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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.

1 Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943; **2**: 217–50.

2 Rutter M. Childhood schizophrenia reconsidered. *J Autism Child Schizophr* 1972; **2**: 315–37.

3 Craddock N, Owen, MJ. The Kraepelinian dichotomy – going, going . . . but still not gone. *Br J Psychiatry* 2010; **196**: 92–5.

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

5 Crespi B, Stead P, Elliot M. Comparative genomics of autism and schizophrenia. *Proc Natl Acad Sci USA* 2010; **107**: 1736–41.

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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