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Revisiting Bleuler: relationship between autism and schizophrenia

Almost a century ago, the great Swiss psychiatrist Eugen Bleuler coined the terms schizophrenia, as the splitting of psychic functions in Kraepelin's *dementia praecox*, and autism, as withdrawal from reality in people with schizophrenia. The term autism was, of course, later redefined by Leo Kanner[1] for a childhood psychiatric condition first considered as a subset of schizophrenia, then regarded as separate and distinct by both himself and Michael Rutter.[2] Most recently, an article by Craddock & Owen[3] not only formally challenges the distinction between schizophrenia and bipolar disorder that followed from Kraepelin's work, but also returns autism to the scene of its Bleulerian birth, in proposing a new model for the relationships between major mental illnesses as a continuum – from intellectual disability, through autism, to schizophrenia and schizoaffective disorder, through to bipolar and unipolar mood disorder. By their model, autism is juxtaposed with schizophrenia on the basis of overlapping neurodevelopmentally based phenotypes of cognitive impairment and negative symptoms, and recent genetic data that show overlap in the genetic risk loci associated with both conditions, including a set of copy number variant loci and specific genes such as *CNTNAP2* and *NRXN1*.

Do such molecular genetic data, dovetailed with data on select phenotypes, imply that Blueler was indeed correct, if not prescient, that autism and schizophrenia are manifestations of similar disease processes? In contrast to Craddock & Owen's[3] proposition, a recent alternative hypothesis posits that not only are autism and schizophrenia not juxtaposed or overlapping, but they are actually diametric psychiatric opposites characterised by underdevelopment *v.* dysregulated overdevelopment of human social-brain phenotypes.[4] This alternative hypothesis for the relationship between autism and schizophrenia has recently been tested using data from the seven copy number variant loci that have been linked statistically with both conditions.[5] The data provide statistical support for the hypothesis that autism and schizophrenia are mediated by reciprocal variants, such that at four distinct loci, deletions predispose to one disorder, whereas duplications predispose to the other – clear support for the diametric model.

Near the end of his life, Kraepelin made it clear that schizophrenia could not be satisfactorily distinguished from bipolar disorder; his supposed dichotomy was indeed false from the near start, and recent genetic data strongly support a dimensional model for the phenotypes that make up these two conditions.[3] But neither Bleuler nor Kanner should sleep soundly, nor should practitioners of psychiatric genetics or therapy, until the relationship between schizophrenia and autism becomes much better understood – the implications for diagnostics, pharmacology and psychiatry in general reach too far. Further targeted tests, based on clear alternative hypotheses with differentiating predictions, will be required – and as Craddock & Owen[3] suggest, such investigations must ultimately focus on reconciling clinical categories and dimensions with normal and abnormal neurological and psychological architecture to dissect and define psychiatric conditions for the next 100 years.

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4 Crespi B, Badcock C. Psychosis and autism as diametrical disorders of the social brain. *Behav Brain Sci* 2008; **31**: 241–61.

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Authors' reply: Dr Crespi's hypothesised model of autism and schizophrenia as diametric opposites is interesting, and it was only space limitations that prevented us discussing it in our article. We favour an 'overlapping' model of the relationship between the two disorders as being both simpler and more consistent with the totality of current data. According to our view, the two disorders share overlapping pathogenic mechanisms arising from disturbances in neurodevelopment, with autism occupying a more severe position on a continuum of neurodevelopmental impairment.[1] This is supported by a number of clinical similarities. Both disorders are more common in males and associated with cognitive impairment, and both are characterised by defects of social cognition. As Crespi mentions in his letter, clinicians used similar terminology in earlier times to refer to both diagnostic concepts (the term autistic was introduced originally to describe clinical features of adults with schizophrenia; for a time the term childhood schizophrenia was used to refer to children with autism). Within individuals, diagnoses of autism and schizophrenia have been reported to be positively associated in a large hospital case diagnosis study.[2] Finally, we note that Swedish family register data show that autism diagnosis is substantially increased by a parental family history of schizophrenia and related diagnoses,[3,4] consistent with some sharing of genetic susceptibility. These various observations seem to us to be more indicative of similarities than of opposites.

Crespi's recent analysis of data from studies of rare copy number (structural genomic) variants in the two disorders has provided some support for the hypothesis that autism and schizophrenia are mediated by reciprocal variants, such that at four distinct loci, deletions predispose to one disorder whereas duplications predispose to the other. However, observations at other loci, such as *NRXN1*, where deletions are associated with both schizophrenia and autism, do not support the diametric model.[4] Moreover, our overlapping model can predict reciprocity by invoking the not unreasonable notion that at some loci it is likely that duplication (i.e. extra genetic material) would have

more severe effects on neurodevelopment than deletion (i.e. loss of genetic material), whereas at other loci the opposite may be the case.

Notwithstanding our differences, we share with Dr Crespi a desire to develop new theoretical frameworks within which to view the increasing volume of novel genetic insights coming from genetics.[5] This will allow us to test specific biological hypotheses that can advance understanding of psychiatric illness in general and the relationship between schizophrenia and autism in particular. This will help move psychiatric classification from descriptive traditions based upon expert opinion towards robust empirical evidence that more closely relates to the workings of the brain.

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'Stoned': Schneiderian first-rank symptoms as a manifestation of bilateral obstructive urolithiasis

In October 2009, a 22-year-old student living with his parents requested treatment in our emergency ward. The patient seemed very troubled. During psychiatric evaluation, he reported that for 10 days he had been hearing voices that had commented on his actions and had commanded him not to think specific thoughts. He also felt that some of his thoughts had been introduced into his brain. The voices had discussed that people in his environment were controlled by computer software. Furthermore, the patient reported to have the impression that his body parts had been manipulated in size, and that he had been exhausted during the past week, suffering from episodes of mild fever. The degree of psychiatric symptoms had been increasing slowly over time. His general practitioner, who had only been informed about the general feeling of illness and episodes of fever, had suspected tonsillitis and treated the patient with methyl penicillin for 7 days. Because the somatic symptoms had not improved satisfactorily, treatment had been switched to azithromycin. The patient further reported a history of cannabis use and abstinence of 3 years. He had never before experienced psychotic symptoms, and none of his first-degree relatives had been diagnosed with psychiatric illnesses.

The patient was well oriented and awake. There were no pathological findings in the general examination and no focal neurological signs. A cranial computed tomography scan was without pathological findings, and analysis of the cerebrospinal fluid showed normal values. Laboratory testing revealed high levels of leucocytes (8.9/nl), c-reactive protein (203.7 mg/l) and procalcitonin (7.03 ng/ml) as well as of serum creatinine (3.32 mg/dl) and urea (90 mg/dl). While diagnostics were performed, the patient developed fever with an axillary temperature of 39°C. Ultrasound investigation showed primary bilateral hydronephrosis and a native low-dose computerised tomography scan of the abdomen revealed bilateral urinary stones, causing urinary retention, renal failure and finally urosepsis.

After admission to the intermediate care unit, the patient was treated with intravenous paracetamol and meropenem, but he refused the recommended psychopharmacological medication. Urinary retention was managed via bilateral placement of J-stents. The left prevesical stone was completely extracted via ureteroscopy on day 13 without complications. The right stone was extracted in a second intervention. Further testing revealed no detectable causes for urolithiasis, including normal values for calcium and parathyroid hormone. After relief of obstruction and at 2 weeks follow-up, the psychopathological symptoms were fully remitted without antipsychotic treatment.

In summary, the following clinical course has to be assumed: bilateral urolithiasis with urinary retention had led to a urinary tract infection with intermittent episodes of mild fever, but without noticeable oliguria or severe disability. The patient further developed a first-time acute psychotic episode, displaying first-rank symptoms of schizophrenia in absence of clouding of consciousness or lowering of vigilance (i.e. without the presence of a delirium according to DSM–IV criteria[1]). Although the relation of intermittent fever and psychotic symptoms cannot be reconstructed, symptoms were present at the time of examination in the emergency ward without febrile temperature. Laboratory testing revealed that the patient had finally developed a systemic inflammatory response syndrome and presented with urosepsis requiring emergency treatment.

Despite laboratory signs of post-renal acute renal failure, there was no clinically significant uremia at presentation. Although there are well-known reports on the psychiatric aspects of uremia[2] and paranoid psychoses with uremia,[3] these mechanisms are not sufficiently able to explain the presented case. Furthermore, although a syndrome with anxiety, panic and hallucinations (Hoigné's syndrome) can be induced by therapy with procaine penicillin or amoxicillin,[4] the onset of psychotic symptoms preceded the penicillin regimen in our patient, rendering a causal role of antibiotic treatment improbable.

Thus, this case represents the first published report on urolithiasis with secondary urosepsis presenting with Schneiderian first-rank symptoms. It exemplifies the broad phenomenology of organic psychoses and once more illustrates that profound somatic diagnostics are mandatory during the evaluation of a first psychotic episode. Additionally, it provides further evidence for the non-specificity of first-rank symptoms for schizophrenia as it is currently discussed with respect to the development of DSM–V.[5]

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