributory causes to dopaminergic dysregulation, and as proximal risk factors that can drive the onset of psychosis in vulnerable people or provoke further psychotic episodes after periods of remission. There is considerable evidence that both social isolation in rats and early adversities in healthy volunteers are associated with an increased striatal dopaminergic response to subsequent social stressors and stimulant drugs.[16,17] Moreover, patients affected by psychotic disorders show greater dopaminergic response to social stress tasks than healthy controls,[18] and patients who were abused in childhood are more sensitive to recent life events than patients who were not abused in childhood.[19] Taken together, these findings suggest a process of progressive dysregulation of the dopamine system by both early and subsequent social and biological exposures.

Compared to the previous versions of the dopamine hypothesis, the sociodevelopmental-cognitive model suggests that dopamine dysfunction accounts not only for delusions but also for hallucinations and negative symptoms, such as apathy and amotivation. Its role in hallucinations and amotivation is supported by preclinical evidence suggesting the involvement of midbrain dopamine neurons in perceptual decisions regarding the presence of external stimuli and in the representation of future rewards that motivate goal-directed behaviors.[20,21] Dopamine dysfunction is seen as a dynamic process that may be amplified by biological and social challenges – including developmental insults, drug misuse, social isolation, interpersonal violence, and daily life stressors. More hopefully, the dynamic nature of dopamine dysfunction also suggests that it may be normalized by antipsychotic drugs, by removing the cause of social stress, or by cognitive behavioral therapy (CBT) which addresses the abnormal cognitive schema that emerged in response to previous adversities.

We believe that research about the interaction between biological and social risk factors is likely to provide a better framework for understanding why certain exposures (such as a positive family history for psychotic disorders, childhood adversity, or cannabis misuse) are likely to drive the onset of psychosis in

some, but not in all, individuals. However, such studies will need larger samples than single exposure studies (to have adequate power) and will need to be carefully designed to account for the confounding effect of correlation between risk factors; that is, the extent to which one risk factor might affect the risk of exposure to another risk factor (for instance, the degree to which a teenager might be more exposed to, or indeed attracted by, psychotogenic drugs because of having had neglectful or abusing parents).

7. Conclusion

In his excellent review, Paul Bebbington declares that a "revolution in our understanding of psychosis" has arisen due to a "cross-fertilization between psychosocial epidemiology and cognitive behavior therapy for psychosis". He considers that "The key element is to investigate social and psychological measures in relation to each other". We agree with him, but wish to go further, and contend that a fully comprehensive understanding of psychosis must incorporate advances in biological research. In other words, it is now time to extend Bebbington's prescription, and to investigate not only how psychological and social measures relate to each other but also how they relate to findings from genetics, non-social epidemiology, and neuroscience.

Conflict of interest

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缩小精神病生物学模型与社会心理学模型研究间的差距

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概述：Paul Bebbington 最近发表的专题文章对精神病的社会心理学研究的最新进展做了一个极好的综述。然而，我们对一个仅仅基于社会流行病学和认知理论的模型可以完全描述精神病持有疑虑，并且公平地说，Bebbington 也不认为这个模型可以完全描述。一个完整的模型必须纳入我们从非社会流行病学、神经科学和遗传学中汲取的经验教训。有证据表明，Bebbington 感兴趣的社会风险因素，和诸如滥用兴奋剂和大麻之类的生物危险因素都可以通过纹状体多巴胺失调而激发精神病症状。在精神分裂症样精神病的病因学中，我们也需要考虑神经发育异常。此外，我们对精神病的遗传学理解上的惊人进展为研究探讨基因 - 环境相关性和基因 - 环境相互作用打开一扇令人兴奋的大门。总之，Bebbington 阐述了认知领域的学者与社会研究者互相交流的价值，但偶尔更倾向于生物学方面的角度可能发展出一个更全面的模型。

关键词：精神病；精神分裂症；遗传学；神经发育；多巴胺；社会因素

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