Neurocognitive phenomics: examining the genetic basis of cognitive abilities

Psychological Medicine (2013), **43**, 2027–2036. © Cambridge University Press 2012
doi:10.1017/S0033291712002656

REVIEW ARTICLE

Neurocognitive phenomics: examining the genetic basis of cognitive abilities

G. Donohoe[1]*, I. J. Deary[2], D. C. Glahn[3], A. K. Malhotra[4] and K. E. Burdick[5]

[1] *Department of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Republic of Ireland*
[2] *Department of Psychology, University of Edinburgh, Edinburgh, UK*
[3] *Olin Neuropsychiatry Research Center, Institute of Living, and Department of Psychiatry, Yale University, New Haven, CT, USA*
[4] *The Zucker Hillside Hospital, Glen Oaks, NY, USA*
[5] *Departments of Psychiatry and Neuroscience at Mount Sinai School of Medicine, New York, NY, USA*

Cognitive deficits are core to the disability associated with many psychiatric disorders. Both variation in cognition and psychiatric risk show substantial heritability, with overlapping genetic variants contributing to both. Unsurprisingly, therefore, these fields have been mutually beneficial: just as cognitive studies of psychiatric risk variants may identify genes involved in cognition, so too can genome-wide studies based on cognitive phenotypes lead to genes relevant to psychiatric aetiology. The purpose of this review is to consider the main issues involved in the phenotypic characterization of cognition, and to describe the challenges associated with the transition to genome-wide approaches. We conclude by describing the approaches currently being taken by the international consortia involving many investigators in the field internationally (e.g. Cognitive Genomics Consortium; COGENT) to overcome these challenges.

Received 18 May 2012; Revised 20 September 2012; Accepted 11 October 2012; First published online 30 November 2012

Key words: Cognition, endophenotype, genetics, GWAS, schizophrenia.

Introduction

Progress in understanding the genetic architecture of cognition has derived in no small part from the use of cognition as an intermediate phenotype for psychiatric illness. Research groups working in the areas of Alzheimer's disease, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), intellectual disability and other childhood neurodevelopmental disorders have amassed considerable experience in characterizing the effects of 'candidate' neuropsychiatric risk genes at the level of cognition. Interest in cognitive deficits in neuropsychiatric genetic studies has been fuelled by evidence that these deficits are predictive of psychiatric morbidity (Green *et al*. 2004), more stable (trait-like), and more easily quantifiable than behaviourally defined clinical symptoms (Erlenmeyer-Kimling *et al*. 2000). Recently, this work has resulted in large-scale collaborations to achieve the sample sizes required for adequately powered genome-wide studies of cognition. The challenges for this work are considerable, requiring careful calibration not just of genetic platforms and analysis, but also of cognitive phenotypes across samples. Here we review the main issues involved in combining large datasets that quantify cognitive performance using overlapping but non-identical metrics.

In outlining the considerations for characterizing cognition for the purposes of genetic studies, four methodological issues appear to us to be particularly noteworthy. The first is regarding how best to model the relationship between different aspects of cognition. The second is to determine criteria for selecting individual aspects of cognition to focus on. The third concerns the type of analysis undertaken, whether univariate or multivariate. A fourth consideration is the relative sensitivity of behavioural *versus* imaging-based measures of cognition; this issued has been reviewed extensively elsewhere and will not be addressed here (Rose & Donohoe, 2012). We conclude by considering the main concerns involved in studies of 'neurocognitive phenomics' – genome-wide studies to understand variation in cognition – the studies published to date, and the approach adopted by the Cognitive Genomics Consortium (COGENT) in addressing these issues.

The hierarchy of cognitive functions

Why are some people better than others at performing particular cognitive tasks, such as arithmetical

* Address for correspondence: G. Donohoe, DClinPsych, Ph.D., Department of Psychiatry, School of Medicine, Trinity College Dublin, Dublin, Republic of Ireland.
(Email: donoghug@tcd.ie)

operations? Several possibilities present themselves to us. It might be that some people are just better than others generally in doing cognitive tasks. It might be that some people are better than others at mental work that involves numbers and their manipulation and also other related tasks. It might be that some people are just better than others at doing a particular arithmetical task. Of course, there could be other factors that operate on a particular occasion to produce a good, medium or bad score. The answer is that all of these suggestions are correct: there are demonstrable differences between people in overall cognitive ability, in separable domains of cognitive ability, and in specific cognitive tasks. There are also occasion-specific factors affecting mental performance and error of measurement.

When we try to model variance in cognitive tasks – including genetic contributions to the variance – we need to consider the fact that human cognitive variance occurs at these different levels in a hierarchy. At the highest level of the hierarchy, which covers the most general cognitive variation, is what is known as general cognitive ability. It is also sometimes known as general intelligence or just '*g*'. This was discovered by Spearman (1904) using data from English schoolchildren. Spearman found that there was a tendency for all cognitive tasks to show positive correlations. He hypothesized that people were better at some tasks than others because they were more or less endowed with general cognitive ability and also specific abilities for each particular task. It was realized that this explanation, although accurate, was insufficient. That is because it was empirically demonstrated that some types of tasks correlate more strongly within a particular type of cognitive domain (e.g. spatial or verbal) than with tasks outside of that domain. Therefore, an accommodation was made such that variation in cognitive performance was describable at three levels: at general cognitive ability, at the level of broad cognitive domains, and at the level of specific skills. Probably the first person to describe this hierarchy clearly was Vernon (1940).

The best evidence for the hierarchy of cognitive function variation came from Carroll (1993). In this book, he carried out a massive empirical task by reanalysing over 400 datasets from many laboratories that contained a range of mental tasks applied to large samples. These had been gathered over much of the 20th century. Carroll found that all of these datasets conformed to a correlational structure that was best described in a three-level hierarchy. That is, he confirmed Vernon's suggestion that, to understand the correlations among mental tests, people's performance (variance) was best described as a three-level hierarchy with general cognitive ability at the peak, major cognitive domains at the next level, and specific cognitive abilities at the bottom. The g factor at the peak of the hierarchy tended to account for between 40% and 50% of the total variance in mental test performance.

The three-level hierarchy has further implications. It is important to appreciate that the cognitive domains at the second level are very highly loaded on *g* (Deary *et al*. 2000, 2010; Deary, 2001*a–c*). That is, they are not independent and they derive much of the variation from *g*. Thus, the reason that people are good at domains like verbal, spatial, reasoning, speed and other cognitive domains is that they are high on *g* and also that they have some more specific capability associated with that domain. One should not make the mistake of thinking that ability on a given domain is independent of *g*. This also applies to the specific skills too: being good at a very specific mental ability is partly to do with that specific skill, partly to do with the domain with which it is associated, and also partly to do with general cognitive ability.

The general cognitive ability factor has several advantages for genetic studies. It has high stability of individual differences across most of the human life course (Deary *et al*. 2000). The general factor from different cognitive test batteries ranks people almost identically (Johnson *et al*. 2004). The general factor from a number of cognitive tests can be extracted and used as a score to indicate people's level of general cognitive ability. This can be done using various multivariate statistical methods, such as principal components analysis (PCA), and exploratory and confirmatory factor analysis. Of course, there arises the question of whether people would be ranked the same or differently when the *g* factor was based on different cognitive test batteries. This has been studied, and the result is that, when large samples of people have been tested on different cognitive test batteries, the general cognitive factor (*g*) derived from them correlates very highly, often near to 1; that is, *g* factors derived from different groups of tests rank people almost identically (Johnson *et al*. 2004, 2008). This is useful for genome-wide association studies of general cognitive ability. It means that, although different studies have used different cognitive tests, if each has used a sufficient number of sufficiently diverse cognitive tests, then the *g* derived from each of them may be comparable, and used to indicate a similar trait across studies in meta-analyses. The structural and functional brain correlates of general ability differences are also increasingly well understood (Jung & Haier, 2007; Deary *et al*. 2010). While there are genetic effects – as shown from behavioural genetic studies – at the three levels (Rijsdijk *et al*. 2002; Deary *et al*. 2009, 2010), much of the genetic influence is on the general mental ability factor. The heritability

of general cognitive ability is well established, with an additive genetic contribution that rises from quite low levels in early childhood to over 60% throughout adulthood.

In addition to the three-level hierarchical model of cognitive ability differences – with a general cognitive factor at the apex – having much replication in psychometric studies, it should also be addressed whether there is validating biological evidence for such a structure. This has been addressed by a number of authors, and some key examples are given here. These are examples where biological effects have been examined with respect to the hierarchical model of cognitive differences. In each case formal hypothesis testing using structural equation modelling was used to examine influences on *g* and the other cognitive domains. Thus, for example, the major influence of age is on the *g* level of the hierarchy with some additional effects on memory and processing speed domains (Salthouse, 2004). The well-established, modest correlation between brain size – estimated in healthy individuals using magnetic resonance brain scanning – is largely captured by the association between total brain volume and *g* (MacLullich *et al*. 2002). Other *g*–brain associations are reviewed by Deary *et al*. (2010). In addition, behavioural genetic studies show that the principal genetic influence on cognitive functions is an additive genetic influence on *g*, and that genetic effects on more specific domains of cognitive function largely derive from the genetic influences on *g* (Deary *et al*. 2009).

In summary, the phenotype of cognitive abilities is described by a three-level hierarchy that captures variation in people's mental functioning at different levels of generality. This framework is a good starting point for genetic studies, which may be aimed at different levels. The evidence to date shows that much of the genetic influence is on general ability, and that like human height will have a complex genetic architecture (Lanktree *et al*. 2011). It makes sense therefore to target this level of cognition with regard to molecular genetic studies, including in current genome-wide association study (GWAS) approaches described later in this review.

Choosing between specific cognitive functions and tasks in cognitive phenomic analysis

Several criteria have been put forward for choosing appropriate cognitive measures as phenotypes relevant to psychiatric studies (Cannon, 2005; Gur *et al*. 2007; Donohoe *et al*. 2009). The most obvious criterion, perhaps, is whether and to what extent performance on a given task is heritable. Different classes of relatives share more or less genetic material (e.g. monozygotic twins share 100% of genes, dizygotic twins/siblings 50%, and half-siblings 25%), making it possible to estimate the proportion of individual differences in performance in a population at a given time that are due to genetic differences [termed heritability (h^2)]. In considering heritability, the degree to which performance on a particular function or task shares genetic variance with the underlying risk of the disease is also a significant consideration (Glahn *et al*. 2012). While availability of twin and population-based disease registry data has confirmed the importance of heritability for many psychiatric disorders, including autism and the psychoses (Cardno *et al*. 1999; McGuffin *et al*. 2003), unavailability of twin data for many specific cognitive tests has meant that heritability has been inferred from the familiality of specific cognitive deficits in healthy relatives of patients. Where twin data have been available (Goldberg *et al*. 1990, 1995 and Toulopoulou *et al*. 2007 for schizophrenia; Bidwell *et al*. 2007 for ADHD), evidence for heritability of cognitive deficits has generally been noted.

Shared genetic variation between cognitive and illness phenotypes is a key concept of the 'endophenotype' approach. As originally hypothesized, endophenotypes – measurable components located along the pathway between genotype and disease, such as those derived from cognitive and neuropsychological measures – were suggested to be phenotypically and genetically simpler than the more complex disease syndrome, hence leading to more powerful – and successful – genetic analysis (Gottesman & Gould, 2003). The use of cognitive phenotypes as neuropsychiatric endophenotypes has been reviewed extensively (Glahn *et al*. 2004; Goldberg & Weinberger, 2004; Cannon, 2005; Meyer-Lindenber & Weinberger, 2006; Gur *et al*. 2007; Walters & Owen, 2007; Donohoe *et al*. 2009; Corvin *et al*. 2012). Several questions about the nature and use of cognitive endophenotypes remain. For example, Gottesman's original hypothesis that cognitive phenotypes would represent genetically 'simpler' constructs than genetically complex psychiatric conditions has not generally been supported – cognitive constructs like intelligence appear to be themselves, like other human traits including height and weight, genetically complex (Bilder *et al*. 2011). Furthermore, whether cognitive functions are mediators or moderators of genetic effects on illness remains unclear; psychiatric GWAS studies to date suggest that while the increased risk associated with some common variants is also associated with variation in cognitive function [e.g. calcium channel, voltage-dependent, l type, alpha 1c (CACNA1C); Zhang *et al*. 2012] as either a moderator/mediator of genetic risk or as a pleiotropic effect, other

common variants appear to affect risk largely independently of cognition [e.g. neurogranin (NRGN) in schizophrenia; Donohoe *et al*. 2011]. Finally, although high genetic overlap between cognitive deficits and illness has been reported (e.g. overlapping genetic effects of about 92% between intelligence quotient and schizophrenia; Toulopoulou *et al*. 2007), population-based studies suggest that the actual overlap may be much smaller (Fowler *et al*. 2012). Whether because of these factors, or for pragmatic reasons such as availability of much larger diagnostically phenotyped samples than cognitively phenotyped samples, cognitive phenotype studies in psychiatric illness have more typically been used for following up psychiatric GWAS signals than for discovery. Sometimes termed 'a reverse endophenotyping' strategy, the approach here has been to use neuropsychological measures to characterize the effects of already GWAS-identified risk variants on cognition (for a recent review, see Corvin *et al*. 2012).

Irrespective of whether cognitive phenotypes are used for the purposes of genetic discovery or characterization of already identified risk variants, a further criterion for genetic studies of cognitive functions and associated measures is that they can be quantitatively measured in a reliable manner. That cognitive phenotypes should have enhanced reliability as compared with that afforded by diagnostic categories is an important assumption of the intermediate phenotype approach (Gottesman & Gould, 2003; Bearden & Freimer, 2006). Thus, the inter-rater reliability (the consistency of scores across raters) and test–retest reliability (the consistency of scores over time) of cognitive phenotypes have been widely scrutinized. In patient studies, the importance of state independence (that scores are relatively independent of fluctuations in clinical symptoms) and independence from medication effects has been a particular focus in this regard, particularly for schizophrenia. These studies suggest that while cognitive deficits are somewhat correlated with clinical symptoms (for example, negative symptoms in schizophrenia), the correlation is low ($r^2 < 0.3$) and the amount of variance shared by these variables appears to be small. In factor analysis, cognitive function (as measured in terms of memory and attention) often emerges as a separate factor from clinical symptoms (Donohoe & Robertson, 2003; Good *et al*. 2004; Donohoe *et al*. 2006; Lipkovich *et al*. 2009). Furthermore, changes in cognition following trials of either medication or cognitive remediation are only weakly associated with changes in clinical presentation (Davidson *et al*. 2009; Wykes *et al*. 2011). Finally, data derived from large-scale studies of individuals at risk for developing psychosis, either by virtue of prodromal symptomatology (clinical high risk) or genetic predisposition (genetic high risk), suggest that neurocognitive impairment is present regardless of current symptom status and likelihood of later conversion to psychosis (Seidman *et al*. 2010). Taken together, these data indicate that cognitive phenotypes are, in addition to being heritable, likely to be stable and generally independent of fluctuations in clinical symptomatology.

The utility of several cognitive functions as endophenotypes have been extensively investigated, and to a reasonable extent supported across illness, including memory function (both episodic and working memory), and various aspects of attentional control and executive function. Evidence of the utility of these individual cognitive phenotypes and measures in relation to specific neuropsychiatric disorders has been reviewed extensively, including Gur *et al*. (2007) and Donohoe *et al*. (2009) for schizophrenia, Glahn *et al*. (2004) for bipolar disorder, MacQueen & Frodl (2011) for major depressive disorder, Bellgrove & Mattingly (2008) for ADHD, and Abrahams & Geschwind (2010) for autism. A particular challenge for utilizing these cognitive constructs in GWAS studies, however, is regarding how best to combine test scores between datasets. The requirement for adequately large samples powered to undertake genome-wide analysis means that data need to be combined across datasets, usually from a large number of research groups. However, because of differences between groups in the cognitive measures employed, combining datasets is extremely challenging. Even where similar cognitive and test constructs have been employed between sites – e.g. using the continuous performance test (CPT) to measure attentional control – different versions of the test (e.g. CPT-AX: Identical Pairs, CPT-IP; Degraded-Stimulus, CPT-DS) usually result in non-identical phenotypes between sites.

Univariate *versus* multivariate analysis

A third consideration for cognitive genetics approaches is whether to use a multivariate, rather than univariate, approach. The power of a genetic analysis (e.g. linkage or GWA) to detect an effect can be greatly enhanced by collapsing large cognitive batteries into cognitive domains that can be achieved via factor analysis. The advantage of factor analysis is threefold: (1) the maximum amount of cognitive information is captured by relatively few constructs; (2) reducing a large number of variables to smaller number of latent constructs limits the need for conservative multiple comparison correction; and (3) if employing confirmatory factor analysis measurement error can be accounted for. A potential disadvantage of this approach is that if the grouped measures do not share

common genetic aetiology it actually reduces the power to find an effect. Thus the development of factor models should be guided by the covariance within the cognitive data and the degree to which that covariance can be explained by shared genetic effects (current efforts to address these issues are described by Bilder *et al*. 2011).

Given evidence that shared genetic factors influence *g*, cognitive domains and specific cognitive traits, searching for genes influencing *g* is intrinsically a multivariate analysis. Such an analysis is designed to localize loci associated with each level of the three-level hierarchy. In this context, focusing on *g* should be more effective than searching for the genetic influences of each of the specific cognitive tests alone, as the index of *g* is typically more reliable than individual test scores and a single phenotype is assessed (compared with many), reducing the need for correction for multiple comparisons. However, there is an alternative view. It is possible that the *g* construct is exceptionally polygenetic, with large numbers of genes of very small effect (Lanktree *et al*. 2011), making it very difficult to identify a single genetic target (gene). In contrast, individual tests may have relatively less complex genetic architectures, affording them the potential for gene discovery. Eventually empirical evidence will determine which of these alternatives is more likely. Unfortunately, support for either hypothesis is largely missing at this time.

GWAS era and challenges of power

An extensive literature now exists on cognitive studies of single genes associated with increased illness risk for neuropsychiatric diseases with childhood onset (e.g. autism, ADHD), and adult onset (e.g. schizophrenia, bipolar disorder, Alzheimer's disease). With few exceptions (e.g. apolipoprotein E), however, identifying a specific role in cognition for individual gene variants across these disorders has been challenging (Payton, 2009; Corvin *et al*. 2012). In the majority of cases, individual variants have not been robustly associated with the illness phenotype, and no clear functional variants have been identified, making direct comparison of studies difficult. These difficulties have been further hampered by the differences in the cognitive measures investigated. What is perhaps most striking about this literature is how closely the cognitive phenotype findings recapitulate the illness phenotype findings in term of the small proportion of variation explained (about 1–2%) and the frequent lack of replication. This, together with evidence of a significant negative correlation between observed effect and sample size (Rose & Donohoe, 2012), highlights the necessity of incorporating large samples in order to optimally detect these expected small effects.

Recent (and relatively affordable) technological advances in genotyping platforms have resulted in a move from single-gene studies towards genome-wide association studies using platforms that can assay more than 1 million genomic markers. This GWAS approach has allowed for a relatively hypothesis-free scan of the entire human genome, thereby markedly increasing the genetic information. GWAS platforms offer optimal coverage of common variation for single nucleotide polymorphism (SNP)-based association analyses and simultaneously capture structural variation, such as copy-number variation through the use of intensity data analyses without requiring the implementation of a secondary technology. Imputation, or prediction, strategies capitalize on what is known about the correlation among SNPs and provide meaningful estimates of genomic variation that is not directly genotyped on GWAS platforms and can further improve resolution. These advantages notwithstanding, GWAS methodology has certain challenges, especially for cognitive phenomics.

The use of a genome-wide, hypothesis-free strategy implies the need to handle large quantities of data while attempting to maintain adequate statistical power. While the standard in the field of research for statistical significance has long been set at a p value <0.05, the use of hundreds of thousands, or millions, of statistical tests in GWAS analyses has necessitated multiple-testing corrections that require conservative α values: for example, a p value threshold in and around 5×10^{-8} derived from a Bonferroni correction for about 550 000 observations is often used, although the p value will be smaller for >1 million SNPs. This, together with the likelihood of individual common variants explaining only a modest proportion of variation in cognition, highlights the need for extremely large sample sizes (Manolio, 2010).

In an effort to surmount this problem, several large-scale consortia have been organized across numerous medical and neuropsychiatric disorders, which represent collaborative efforts to merge independent datasets. In addition to increasing sample sizes, optimal power can be achieved through the use of information in the public domain, which can provide for targeted selection of the smallest number of SNPs required to tag common variation across the genome through the use of linkage disequilibrium (LD) data in reference samples.

There have been several genome-wide association studies conducted that directly targeted normal human cognition, each of which highlight the importance of large sample sizes and replication. The first GWAS study of cognition (Papassotiropoulos *et al*. 2006)

focused on episodic memory in 351 young adults from Switzerland and reported a significant effect of the gene, *KIBRA* (kidney- and brain-expressed protein), on free recall performance 5 min and 24 h after initial word presentation. This result was replicated in a second independent cohort of subjects from the USA. Subsequent cognitive GWAS studies have also suggested that KIBRA could influence aspects of cognitive function; Need *et al*. (2009) reported that in a study of over 1000 subjects recruited from college campuses, 10 genes achieved nominal significance for association with specific aspects of cognition, including a SNP (but not the same SNP as originally reported by Papassotiropoulos *et al*. 2006) in KIBRA with verbal learning and memory as assessed with the Cambridge Neuropsychological Test Automated Battery. Other cognitive GWAS studies (e.g. Seshadri *et al*. 2007; Butcher *et al*. 2008) have been unable to observe these effects, however, though substantive differences in both the phenotypic and genotypic assessment strategies hamper the interpretation of these data.

Luciano *et al*. (2011) describe the results of a collaborative meta-analysis of data derived from three cohorts with a total sample size of 2379 individuals. The primary outcome measure of this study was focused on the domain of processing speed, a lower-level cognitive construct that shares a large proportion of genetic variance with higher-order processes (Luciano *et al*. 2004). The primary results indicated no individual marker (SNP) that reached genome-wide statistical significance. More recently, we undertook a GWAS of general intelligence in a sample of 3511 healthy individuals (Davies *et al*. 2011). General intelligence in this study was separated into crystallized intelligence and fluid intelligence, based on a PCA of the overlapping (but non-identical) measures available in the five cohorts. Genome-wide analyses of SNP data in this study indicated that genetic variants in LD with common SNPs account for 40–50% of the variation in general intelligence. We furthermore observed, using gene-based analysis, a genome-wide significant association between general fluid-type intelligence and variation in the formin-binding protein 1-like (*FNBP1L*) gene. Taken together, these cognitive GWAS studies highlight the expectation that small effect sizes for individual loci will be the norm, reinforce the advantages of utilization of comparable genotyping platforms, and emphasize the need for careful consideration of the precise cognitive phenotype for examination.

COGENT

These initial GWAS studies of normal human cognition represent a step forward in our understanding of the genetic architecture of cognitive functions. Moreover, like other complex brain-based phenotypes, such as schizophrenia and bipolar disorder, these studies provide strong evidence of polygenic influence on cognitive performance. They also highlight the need for much larger samples of healthy subjects who have been comprehensively phenotyped. To this end, we have initiated an international collaborative effort entitled 'The Cognitive Genomics Consortium (COGENT)'. The primary goal of COGENT is to bring together existing databases with information on normal human cognitive function (healthy individuals) as well as genetic information in the form of already completed genotyping conducted on a genome-wide platform. By combining efforts, we hope to achieve sample sizes of >8000 subjects and the resultant statistical power necessary to detect genetic loci associated with cognition with small effects. In brief, the consortium currently consists of nine sites across seven countries and is led by the Zucker Hillside Hospital – North Shore Long Island Jewish Health System site in New York, USA. Each site is contributing existing neurocognitive phenotype data linked with genotype data from a high-quality genome-wide platform. Although platforms and phenotype measures vary by site, the consortium has formed several committees to best handle synchronization and several other practical issues in dealing with the merging of data.

With data in hand, the first phase of analysis will focus on identifying genetic variation associated with general cognitive ability (*g*), as in Davies *et al*. (2011). As mentioned in the first section of our review there are several reasons to choose *g*, including (1) its ability to account for, and indeed predict, a substantial percentage of the variance (about 40–50%) in performance on domain-specific cognitive functions (Deary *et al*. 2009); (2) its well-established and high heritability; (3) the feasibility of extracting a measure of *g* from the wide variety of cognitive tasks collected across sites using PCA; and (4) its stability and comparability across samples even when different tasks are used (Deary *et al*. 2009). Initial approaches will utilize meta-analytic techniques to identify common variants associated with *g*; extensive discussions by the COGENT phenotype committee led to the view that merging *g* across sites with different ascertainment and subject characteristics would be too problematic for a mega-analytic approach. Several key decisions have been made in an effort to make the calculation of *g* uniform across sites including: (1) a minimum of three tests will be needed to calculate a valid *g*; (2) only one (best representative) variable per neurocognitive task will be included in the calculation of *g*; (3) missing data will be addressed on a

site-by-site basis, as it is largely dependent on the total number of variables used to calculate *g* and the total number of missing values per subject; and (4) age and sex will be controlled for *a priori* using regression. Follow-up analyses, dependent on initial results, may entail pathway-based approaches, additional sequencing plans, and prospective data collection; a mega-analysis of individual measures for which significant overlap across sites is available is also intended as a second-phase analysis. Finally, we also anticipate that COGENT will grow large enough to serve as a database which will allow future questions related to relationships between specific neuropsychiatric disorder susceptibility genes and cognitive phenotypes to be explored. Much larger samples will be required for investigation of rare variation; however, dependent on the final sample size, this may become a viable option in the future.

Conclusion

Cognitive genomics is a rapidly changing field due to the pace of technological advances in this area. Advances in our understanding of the genetic architecture of cognition has derived in no small part from the use of cognition as an intermediate phenotype relevant to understanding how risk for psychiatric illness is conferred at the level of brain function. Research groups working in schizophrenia, autism and ADHD, as well as in intellectual disability and other childhood neurodevelopmental disorders have amassed considerable experience in characterizing the effects of 'candidate' genes at the level of cognition. As with illness consortia involving the collaboration of dozens if not hundreds of researchers to achieve the sample size required for adequately powered genome-wide studies, cognitive genomic researchers have also engaged in large-scale collaborations. As reviewed here, doing so requires careful calibration not just of genetic platforms and analysis, but also of cognitive phenotypes across samples. This involves understanding and modelling the hierarchical relationship between different domains of cognition and the resultant correlation between individual tests. It involves selecting measures of cognitive domains that have already demonstrated heritability. In the case of multiple tests, and non-identity between these tests, factor analysis has been discussed as a method for reducing the burden of multiple testing and extracting an index of function across non-identical tests used by different research sites. Use of Spearman's *g* has been described as one example of this approach in the field. Extending this approach to other cognitive phenotypes that have already been associated with genetic variation (e.g. indices of memory and working memory) is also likely to be of value. Finally, this review highlights the close interplay between the fields of cognitive and psychiatric genetics and the relevance for discoveries that each may have to the other.

Declaration of Interest

None.

References

Abrahams BS, Geschwind DH (2010). Connecting genes to brain in the autism spectrum disorders. *Archives of Neurology* **67**, 395–399.

Bearden CE, Freimer NB (2006). Endophenotypes for psychiatric disorders: ready for primetime? *Trends in Genetics* **22**, 306–313.

Bellgrove MA, Mattingley JB (2008). Molecular genetics of attention. *Annals of the New York Academy of Science* **1129**, 200–212.

Bidwell LC, McClernon FJ, Kollins SH (2011). Cognitive enhancers for the treatment of ADHD. *Pharmacology, Biochemistry and Behavior* **99**, 262–274.

Bidwell LC, Willcutt EG, Defries JC, Pennington BF (2007). Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biological Psychiatry* **62**, 991–998.

Bilder RM, Howe A, Novak N, Sabb FW, Parker DS (2011). The genetics of cognitive impairment in schizophrenia: a phenomic perspective. *Trends in Cognitive Sciences* **15**, 428–435.

Butcher LM, Davis OS, Craig IW, Plomin R (2008). Genome-wide quantitative trait locus association scan of general cognitive ability using pooled DNA and 500k single nucleotide polymorphism microarrays. *Genes, Brain, and Behavior* **7**, 435–446.

Cannon TD (2005). The inheritance of intermediate phenotypes for schizophrenia. *Current Opinion in Psychiatry* **18**, 135–140.

Cardno AG, Marchall JE, Coid B, MacDonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM (1999). Heritability estimates for psychotic disorders. *Archives of General Psychiatry* **56**, 162–168.

Carroll JB (1993). *Human Cognitive Abilities: A Survey of Factor-Analytical Studies*. Cambridge University Press: New York.

Corvin A, Donohoe G, Hargreaves A, Gallagher L, Gill M (2012). The cognitive genetics of neuropsychiatric disorders. *Current Topics in Behavioral Neuroscience* **12**, 579–613.

Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, Boter H, Keet IP, Prelipceanu D, Rybakowski JK, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Kahn RS (2009). Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform

disorder: a randomized, open-label clinical trial (EUFEST). *American Journal of Psychiatry* **166**, 675–682.

Davies G, Tenesa A, Payton A, Yang J, Harris SE, Liewald D, Ke X, Le Hellard S, Christoforou A, Luciano M, McGhee K, Lopez L, Gow AJ, Corley J, Redmond P, Fox HC, Haggarty P, Whalley LJ, McNeill G, Goddard ME, Espeseth T, Lundervold AJ, Reinvang I, Pickles A, Steen VM, Ollier W, Porteous DJ, Horan M, Starr JM, Pendleton N, Visscher PM, Deary IJ (2011). Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular Psychiatry* **16**, 996–1005.

Deary IJ (2001*a*). Human intelligence differences: a recent history. *Trends in Cognitive Sciences* **5**, 127–130.

Deary IJ (2001*b*). Human intelligence differences: towards a combined experimental–differential approach. *Trends in Cognitive Sciences* **5**, 164–170.

Deary IJ (2001*c*). Individual differences in cognition: British contributions over a century. *British Journal of Psychology* **92**, 217–237.

Deary IJ, Johnson W, Houlihan LM (2009). Genetic foundations of human intelligence. *Human Genetics* **126**, 215–232.

Deary IJ, Penke L, Johnson W (2010). The neuroscience of human intelligence differences. *Nature Reviews Neuroscience* **11**, 201–211.

Deary IJ, Whalley LJ, Lemmon H, Crawford JR, Starr JM (2000). The stability of individual differences in mental ability from childhood to old age: follow-up of the 1932 Scottish Mental Survey. *Intelligence* **28**, 49–55.

Donohoe G, Corvin A, Robertson I (2006). Evidence that specific executive functions predict symptom variance among schizophrenia patients with a predominantly negative symptom profile. *Cognitive Neuropsychiatry* **11**, 13–32.

Donohoe G, Goldberg TE, Corvin A (2009). Cognitive intermediate phenotypes in schizophrenia genetics. In *The Genetics of Cognitive Neuroscience* (ed. T. E. Goldberg and D. Weinberger), pp. 195–220. MIT Press: Boston.

Donohoe G, Robertson IH (2003). Can specific deficits in executive functioning explain the negative symptoms of schizophrenia? A review. *Neurocase* **9**, 97–108.

Donohoe G, Walters J, Morris DW, Da Costa A, Rose E, Hargreaves A, Maher K, Hayes E, Giegling I, Hartmann AM, Möller HJ, Muglia P, Moskvina V, Owen MJ, O'Donovan MC, Gill M, Corvin A, Rujescu D (2011). A neuropsychological investigation of the genome wide associated schizophrenia risk variant NRGN rs12807809. *Schizophrenia Research* **125**, 304–306.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Hilldoff Adamo U, Gottesman II (2000). Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *American Journal of Psychiatry* **157**, 1416–1422.

Fowler T, Zammit S, Owen MJ, Rasmussen F (2012). A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. *Psychological Medicine* **69**, 460–466.

Glahn DC, Bearden CE, Niendam TA, Escamilla MA (2004). The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. *Bipolar Disorders* **6**, 171–182.

Glahn DC, Curran JE, Winkler AM, Carless MA, Kent JW, Charlesworth JC, Johnson MP, Goring HH, Cole SA, Dyer TD, Moses EK, Olvera RL, Kochunov P, Duggirala R, Fox PT, Almasy L, Blangero J (2012). High dimensional endophenotype ranking in the search for major depression risk genes. *Biological Psychiatry* **71**, 6–14.

Goldberg TE, Ragland JD, Torrey EF, Gold JM, Bigelow LB, Weinberger DR (1990). Neuropsychological assessment of monozygotic twins discordant for schizophrenia. *Archives of General Psychiatry* **47**, 1066–1072.

Goldberg TE, Torrey EF, Gold JM, Bigelow LB, Ragland RD, Taylor E, Weinberger DR (1995). Genetic risk of neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder. *Schizophrenia Research* **17**, 77–84.

Goldberg TE, Weinberger DR (2004). Genes and the parsing of cognitive processes. *Trends in Cognitive Sciences* **8**, 325–335.

Good KP, Rabinowitz J, Whitehorn D, Harvey PD, DeSmedt G, Kopala LC (2004). The relationship of neuropsychological test performance with the PANSS in antipsychotic naive, first-episode psychosis patients. *Schizophrenia Research* **68**, 11–19.

Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* **160**, 636–645.

Green MF, Kern RS, Heaton RK (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research* **72**, 41–51.

Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS (2007). The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. *Schizophrenia Bulletin* **33**, 49–68.

Johnson W, Bouchard TJ, Krueger RF, McGue M, Gottesman II (2004). Just one *g*: consistent results from three test batteries. *Intelligence* **32**, 95–107.

Johnson W, te Nijenhuis J, Bouchard TJ (2008). Still just 1 *g*: consistent results from five test batteries. *Intelligence* **36**, 81–95.

Jung RE, Haier RJ (2007). The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behavioral and Brain Sciences* **30**, 135–187.

Lanktree MB, Guo Y, Murtaza M, Glessner JT, Bailey SD, Onland-Moret NC, Lettre G, Ongen H, Rajagopalan R, Johnson T, Shen H, Nelson CP, Klopp N, Baumert J, Padmanabhan S, Pankratz N, Pankow JS, Shah S, Taylor K, Barnard J, Peters BJ, Maloney CM, Lobmeyer MT, Stanton A, Zafarmand MH, Romaine SP, Mehta A, van Iperen EP, Gong Y, Price TS, Smith EN, Kim CE, Li YR, Asselbergs FW, Atwood LD, Bailey KM, Bhatt D, Bauer F, Behr ER, Bhangale T, Boer JM, Boehm BO, Bradfield JP, Brown M, Braund PS,

Burton PR, Carty C, Chandrupatla HR, Chen W, Connell J, Dalgeorgou C, Boer A, Drenos F, Elbers CC, Fang JC, Fox CS, Frackelton EC, Fuchs B, Furlong CE, Gibson Q, Gieger C, Goel A, Grobbee DE, Hastie C, Howard PJ, Huang GH, Johnson WC, Li Q, Kleber ME, Klein BE, Klein R, Kooperberg C, Ky B, Lacroix A, Lanken P, Lathrop M, Li M, Marshall V, Melander O, Mentch FD, Meyer NJ, Monda KL, Montpetit A, Murugesan G, Nakayama K, Nondahl D, Onipinla A, Rafelt S, Newhouse SJ, Otieno FG, Patel SR, Putt ME, Rodriguez S, Safa RN, Sawyer DB, Schreiner PJ, Simpson C, Sivapalaratnam S, Srinivasan SR, Suver C, Swergold G, Sweitzer, NK, Thomas KA, Thorand B, Timpson NJ, Tischfield S, Tobin M, Tomaszewski M, Verschuren WM, Wallace C, Winkelmann B, Zhang H, Zheng D, Zhang L, Zmuda JM, Clarke R, Balmforth AJ, Danesh J, Day IN, Schork NJ, de Bakker PI, Delles C, Duggan D, Hingorani AD, Hirschhorn JN, Hofker MH, Humphries SE, Kivimaki M, Lawlor DA, Kottke-Marchant K, Mega JL, Mitchell BD, Morrow DA, Palmen J, Redline S, Shields DC, Shuldiner AR, Sleiman PM, Smith GD, Farrall M, Jamshidi Y, Christiani DC, Casas JP, Hall AS, Doevendans PA, Christie JD, Berenson GS, Murray SS, Illig T, Dorn 2nd GW, Cappola TP, Boerwinkle E, Sever P, Rader DJ, Reilly MP, Caulfield M, Talmud PJ, Topol E, Engert JC, Wang K, Dominiczak A, Hamsten A, Curtis SP, Silverstein RL, Lange LA, Sabatine MS, Trip M, Saleheen D, Peden JF, Cruickshanks KJ, Marz W, O'Connell JR, Klungel OH, Wijmenga C, Maitland-van der Zee AH, Schadt EE, Johnson JA, Jarvik GP, Papanicolaou GJ, Grant SF, Munroe PB, North KE, Samani NJ, Koenig W, Gaunt TR, Anand SS, van der Schouw YT, Soranzo N, Fitzgerald GA, Reiner A, Hegele RA, Hakonarson H, Keating BJ (2011). Meta-analysis of dense genecentric association studies reveals common and uncommon variants associated with height. *American Journal of Human Genetics* **88**, 6–18.

Lipkovich IA, Deberdt W, Csernansky JG, Sabbe B, Keefe RS, Kollack-Walker S (2009). Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: a path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. *BMC Psychiatry* **9**, 44.

Luciano M, Hansell NK, Lahti J, Davies G, Medland SE, Räikkönen K, Tenesa A, Widen E, McGhee KA, Palotie A, Liewald D, Porteous DJ, Starr JM, Montgomery GW, Martin NG, Eriksson JG, Wright MJ, Deary IJ (2011). Whole genome association scan for genetic polymorphisms influencing information processing speed. *Biological Psychology* **86**, 193–202.

Luciano M, Wright MJ, Geffen GM, Geffen LB, Smith GA, Martin NG (2004). A genetic investigation of the covariation among inspection time, choice reaction time, and IQ subtest scores. *Behavior Genetics* **34**, 41–50.

MacLullich AMJ, Ferguson KJ, Deary IJ, Seckl JR, Starr JM, Wardlaw JM (2002). Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. *Neurology* **59**, 169–174.

MacQueen G, Frodl T (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? *Molecular Psychiatry* **16**, 252–264.

Manolio TA (2010). Genomewide association studies and assessment of the risk of disease. *New England Journal of Medicine* **363**, 166–176.

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry* **60**, 497–502.

Meyer-Lindenberg A, Weinberger DR (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Reviews Neuroscience* **7**, 818–827.

Need AC, Attix DK, McEvoy JM, Cirulli ET, Linney KL, Hunt P, Ge D, Heinzen EL, Maia JM, Shianna KV, Weale ME, Cherkas LF, Clement G, Spector TD, Gibson G, Goldstein DB (2009). A genome-wide study of common SNPs and CNVs in cognitive performance in the CANTAB. *Human Molecular Genetics* **18**, 4650–4661.

Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, Huynh K, Brunner F, Corneveaux J, Osborne D, Wollmer MA, Aerni A, Coluccia D, Hanggi J, Mondadori CRA, Buchman A, Reiman EM, Caselli RJ, Henke K, de Quervain DJF (2006). Common *Kibra* alleles are associated with human memory performance. *Science* **314**, 475–478.

Payton A (2009). The impact of genetic research on our understanding of normal cognitive ageing: 1995 to 2009. *Neuropsychology Review* **19**, 451–477.

Rijsdijk FA, Vernon PA, Boomsma DI (2002). Application of hierarchical genetic models to Raven and WAIS subtests: a Dutch twin study. *Behavior Genetics* **32**, 199–210.

Rose EJ, Donohoe G (2012). Brain vs behavior: an effect size comparison of neuroimaging and cognitive studies of genetic risk for schizophrenia. *Schizophrenia Bulletin*. Published online 12 April 2012. doi:10.1093/schbul/sbs056.

Salthouse TA (2004). Localising age-related individual differences in a hierarchical structure. *Intelligence* **32**, 541–561.

Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Tsuang MT, Walker EF, Woods SW, Bearden CE, Christensen BK, Hawkins K, Heaton R, Keefe RS, Heinssen R, Cornblatt BA; North American Prodrome Longitudinal Study (NAPLS) Group (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of General Psychiatry* **67**, 578–588.

Seshadri S, DeStefano AL, Au R, Massaro JM, Beiser AS, Kelly-Hayes M, Kase CS, D'Agostino Sr RB, Decarli C, Atwood LD, Wolf PA (2007). Genetic correlates of brain aging on MRI and cognitive test measures: a genome-wide association and linkage analysis in the Framingham study. *BMC Medical Genetics* **8** (Suppl. 1), S15.

Spearman C (1904). '"General intelligence,' objectively determined and measured". *American Journal of Psychology* **15**, 201–293.

Toulopoulou T, Picchioni M, Rijsdijk F, Hua-Hall M, Ettinger U, Sham P, Murray R (2007). Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Archives of General Psychiatry* **64**, 1348–1355.

Vernon PE (1940). *The Measurement of Abilities*. University of London Press: London.

Walters JT, Owen MJ (2007). Endophenotypes in psychiatric genetics. *Molecular Psychiatry* **12**, 886–890.

Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry* **168**, 472–485.

Zhang Q, Shen Q, Xu Z, Chen M, Cheng L, Zhai J, Gu H, Bao X, Chen X, Wang K, Deng X, Ji F, Liu C, Li J, Dong Q, Chen C (2012). The effects of CACNA1C gene polymorphism on spatial working memory in both healthy controls and patients with schizophrenia or bipolar disorder. *Neuropsychopharmacology* **37**, 677–684.