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## 'I can't go on, I'll go on'

The title of this letter is from Samuel Beckett, and well summarizes the current state of psychiatric genetics. We are confronted by the fact that genetics makes a major contribution to psychiatric disorders but the identification of the responsible genes has so far been elusive. The lack of success is a result of the complex inheritance of the responsible loci, as well as their unknown interactions with the environment. This has been reflected by the confusing lack of replicability in the literature[1]. Perhaps the one bright spot, so far, has been in the field of psychopharmacogenomics, which has recently yielded some interesting results relating to tardive dyskinesia[2] and the therapeutic responses to antidepressants[3].

Looking to the future, there is increasing interest in high-density maps of single nucleotide polymorphisms (SNPs) for association studies in psychiatric disorders. These maps should also enable the creation of maps of linkage disequilibrium in the human genome[4]. In addition to providing interesting insights into population structure, this resource could simplify genetic studies by using a small number of SNPs to genotype large blocks of the genome. However, there is a possible dark side to this enthusiasm. It could be possible to convincingly identify blocks of linkage disequilibrium that are responsible for psychiatric disorders, at the same time being unable to identify the genes within these blocks. This would be a major disappointment, as actual gene identification will be important for further understanding of psychiatric disorders, as well as designing novel therapies.

A major advance would be the discovery of large kindreds, where a psychiatric disorder segregates as a monogenic trait. For decades, it had been held that Parkinson's disease had no genetic contributions, until the discovery of rare families where the disorder clearly segregated as a single gene disorder[5]. The subsequent identification of the responsible genes provided new insights into the causation of this affliction. Similar families have yet to be identified for the psychiatric disorders, although an unusually strong linkage for schizophrenia was recently described in families of Celtic descent[6]. Overall, perhaps the most promising neuropsychiatric disorders for genetic analysis are those with very high heritability, such as autism. Other constructive approaches involve careful phenotypic characterization using endophenotypes rather than the disorders themselves. One possible example would be the use of sensorimotor gating in schizophrenia.

Considering all of this, it might seem like the search for psychiatric genes will continue to be a black hole of wasted resources but this is not the time for pessimism. No other approach has quite the same promise for providing the insights that are essential for a molecular understanding of these disorders. I can't go on, I'll go on.

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## The broader applications of neural and genetic modelling methods

The recent article by Terfloth and Gasteiger[1] provides a brief but compelling review of the role of genetic

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algorithms and neural networks in rational drug design. These methods have several useful properties that make them ideally suited for extracting information from the complex, nonlinear systems that are often encountered in drug discovery. They are generally robust methods that remove the necessity for making subjective decisions about the types of (often nonlinear) functional relationships encountered, for example, in mapping molecular structures to biological activity. Recent improvements, such as the addition of Bayesian regularization to backpropagation neural nets[2], have improved the robustness of these methods. Genetic algorithms and Bayesian methods, such as artificial relevance determination (ARD)[3], are showing considerable promise as methods of selecting appropriate descriptors for building drug or ADME quantitative-SAR (QSAR) models.

Neural methods are becoming more widely used in drug design. Their initial successes in QSAR have led to their adoption in the prediction of physicochemical properties (QSPR) and toxicity (QSTR). They are also playing an important role in combinatorial library design[4], analysis of HTS data (because of their inherent ability to deal with missing, noisy or linearly dependent data) and molecular docking methods. Genetic algorithms are also being used in docking [e.g. GOLD (Ref. 5) and FlexiDock (Tripos Associates, St Louis, MO, USA; http://www.tripos.com)] and molecular alignment [GASP; http://www.tripos.com)]

Research groups are continuing to find new applications for these novel methods and I am sure that the future will see an increasing number of applications in drug discovery and related fields where the pattern-recognition capabilities of neural networks, or the efficiencies of genetic algorithms, will be very beneficial.

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