DOCUMENT SUMMARY

This document is a reappraisal article by Craddock and Owen (2010) arguing that the "**Kraepelinian dichotomy**"—the traditional psychiatric division between schizophrenia and bipolar (manic-depressive) illness—is no longer tenable in light of modern genetic evidence. The authors summarize findings from large-scale family and molecular studies (including **GWAS** and **CNV** research) that show a significant overlap in genetic susceptibility between schizophrenia, bipolar disorder, and even neurodevelopmental disorders like autism. They propose moving away from rigid, separate disease categories toward a more biologically plausible dimensional model that conceptualizes these conditions along a gradient of neurodevelopmental and affective pathology.

FILENAME

Craddock_2010_research_reappraisal_article_kraepelinian_dichotomy

METADATA

- **Primary Category**: RESEARCH
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- **Tags**: #kraepelinian-dichotomy, #schizophrenia, #bipolar-disorder, #nosology, #psychosis, #genetics, #gwas, #cnv, #autism, #dimensional-model
- **Related Docs**: This paper directly challenges the diagnostic systems critiqued in "Kapur_2012_research_perspective_article_psychiatric_clinical_tests" and provides a genetic basis for the overlapping clinical features seen in neurodivergent populations.

FORMATTED CONTENT

The Kraepelinian dichotomy – going, going.. but still not gone

Nick Craddock and Michael J. Owen

Summary

Recent genetic studies reinforce the view that current approaches to the diagnosis and classification of major psychiatric illness are inadequate. These findings challenge the distinction between schizophrenia and bipolar disorder, and suggest that more attention should be given to the relationship between the functional psychoses and neurodevelopmental disorders such as autism. We are entering a transitional period of several years during which psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain.

Findings inconsistent with the Kraepelinian dichotomy

Several studies have been published in the past 5 years that provide compelling evidence that genetic susceptibility and, by implication, elements of the underlying pathogenetic mechanisms are shared between **bipolar disorder** and **schizophrenia**.

Key findings include the largest family study of the two disorders ever conducted that shows overlap in genetic susceptibility across **bipolar disorder** and **schizophrenia**. This study... showed that there are increased risks of both schizophrenia and bipolar disorder in first-degree relatives of probands with either disorder.

Additionally, **genome-wide association studies (GWAS)** have demonstrated the existence of common DNA variants (single nucleotide polymorphisms) that influence risk of both **schizophrenia** and **bipolar disorder**. Perhaps most compellingly, there is strong evidence that the aggregate polygenic contribution of many alleles of small effect to susceptibility for **schizophrenia** also influences susceptibility to **bipolar disorder**.

> Although a great deal of work remains to be undertaken... the studies described above indicate that schizophrenia and bipolar disorder (and recurrent depression) do not 'breed true', but have an overlap in genetic risk and are therefore likely to share some aspects of pathogenesis. This does not equate to a simple dichotomous notion of completely distinct and unrelated disease categories and allows us to reject the traditional, simplistic view of the dichotomy.

Findings indicating the need to reconsider the interface between psychosis and autism

It has recently been recognised that structural genomic variants of small or modest size (**copy number variants (CNVs)** of stretches of DNA of 1000 base pairs or more) are a common cause of genetic variation in humans, and such variants have been reported in neuropsychiatric phenotypes, including **autism**, 'mental retardation' (intellectual disability) and **schizophrenia**.

The specific **CNVs** associated with risk of **schizophrenia** also confer risk of multiple neuropsychiatric phenotypes, including **autism** and mental retardation. This indicates an overlap of genetic susceptibility and pathogenesis across the categories of **schizophrenia**, **autism** and other neurodevelopmental disorders and challenges the view that these are completely unrelated diagnostic entities.

Findings suggesting that bipolar disorder and schizophrenia do not have a single underlying cause and are not the same clinical entity

Although we can reject a simple model of separate, unrelated disease categories, the data do not support a model of a single-disease category... For example, the same large family study that demonstrated a substantial overlap in genetic susceptibility to

bipolar disorder and **schizophrenia** also provided clear evidence for the existence of non-shared genetic risk factors.

Recent studies suggest that some of this specificity might be due to **CNVs**. Although there is emerging evidence that **CNVs** have some influence on the risk of **bipolar disorder**, they appear to contribute less to the susceptibility to **bipolar disorder** than to **schizophrenia**... these findings are consistent with the view that **schizophrenia** has a stronger neurodevelopmental component than **bipolar disorder** and suggest that it lies on a gradient of decreasing neurodevelopmental impairment between syndromes such as mental retardation and **autism** on one hand, and **bipolar disorder** on the other (Fig. 1).

Moving towards more biologically plausible and clinically useful models of psychosis

The main clinical aims of diagnosis include the optimisation of treatments and allowing useful prognostic statements to be made. The history of medicine suggests that therapeutic and prognostic decision-making are usually facilitated... as classifications move closer to the underlying biological mechanisms.

> In our 2005 editorial we suggested that recent evidence made it necessary to consider a mood-psychosis clinical dimension with at least three possible overlapping broad domains of psychopathology ('prototype schizophrenia', 'schizoaffective' and 'prototype bipolar'). More recent genetic data are broadly consistent with such a model. However, these newer data also point to the need to consider a broader clinical spectrum that includes also **autism** and mental retardation/cognitive impairment at one end and non-psychotic mood disorder at the other.

Conclusion

At a time of transition it will be necessary to be open-minded and flexible. Care must be taken to ensure that the diagnostic entities (be they dimensions, categories or a mixture) are based on solid data, are usable and have proven clinical utility. Inevitably, research must move faster and be willing to explore a wide range of options unconstrained by current diagnostic categories.

> In our view, the most pragmatic solution to current needs is to encourage the careful measurement and reappraisal of psychopathology by using dimensional measures of key domains of psychopathology which can sit alongside the use of categories.

At the beginning of the 21st century, we must set our sights higher.