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INVITED REVIEW

The endophenotype concept in psychiatric genetics

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ABSTRACT

The idea that some phenotypes bear a closer relationship to the biological processes that give rise to psychiatric illness than diagnostic categories has attracted considerable interest. Much effort has been devoted to finding such endophenotypes, partly because it is believed that the genetic basis of endophenotypes will be easier to analyse than that of psychiatric disease. This belief depends in part on the assumption that the effect sizes of genetic loci contributing to endophenotypes are larger than those contributing to disease susceptibility, hence increasing the chance that genetic linkage and association tests will detect them. We examine this assumption by applying meta-analytical techniques to genetic association studies of endophenotypes. We find that the genetic effect sizes of the loci examined to date are no larger than those reported for other phenotypes. A review of the genetic architecture of traits in model organisms also provides no support for the view that the effect sizes of loci contributing to phenotypes closer to the biological basis of disease is any larger than those contributing to disease itself. While endophenotype measures may afford greater reliability, it should not be assumed that they will also demonstrate simpler genetic architecture.

Introduction

This review examines what is known about the genetic architecture of endophenotypes and assesses the claim that endophenotypes are more suitable than psychiatric diagnostic categories for genetic dissection, by which we mean the application of genetic linkage and association strategies to identify genes associated with psychiatric disease and component mechanisms. We start with a brief introduction to endophenotypes and then proceed to examine examples where sufficient genetic data have accumulated for our purpose. We do not provide a comprehensive review of all endophenotypes employed in psychiatric genetics.

The concept of the endophenotype was introduced to psychiatry over 30 years ago by Gottesman & Shields (1973), but its popularity is more recent: there are eight PubMed entries before 2000 compared to 150 in the current century. Gottesman & Shields (1973) adapted the term from a 1966 paper that attributed the geographical distribution of grasshoppers to the insects' 'endophenotype' (John & Lewis, 1966), a neologism alluding to a phenotype that was microscopic and internal, and therefore obscure to casual observation. Endophenotypes in psychiatry retain the notion of an internal process, but one that can be objectively measured, ideally in a robust and reliable fashion, a characteristic often lacking in the diseases with which they are associated.

Gottesman's definition of an endophenotype is that it should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease is not (i.e. state independent), and be found in non-affected family members at a higher rate than in the population (Gottesman & Gould, 2003). The criterion of state independence was modified to take into account the

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importance of epigenetic and developmental factors so that the endophenotype can be manifest only at a certain age and/or after a challenge (in the same way that a glucose challenge is used for a glucose tolerance test) (Hasler *et al.* 2006). Others have added criteria that require endophenotypes to be part of the causal process by which disease arises (Lavori *et al.* 2002), or at least be involved in a biologically plausible mechanism of pathogenesis (Tsuang *et al.* 1993; Castellanos & Tannock, 2002), or, following Almasy & Blangero (2001), require that an endophenotype 'should be continuously quantifiable, should predict disorder probabilistically and should be closer to the site of primary causative agent (whether genetic or environmental) than to diagnostic categories'. It has also been suggested, that 'priority should be given to endophenotypes that are based or anchored in neuroscience' (Doyle *et al.* 2005).

Table 1 lists commonly investigated endophenotypes in psychiatry and reveals a number of features. First, a small number of endophenotypes have attracted disproportionate attention. Second, work on many endophenotypes often predates the development of the endophenotype concept and goes beyond its concern with genetics. Interest in endophenotypes reflects a longstanding interest in investigating the biological correlates of psychiatric disease. Third, endophenotypes can be categorized into six groups: anatomical, developmental, electrophysiological, metabolic, sensory or psychological/cognitive. Fourth, we identified papers claiming endophenotypes for just seven psychiatric disorders. Together, these observations indicate that there is plenty of scope to find new endophenotypes in psychiatry, both by analysis of other psychiatric disorders and by searching for new features that have the relevant characteristics.

One important reason for the popularity of endophenotypes is that they are believed to improve the chances of detecting at a molecular level the genetic variants that contribute to disease susceptibility (Freimer & Sabatti, 2003, 2004). We can summarize the argument as follows: endophenotypes provide a genetically tractable target, one that lies in the gap between gene and disease process, so that by dissecting their genetic basis we would understand something about the biology of a psychiatric disease. An example will clarify the idea.

Consider the difficulties of determining the molecular basis of schizophrenia. We have convincing evidence from twin, family and adoption studies that there is a substantial genetic contribution to the illness (Kendler & Diehl, 1993). Although diagnosis is not easy, the limitations of the diagnostic categories and the potential overlaps with other disorders are appreciated. Consequently we can categorize patients in ways that allow genetic analysis. Nevertheless, mapping genetic determinants by linkage or identifying genetic variants by association has proved extremely difficult, an observation that can be explained by assuming that schizophrenia has a complex genetic architecture, consisting of multiple genetic effects that individually alter susceptibility by a small degree and operate via interactions with each other and the environment (Riley & Kendler, 2006). The complex genetic architecture means that gene finding, using current methodologies, is extremely hard. Despite an enormous and rapidly growing molecular genetic literature, only a handful of candidate genes have been identified and there remains considerable controversy regarding the reliability of these findings (Riley & Kendler, 2006).

An attractive alternative is to work with endophenotypes because 'endophenotypes represent more defined and quantifiable measures that are envisioned to involve fewer genes, fewer interacting levels and ultimately activation of a single set of neuronal circuits. The fewer the pathways that give rise to an endophenotype, the better the chances of efficiently discovering its genetic and neurobiological underpinnings' (Gottesman & Gould, 2003). In short, the genetic basis of endophenotypes is assumed to be less complicated than that of their cognate psychiatric illness, their genetic determination is more direct, and, in consequence, they are potentially more tractable to genetic dissection than the disease states themselves. This presumption is made in most papers that seek to document endophenotypes, but has not so far been rigorously tested, due in large part to the paucity of relevant genetic studies. Our aim in this review is to find out whether the genetic basis of endophenotypes is indeed more tractable to genetic dissection than that of

Table 1. *Endophenotype measures in psychiatric disease*

Disease	Type of deficit	Endophenotype measure	Reference
ADHD	Psychological	Attention deficits (measured by the CPT)	Oh *et al.* (2003)
ADHD	Psychological	Delay gradients, temporal processing, working memory	Castellanos & Tannock (2002)
ADHD	Psychological	Executive performance: response inhibition	Slaats-Willemse *et al.* (2003)
Alcoholism	Electrophysiological	EEG coherence (cortical synchronization)	Winterer *et al.* (2003)
Alcoholism	Electrophysiological	Oscillatory correlates during cognitive processing	Kamarajan *et al.* (2004)
Alcoholism	Electrophysiological	Event-related potential: P300 amplitude	Prabhu *et al.* (2001); Carlson *et al.* (2002)
Anxiety	Metabolic	Cortisol secretion	Goldsmith & Lemery (2000)
Anxiety	Psychological	Perception of affect	Bolte & Poustka (2003)
Anxiety	Psychological	Personality	Smoller & Tsuang (1998)
Autism	Developmental	Age at first word	Alarcon *et al.* (2002, 2003)
Autism	Psychological	Spatial memory deficits	Koczat *et al.* (2002)
Bipolar disorder	Anatomical	MRI hyperintensities	Ahearn *et al.* (2002)
Bipolar disorder	Metabolic	Circadian rhythm	Benedetti *et al.* (2004)
Bipolar disorder	Metabolic	Basal intracellular calcium levels	Yoon *et al.* (2001)
Bipolar disorder	Metabolic	Reduced 5-HTT function	Leboyer *et al.* (1999)
Bipolar disorder	Psychological	Response to tryptophan depletion	Quintin *et al.* (2001); Sobczak *et al.* (2002)
Bipolar disorder	Psychological	Prefrontal cognitive function (measured by WCST)	Rybakowski *et al.* (2003)
Bipolar disorder	Psychological	Subthreshold mood lability	Perugi & Akiskal (2002)
Depression	Metabolic	Occupancy of 5-HT_{1A} autoreceptors by pindolol	Rabiner *et al.* (2002)
Depression	Metabolic	Changes in the HPA axis	Kuenzel *et al.* (2002)
Depression	Metabolic	Depressive response to tryptophan depletion	Moreno *et al.* (2002)
Depression	Psychological	Personality	Willis-Owen *et al.* (2005)
Schizophrenia	Anatomical	Cerebellar abnormalities	Marcelis *et al.* (2003)
Schizophrenia	Anatomical	Olfactory bulb volumes	Turetsky *et al.* (2003)
Schizophrenia	Anatomical	Ventricular enlargement	Garver *et al.* (1999); McDonald *et al.* (2002)
Schizophrenia	Anatomical	Decreased grey matter in insular and left entorhinal cortex	Yoneyama *et al.* (2003)
Schizophrenia	Anatomical	Temporal lobe grey matter abnormalities	Dickey *et al.* (1999)
Schizophrenia	Electrophysiological	Exploratory eye movement	Takahashi *et al.* (2003)
Schizophrenia	Electrophysiological	Event-related potential: mismatch negativity amplitude	Michie *et al.* (2002); Umbricht *et al.* (2003); Bramon *et al.* (2004)
Schizophrenia	Electrophysiological	Event-related potential: P300 and P50 responses	Blackwood (2000); Freedman *et al.* (2000); Turetsky *et al.* (2000); Cadenhead (2002); Cadenhead *et al.* (2002); Malone *et al.* (2002); Myles-Worsley (2002); Raux *et al.* (2002)
Schizophrenia	Metabolic	Niacin skin test	Smesny *et al.* (2003)
Schizophrenia	Sensory	Olfactory sensitivity	Kanes *et al.* (2003)
Schizophrenia	Psychological	Personality	Carmine *et al.* (2003*a*, *b*); Mityushina *et al.* (2003)
Schizophrenia	Psychological	Event-related potential: prepulse inhibition	Cadenhead *et al.* (1996, 1997, 1999); Braff *et al.* (2001); Swerdlow *et al.* (2002)
Schizophrenia	Psychological	Executive performance	Dollfus *et al.* (2002)
Schizophrenia	Psychological	Spatial and verbal memory	Cannon *et al.* (2001); Krabbendam *et al.* (2001); Myles-Worsley & Park (2002); Tuulio-Henriksson *et al.* (2002, 2003); Appels *et al.* (2003); Gasperoni *et al.* (2003); Glahn *et al.* (2003)
Schizophrenia	Psychological	Verbal and spatial attentional processes	Chen & Faraone (2000); Cornblatt & Malhotra (2001)
Schizophrenia	Sensory	Activity of magnocellular visual pathway	Bedwell *et al.* (2003)
Schizophrenia	Sensory	Smooth pursuit eye movements	Amador *et al.* (1995); Clementz *et al.* (1995); Gooding *et al.* (2000); Curtis *et al.* (2001); Ross *et al.* (2002); Rybakowski & Borkowska (2002); Rybakowski *et al.* (2002); Calkins *et al.* (2003, 2004); Gooding *et al.* (2003); Kathmann *et al.* (2003); Ettinger *et al.* (2004, 2006); Ross *et al.* (2005)

ADHD, Attention deficit hyperactivity disorder; CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Task.

Table 2. *Meta-analyses of case-control genetic association studies indicating possible association with schizophrenia*

Reference	Year	Gene	Cases	Controls	*k*	*p* value	OR
Glatt *et al.* (2003)	2003	*DRD2*	3733	5373	24	0·007	1·3
Abdolmaleky *et al.* (2004)	2004	*5-HT$_{2A}$*	4632	4410	31	0·015	1·1
Fan & Sklar (2005)	2005	*SLC6A4*	2177	2369	12	0·00014	1·2
Ma *et al.* (2006)	2006	*G72/G30*	1125	1126	2	0·001	1·2
Talkowski *et al.* (2006)	2006	*RGS4*	3486	3755	8	0·01	1·2

OR, Odds ratio.

psychiatric disease. In order to do so, we need to establish criteria by which to assess whether a phenotype is likely to be genetically tractable.

Genetic effect sizes in psychiatric disorders

A critical measure of the genetic architecture of a phenotype is the effect size of a locus, by which we mean the extent to which a locus contributes to the variance of a phenotype or, as in the case here when disease outcome is involved, the extent to which it increases the risk of disease susceptibility. The power to detect an allele with a given relative risk depends on the size of the odds ratio, or percentage of phenotypic variance explained, and also on the allele frequency. For a locus with two alleles, power to detect is maximal when the allele frequency is 0·5 and the relative risk is large. This is the characteristic we expect to find at loci that contribute to disease susceptibility in a genetically tractable phenotype.

Can we establish the effect size that would make detection relatively straightforward? Instead of an absolute criterion for effect size, we can instead establish a relative one: we can compare the effect sizes of loci that contribute to psychiatric disease with those of loci contributing to variation in endophenotypes. Are the latter larger? Our problem is that there are very few robust estimates of the effect sizes for susceptibility loci in either psychiatric disease or endophenotypes. One approach to obtain good estimates is to combine studies using meta-analytical techniques.

Table 2 lists results from those meta-analyses of candidate genes for susceptibility to schizophrenia that found evidence of a positive genetic association. The summary presented suggests that genetic effects are small. The average odds ratio for the associations is 1·2, equivalent to ~0·2% of the phenotypic variance, a figure consistent with that obtained from meta-analyses of other complex traits (Ioannidis *et al.* 2001).

This odds ratio is useful as it allows us also to estimate the size of studies needed to detect such effects and thereby assess the value of individual studies. Table 3 illustrates the total number of cases required (assuming that the total sample would in addition include an equal number of controls) in order to achieve 80% power to detect a range of effect sizes for a range of minor allele frequencies. As we can see, the majority of individual primary studies conducted are likely to be grossly under-powered to detect effect sizes of the magnitude indicated by the meta-analyses.

For the discussion that follows next, it is important to consider the results of one negative meta-analysis. We recently conducted a meta-analysis of case-control genetic association studies of the *COMT* Val$^{158/108}$ Met polymorphism in healthy control groups and clinically diagnosed schizophrenia patients (Munafo *et al.* 2005). The *COMT* gene has been regarded as a promising candidate gene for schizophrenia for some time, as it is the gene coding for the catechol *O*-methyltransferase enzyme, which inactivates catechols at post-synaptic sites in the human brain. *COMT* contains a functional polymorphism, a single nucleotide polymorphism at position 158/108 that results in a change from valine (Val) to methionine (Met) (Chen *et al.* 2004).

The results of our meta-analysis, which included data from 18 published studies, did not support an association between the *COMT* Val allele and schizophrenia case status. We concluded that if a genuine association exists between the *COMT* gene and schizophrenia, the

Table 3. *Power analysis*

Prev.	Alpha	Odds ratio	Power 80%			Power 90%		
			Minor allele frequency					
			0·1	0·3	0·5	0·1	0·3	0·5
1%	0·05	2	139	69	67	186	93	90
1%	0·01	2	207	103	100	263	132	128
1%	0·001	2	302	151	147	370	185	179
1%	0·05	1·6	325	154	143	435	206	191
1%	0·01	1·6	483	229	212	616	292	270
1%	0·001	1·6	706	335	310	865	410	380
1%	0·05	1·2	2394	1066	929	3205	1426	1244
1%	0·01	1·2	3562	1586	1382	4538	2020	1761
1%	0·001	1·2	5208	2318	2021	6376	2838	2474
5%	0·05	2	127	64	62	169	85	83
5%	0·01	2	188	95	93	240	121	118
5%	0·001	2	275	139	135	337	170	166
5%	0·05	1·6	297	141	131	397	189	176
5%	0·01	1·6	442	211	196	563	268	249
5%	0·001	1·6	646	308	286	790	377	350
5%	0·05	1·2	2198	980	856	2942	1312	1145
5%	0·01	1·2	3270	1458	1273	4166	1857	1622
5%	0·001	1·2	4781	2131	1861	5853	2610	2279
10%	0·05	2	112	57	56	150	76	75
10%	0·01	2	166	85	83	212	108	106
10%	0·001	2	243	124	122	298	152	149
10%	0·05	1·6	264	126	118	353	169	158
10%	0·01	1·6	392	188	176	500	240	224
10%	0·001	1·6	573	275	257	702	337	315
10%	0·05	1·2	1964	878	768	2629	1175	1028
10%	0·01	1·2	2923	1306	1143	3724	1664	1456
10%	0·001	1·2	4273	1909	1671	5231	2338	2045

Prev., Prevalence.

risk conferred is likely to be extremely small, with the largest (albeit non-significant) effect size observed in our meta-analysis being an odds ratio of 1·13, accounting for less than 0·2% of the phenotypic variance. Therefore, given a Val allele frequency of 50% and a disease prevalence of 1%, a sample consisting of in excess of 900 cases and an equal number of controls would be required to detect this effect with 80% power at a relatively non-conservative alpha of 0·05 (Table 3).

Can endophenotype measures afford larger effect sizes?

We need next to examine the genetic architecture of endophenotypes. We start by considering some of the most heavily investigated endophenotypes in schizophrenia, measures of neuropsychological dysfunction, and particularly those that reflect activity in the prefrontal and temporo-limbic systems (Cannon *et al.* 2000). Abnormalities of working memory, episodic learning, attention and reaction time aggregate in the families of schizophrenia patients and probably arise from a common genetic susceptibility (Cannon *et al.* 2000), as expected for an endophenotype of schizophrenia.

One reason for the interest in working memory is because it may reflect function in the meso-cortical dopamine (DA) pathway. Experimental manipulation of DA metabolism by pharmacological challenge in humans and animals supports the assumption that the DA system is involved in cognition: reduced DA transmission in the rat prefrontal cortex impairs cortical-dependent cognition (Jentsch *et al.* 1997), administration of a selective inhibitor of COMT improves cognitive function (including working memory) in patients with Parkinson's disease (Gasparini *et al.* 1997), while injection of D_1 antagonists into the dorsolateral prefrontal cortex impairs tasks that require working memory (Sawaguchi & Goldman-Rakic, 1991; Williams & Goldman-Rakic, 1995). As mentioned above, COMT plays an important role in DA metabolism in the frontal cortex and the Val/Met polymorphism is a critical factor in determining COMT efficiency: the Val isoform has higher activity which may lead to lower synaptic DA levels in the prefrontal cortex (Chen *et al.* 2004). Thus there is a strong prior hypothesis that implicates DA regulation in prefrontal cortical function, and particularly that variation in *COMT* genotype could be associated with an endophenotype of schizophrenia, even if it is not associated with schizophrenia case status (Munafo *et al.* 2005). Consequently a number of investigators have carried out genetic studies of *COMT* genotype and cognitive function. These studies allow us to compare the effect sizes observed in case-control studies of psychiatric disease with those observed in endophenotype studies.

COMT genotype and Wisconsin Card Sorting Task performance

We carried out a meta-analysis of published studies reporting data on the association between *COMT* genotype and Wisconsin Card Sorting Task (WCST) performance (in particular, perserverative errors), a recognized measure of precortical function (Goldberg & Weinberger, 1988). Recall that our recent meta-analysis of *COMT* genotype and schizophrenia case status

Table 4. *Studies of* COMT *genotype and WCST perseverative errors*

Author	Year	Location	Subjects	Ethnicity	Met/Met			Val/Met + Val/Val		
					Mean	S.D.	*n*	Mean	S.D.	*n*
Egan *et al.* (2001) (a)[a]	2001	NIMH	SZ	European	34·00	7·41	28	38·13	14·99	147
Egan *et al.* (2001) (b)[a]	2001	NIMH	Sibs of SZ	European	45·00	8·74	39	45·25	12·68	183
Egan *et al.* (2001) (c)[a]	2001	NIMH	Healthy	European	45·00	4·43	10	50·67	7·80	45
Bilder *et al.* (2002)	2002	New York	SZ	Mixed	44·80	21·10	4	49·61	27·73	41
Joober *et al.* (2002) (a)	2002	Quebec	SZ	N.A.	19·42	16·87	18	34·05	25·10	76
Joober *et al.* (2002) (b)	2002	Quebec	Healthy	N.A.	16·19	20·29	13	10·47	10·75	18
Malhotra *et al.* (2002)	2002	NIMH	Healthy	Mixed	7·46	4·01	13	12·63	10·14	60
Tsai *et al.* (2003)	2003	Taipei	Healthy	Asian	14·20	8·00	6	17·76	11·41	114
Mattay *et al.* (2003)	2003	NIMH	Healthy	European	7·70	2·00	6	12·85	8·75	11
Rosa *et al.* (2004) (a)	2004	Barcelona	SZ	European	26·90	22·70	15	21·06	12·93	60
Rosa *et al.* (2004) (b)	2004	Barcelona	Sibs of SZ	European	11·20	7·30	16	17·40	13·44	63
Taerk *et al.* (2004)[a]	2004	Quebec	ADHD	N.A.	100·60	12·20	29	98·38	12·70	89
Galderisi *et al.* (2005)	2005	Naples	SZ	European	27·80	21·92	28	27·57	17·89	78
Bruder *et al.* (2005)	2005	New York	Healthy	Mixed	8·60	9·40	43	10·97	10·51	201
Ho *et al.* (2005) (a)	2005	Iowa	Healthy	European	8·22	5·92	18	7·45	4·33	66
Ho *et al.* (2005) (b)	2005	Iowa	SZ	European	12·49	10·16	38	11·75	7·30	121
Lipsky *et al.* (2005)	2005	Washington	Brain injury	Mixed	11·20	6·20	25	12·70	12·17	88
Ohnishi *et al.* (2006) (a)	2006	Tokyo	SZ	Asian	Data not available			Data not available		
Ohnishi *et al.* (2006) (b)	2006	Tokyo	Healthy	Asian						
Minzenberg *et al.* (2006) (a)	2006	New York	SPD	European	9·00	2·65	3	16·30	15·00	20
Minzenberg *et al.* (2006) (b)	2006	New York	NSPD	European	9·78	9·26	18	10·91	9·68	33
Minzenberg *et al.* (2006) (c)	2006	New York	Healthy	European	10·50	10·38	4	10·11	9·69	18
Rybakowski *et al.* (2006)	2006	Poland	Healthy	European	19·50	11·72	24	16·47	9·99	55
Szoke *et al.* (2006) (a)	2006	France	SZ	European	12·03	14·91	23	15·57	16·03	131
Szoke *et al.* (2006) (b)	2006	France	BPD	European	29·22	19·52	15	21·21	19·36	43
Szoke *et al.* (2006) (c)[b]	2006	France	Healthy	European	12·17	11·50	30	15·65	11·68	63

WCST, Wisconsin Card Sorting Task; NIMH, National Institute of Mental Health; SZ, schizophrenia; ADHD, attention deficit hyperactivity disorder; SPD, schizotypal personality disorder; NSPD, non-schizotypal personality disorder; BPD, bipolar disorder; N.A., not available.

[a] Scoring of normalized *t* scores reversed to give consistent effect size estimate.

[b] Includes healthy controls and unaffected first-degree relatives of SZ and BPD patients.

(Munafo *et al.* 2005) described above did not offer any evidence in support of association between the gene and the disease, so a positive association with the endophenotype would be evidence that the endophenotype strategy is more powerful, regardless of the effect size. Analysis of the association between *COMT* genotype and WCST performance should provide a good test of the value of the endophenotype approach in genetics.

We searched for relevant publications in PubMed, PsycInfo and Medline, up to 31 May 2006, using the search terms 'Wisconsin', 'card sorting', 'WCST', 'COMT', 'catechol *O*-methyl transferase'. Bibliographies of all articles obtained in this way were hand-searched for additional references. Data extraction and analysis procedures were similar to those employed in our previous meta-analyses (Munafo *et al.* 2005). Briefly, a fixed-effects framework, using inverse variance methods, was employed initially, and the assumption that the effect of allele frequency is constant across samples checked using a χ^2 test of goodness of fit for homogeneity. When there was evidence of significant association in the presence of significant between-sample heterogeneity, the analysis was re-run using a random-effects framework, using Der Simonian and Laird methods.

A total of 16 studies (Egan *et al.* 2001; Bilder *et al.* 2002; Joober *et al.* 2002; Malhotra *et al.* 2002; Mattay *et al.* 2003; Tsai *et al.* 2003; Rosa *et al.* 2004; Taerk *et al.* 2004; Bruder *et al.* 2005; Galderisi *et al.* 2005; Ho *et al.* 2005; Lipsky *et al.* 2005; Minzenberg *et al.* 2006; Ohnishi *et al.* 2006; Rybakowski *et al.* 2006; Szoke *et al.* 2006) published between 2001 and 2006 and comprising 26 independent samples were identified by the search strategy and met the inclusion criteria (Table 4). Where data were not available in an appropriate format for inclusion, we attempted to contact authors directly. Data from two studies (Egan *et al.* 2001; Taerk *et al.* 2004) comprised normalized *t* scores (i.e. higher scores

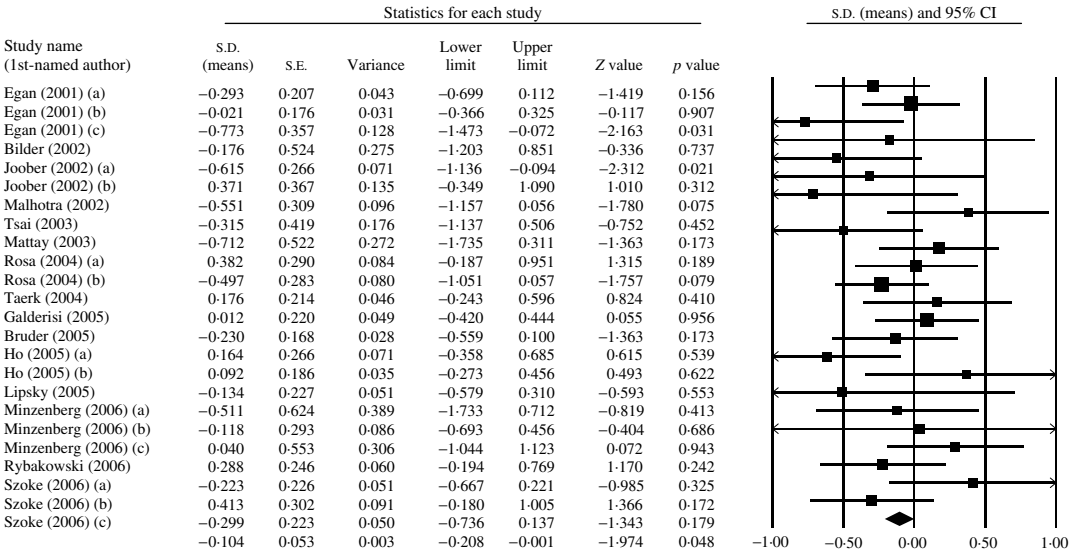

FIG. 1. Meta-analysis of association of *COMT* genotype with WCST performance (perseverative errors). Meta-analysis indicates marginal evidence of association between *COMT* genotype and WCST performance, with a direction of effect consistent with increased perseverative errors in the Val/Met + Val/Val group compared to the Met/Met group. Bars represent individual study 95% confidence intervals, with a central block proportional to study size. The summary diamond bar represents the summary effect size estimate and 95% confidence interval.

reflecting better performance) and were reversed for consistency with other studies. One study (Ohnishi *et al*. 2006), comprising two independent samples, had to be excluded because we could not obtain appropriate data.

A fixed-effects model indicated evidence of association between *COMT* genotype and WCST performance ($k=24$, $Z=1{\cdot}97$, $p=0{\cdot}048$), with increased perseverative errors in the Val/Met + Val/Val group compared to the Met/Met group ($d=0{\cdot}10$). There was no evidence of between-sample heterogeneity [$\chi^2(23)=30{\cdot}06$, $p=0{\cdot}148$]. These data are presented graphically in Fig. 1.

Given evidence that the first published study of a genetic association frequently represents an over-estimation of the true effect size (Trikalinos *et al*. 2004), we re-ran our analysis excluding data from the three samples reported in the first published study (Egan *et al*. 2001). This resulted in non-significant evidence for association ($p=0{\cdot}166$) and a reduction in the pooled effect-size estimate ($d=0{\cdot}08$).

Our meta-analysis shows that if a genuine association exists between the *COMT* gene and WCST performance, the likely effect size is a standardized mean difference of 0·10, accounting for less than 0·5% of the phenotypic variance. Therefore, given a Val allele frequency of 50%, a sample consisting of in excess of 1700 subjects would be required to detect this effect with 80% power at a relatively non-conservative alpha of 0·05.

One potential criticism of the use of WCST performance as a schizophrenia endophenotype is that it reflects a complex behavioural phenotype which may only partially recruit prefrontal function. A more cognitively 'pure' task which more specifically recruits the prefrontal cortex may, therefore, represent a better assay for the purposes of genetic dissection. We consider next one such phenotype, the N-Back working memory task.

It is well-established that schizophrenia is associated with a deficit in working memory (Lee & Park, 2005), and is regarded as a cardinal cognitive symptom. The N-Back task requires participants to monitor a series of stimuli and to respond whenever a stimulus is presented that is the same as the one presented N trials previously, where N is a pre-specified integer, usually 1, 2, or 3. The task requires online monitoring, updating, and manipulation of remembered information and therefore places

Table 5. *Studies of* COMT *genotype and N-Back 2 performance* (*% accuracy*)

					Met/Met			Val/Met + Val/Val		
Author	Year	Location	Subjects	Ethnicity	Mean	S.D.	*n*	Mean	S.D.	*n*
Goldberg *et al.* (2003) (a)	2003	NIMH	SZ	N.A.	0·54	0·22	39	0·48	0·23	109
Goldberg *et al.* (2003) (b)	2003	NIMH	Sibs of SZ	N.A.	0·72	0·19	57	0·67	0·20	198
Goldberg *et al.* (2003) (c)	2003	NIMH	Healthy	N.A.	0·78	0·18	50	0·76	0·19	152
Stefanis *et al.* (2004)	2004	Athens	Healthy	European	87·33	7·42	96	87·66	7·80	362
Bruder *et al.* (2005)[a]	2005	New York	Healthy	Mixed	3·65	0·66	66	3·66	0·55	335
Bertolino *et al.* (2006)	2006	Bari	Healthy	N.A.	88·17	7·47	14	79·24	6·40	48

NIMH, National Institute of Mental Health; SZ, schizophrenia; N.A., not available.
[a] Overall measure of sensitivity for detecting targets and avoiding non-targets (*d'*).

demands on key processes within working memory. Across studies, many different types of stimuli have been used via various input modalities (visuospatial, auditory, and olfactory) making demands on different processing systems.

A large number of studies have investigated working-memory performance in schizophrenia. Meta-analysis of these studies confirms that task performance is impaired in schizophrenia more than in controls (Lee & Park, 2005), and furthermore, working-memory tasks such as the N-Back have been demonstrated in fMRI investigations to heavily recruit the prefrontal cortex (Carpenter *et al.* 2000); working-memory performance is also highly heritable (Ando *et al.* 2001). N-Back task performance phenotypes satisfy the criteria for an endophenotype of schizophrenia.

COMT genotype and N-Back performance

We carried out a meta-analysis of published studies reporting data on the association between *COMT* genotype and N-Back performance. Recall that a potential criticism of our analysis of WCST data is that the latter represent a complex behavioural phenotype which only partially recruits prefrontal function. Analysis of the association between *COMT* genotype and N-Back performance allows us to investigate an endophenotype that is less subject to this criticism.

We searched for relevant publications in PubMed, PsycInfo and Medline, up to 31 May 2006, using the search terms 'N-Back', 'working memory', 'COMT', 'catechol *O*-methyl transferase'. Data extraction and analysis procedures were identical to those described above.

A total of four studies (Goldberg *et al.* 2003; Stefanis *et al.* 2004; Bruder *et al.* 2005; Bertolino *et al.* 2006) published between 2003 and 2006 and comprising six independent samples were identified by the search strategy and met the inclusion criteria (Table 5). Where data were not available in an appropriate format for inclusion, we attempted to contact authors directly.

A fixed-effects model indicated marginal evidence of association between *COMT* genotype and N-Back performance ($k=6$, $Z=1{\cdot}96$, $p=0{\cdot}050$), with a direction of effect consistent with decreased accuracy in the Val/Met + Val/Val group compared to the Met/Met group ($d=0{\cdot}12$). There was evidence of significant between-sample heterogeneity [$\chi^2(4)=18{\cdot}44$, $p<0{\cdot}002$] and when the analysis was re-run using a random-effects model the evidence for association was no longer significant ($p=0{\cdot}085$). These data are presented graphically in Fig. 2.

Assuming that a genuine association exists between the *COMT* gene and N-Back performance, the likely effect size indicated in our meta-analysis is a standardized mean difference of 0·12, accounting for less than 0·5% of the phenotypic variance. Therefore, given a Val allele frequency of 50%, a sample consisting of in excess of 1700 subjects would be required to detect this effect with 80% power at a relatively non-conservative alpha of 0·05.

One further criticism of the data which we present above is that the genetic architecture of a WCST and N-Back performance may be more complex than that of other endophenotypes. Perhaps other endophenotypes, for example those that involve physiological or anatomical measures, are more proximal to their genetic

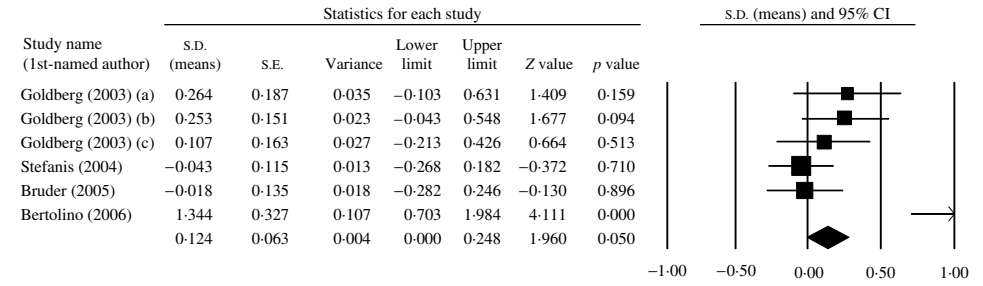

FIG. 2. Meta-analysis of association of *COMT* genotype with N-Back performance (2-Back). Meta-analysis indicates marginal evidence of association between *COMT* genotype and N-Back 2 performance, with a direction of effect consistent with decreased accuracy in the Val/Met + Val/Val group compared to the Met/Met group. Bars represent individual study 95% confidence intervals, with a central block proportional to study size. The summary diamond bar represents the summary effect size estimate and 95% confidence interval.

antecedents. We consider next one such phenotype, the P300 event-related potential.

There has been considerable interest in event-related potentials as a biological marker of schizophrenia from the early 1970s (Roth & Cannon, 1972) when reduced amplitude and delayed latency of the P300 waveform were first reported. An auditory, visual, or somatosensory random and salient stimulus is presented to subjects who must make a response, such as pressing a button. Around 300 ms after the stimulus, an event-related potential can be detected across the scalp. This P300 waveform recorded from the scalp has several components that reflect selective attention and working memory in response to an unexpected change in the environment.

A large number of studies have investigated the P300 in schizophrenia. Meta-analysis of these studies confirms that P300 amplitude reductions and latency delays occur in schizophrenia more than in controls (Bramon *et al.* 2005); furthermore P300 phenotypes are heritable (van Beijsterveldt & van Baal, 2002). P300 phenotypes satisfy the criteria for an endophenotype of schizophrenia.

COMT genotype and schizophrenia P300 amplitude and latency

We carried out a meta-analysis of published studies reporting data on the association between *COMT* genotype and P300 amplitude and latency. Recall that a potential criticism of our analysis of WCST and N-Back data is that they do not represent a truly biological endophenotype marker. Analysis of the association between *COMT* genotype and P300 amplitude and latency should provide a best-case scenario for the value of the endophenotype approach in genetics.

We searched for relevant publications in PubMed, PsycInfo and Medline, up to 31 May 2006, using the search terms 'P300', 'ERP', 'event-related potential', 'COMT', 'catechol *O*-methyl transferase'. Data extraction and analysis procedures were identical to those described above.

A total of three studies (Gallinat *et al.* 2003; Tsai *et al.* 2003; Bramon *et al.* 2006) published between 2003 and 2006 and comprising six independent samples were identified by the search strategy and met the inclusion criteria (Table 6). Where data were not available in an appropriate format, we attempted to contact authors directly, which resulted in all available data being included in the meta-analysis.

A fixed-effects model indicated no evidence of association between *COMT* genotype and P300 amplitude ($k=6$, $Z=0{\cdot}14$, $p=0{\cdot}887$) and latency ($Z=0{\cdot}14$, $p=0{\cdot}892$), although the direction of effect was consistent with increased amplitude and latency in the Val/Met + Val/Val group compared to the Met/Met group ($d=0{\cdot}02$ and $d=0{\cdot}05$ respectively). There was evidence of significant between-sample heterogeneity in the case of amplitude [$\chi^2(5)=11{\cdot}99$, $p=0{\cdot}035$] but not latency [$\chi^2(5)=7{\cdot}22$, $p=0{\cdot}204$]. These data are presented graphically in Fig. 3.

The likely effect size attributable to the *COMT* gene, if genuine, is therefore a standardized mean difference of 0·02, accounting for ~0·01% of the phenotypic variance.

Table 6. *Studies of* COMT *genotype and P300 amplitude and latency*

Author	Year	Location	Subjects	Ethnicity	Met/Met			Val/Met + Val/Val		
					Mean	S.D.	*n*	Mean	S.D.	*n*
					Amplitude					
Tsai *et al.* (2003)	2003	Taipei	Healthy	Asian	11·30	6·00	6	9·00	3·67	49
Gallinat *et al.* (2003) (a)	2003	Germany	SZ	European	11·50	6·10	17	15·31	6·37	141
Gallinat *et al.* (2003) (b)	2003	Germany	Healthy	European	13·40	5·60	48	14·19	6·15	36
Bramon *et al.* (2006) (a)	2006	London	SZ	N.A.	10·72	7·24	16	7·95	6·76	46
Bramon *et al.* (2006) (b)	2006	London	Sibs of SZ	N.A.	10·01	6·02	27	10·59	6·46	64
Bramon *et al.* (2006) (c)	2006	London	Healthy	N.A.	17·06	8·05	13	12·67	8·07	24
					Latency					
Tsai *et al.* (2003)	2003	Taipei	Healthy	Asian	290·30	18·50	6	317·71	31·72	49
Gallinat *et al.* (2003) (a)	2003	Germany	SZ	European	316·60	32·80	17	318·00	32·45	141
Gallinat *et al.* (2003) (b)	2003	Germany	Healthy	European	324·80	44·00	48	328·28	37·41	36
Bramon *et al.* (2006) (a)	2006	London	SZ	N.A.	383·62	57·18	16	391·10	53·29	46
Bramon *et al.* (2006) (b)	2006	London	Sibs of SZ	N.A.	416·61	50·04	28	394·81	60·89	66
Bramon *et al.* (2006) (c)	2006	London	Healthy	N.A.	357·77	51·72	13	357·15	53·21	24

SZ, Schizophrenia; N.A., not available.

We can summarize the results of the meta-analyses by noting that the sample sizes required to detect the genetic loci contributing to endophenotypes are of equivalent size to those required to analyse the cognate psychiatric disease. In short, we find no evidence that the genetic architecture of endophenotypes is any simpler than that of psychiatric illness.

Conclusions

We have so far considered examples where we consider there to be sufficient genetic data available to arrive at an estimate of the effect size. Our conclusions, that the effect sizes found in genetic studies of endophenotypes are not considerably greater than those found in psychiatric diseases, may be biased because we have been limited to studying the *COMT* locus, or because so far no large effects have been found. The first issue is difficult to tackle. Significant associations reported for other genetic loci are based on either a single, or a very small number, of studies, so that we do not yet know how robust these findings are.

Two examples illustrate the point. The first concerns fMRI measures which are difficult to obtain in large numbers of people. Hariri and colleagues reported that a polymorphism in the serotonin transporter gene (*5-HTT*) was associated with the response of the amygdala to fearful stimuli (Hariri *et al.* 2002). In a comparison of two groups of 14 individuals, carriers of the *s* allele at the *5-HTT* gene promoter were found to exhibit an increased amygdala fearful response compared with those homozygous for the *l* allele (Hariri *et al.* 2002): the means of the two groups were 0·28 (S.D. = 0·22) and 0·03 (S.D. = 0·19) with respect to % blood-oxygen-level-dependent (BOLD) signal change for fearful stimuli compared to neutral stimuli. In comparison with the data we have reviewed, this represents an enormous effect size (equivalent to ~40% of phenotypic variance) that could be detected at a significance threshold of 0·05 with just 18 subjects. This finding could be due to chance statistical fluctuation. Indeed, a subsequent study of 92 individuals (including 19 from the first study) carried out by the same group again showed a significant effect, but with a reduction in the effect size. The reported mean values were this time 0·16 and 0·03 for the two groups (Hariri *et al.* 2005), equivalent to an effect size of just over 10% of the phenotypic variance. Additional studies are needed to confirm whether the effect is indeed this large.

The second example is the investigation into the genetic basis of an event-related potential, the P50. This is another endophenotype for schizophrenia, in which two stimuli are presented. At interstimulus intervals exceeding 8 s, two event-related potentials are detected. If the

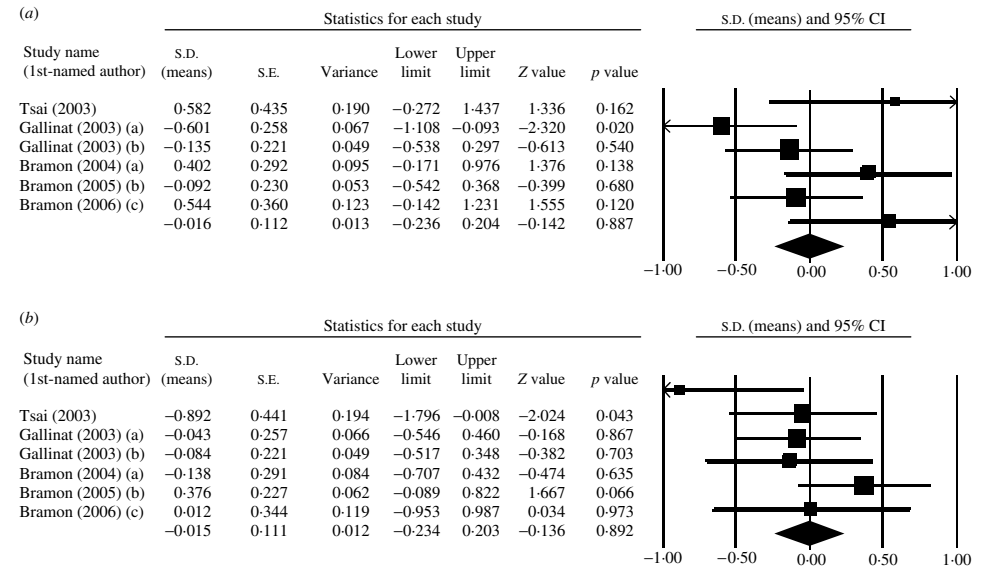

FIG. 3. Meta-analysis of association of *COMT* genotype with P300 amplitude and latency. Meta-analysis indicates no evidence of association between *COMT* genotype and P300 amplitude (*a*) and latency (*b*), with a direction of effect consistent with increased amplitude and latency in the Val/Met + Val/Val group compared to the Met/Met group. Bars represent individual study 95% confidence intervals, with a central block proportional to study size. The summary diamond bar represents the summary effect size estimate and 95% confidence interval.

second stimulus occurs within 8 s of the first, normal subjects inhibit the response to the second stimulus. Schizophrenia subjects have a deficit in such inhibition, a finding supported by a recent meta-analysis (Bramon *et al*. 2005). The difference in inhibition is maximal when the second stimulus follows the first by 500 ms (Adler *et al*. 1982).

Interest in the molecular basis of the P50 phenotype was spurred by a 1997 report that a locus on chromosome 15 had been identified by linkage mapping (Freedman *et al*. 1997). The report was important because the locus contained a gene, the alpha 7-nicotinic acid receptor, which was later reported by the same group to be significantly associated with failure to inhibit the P50 auditory-evoked potential (Leonard *et al*. 2002). Furthermore, the group has presented evidence that functional variants in the promoter of the gene are present at significantly greater frequencies in schizophrenia subjects compared to controls (Leonard *et al*. 2002). A second group has independently reported that a 2 bp deletion in exon 6 of the gene and a polymorphism in the promoter are associated with the P50 phenotype (Raux *et al*. 2002; Houy *et al*. 2004) but not with schizophrenia. Clearly, given the findings for other complex traits, these results must be replicated in large samples if they are to be regarded as genuine.

The two examples encourage the view that some endophenotypes may be more genetically tractable than the ones we have discussed. Our concern is that as additional data accumulate these findings may turn out to be false positives, or at least the effect sizes will be much smaller than initially reported, as has often been found with genetic association studies (Trikalinos *et al*. 2004). Indeed, removing samples from the first published study in our analysis of WCST data rendered the association with *COMT* genotype non-significant and reduced the pooled effect size estimate by 20%.

The second issue is whether the current failure to find large genetic effects in endophenotypes can be read as a general indication of the complexity of genetic architecture for all phenotypes. Endophenotypes are assumed to have a relatively simple genetic architecture because there are relatively few pathways from gene to phenotype. The consequence is that sequence

variants interact relatively directly with the phenotype so the correlation should be easier to detect. We have so far examined this assumption by investigating what is known about the genetic architecture of commonly investigated endophenotypes, and have shown that there is little evidence that it is considerably simpler than that of psychiatric disease. Perhaps we happen to have selected those phenotypes that have a complex genetic architecture. In the absence of detailed genetic analyses of multiple endophenotypes we cannot gainsay this point. However, we are able to approach this question from another point of view. We can ask what is known about the genetic architecture of phenotypes which have a much closer relationship to their genetic basis than endophenotypes for psychiatric disease.

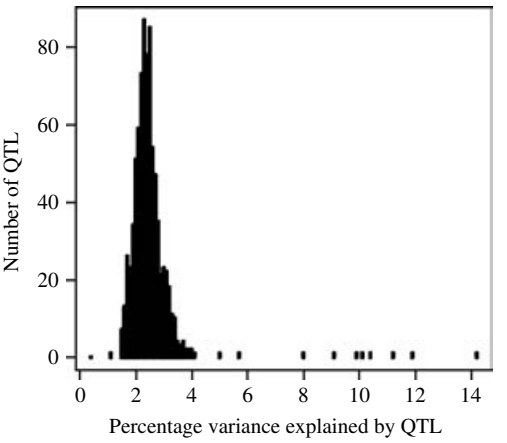

FIG. 4. Distribution of effect sizes of 843 mouse quantitative trait loci (QTL).

Analyses of model organisms provide the relevant information. We will discuss two examples. The first is genetic analysis of phenotypes in the mouse, from which we have robust genome-wide association data for multiple phenotypes, behavioural and physiological, and associated estimates of locus effect sizes. These data allow us to compare the genetic architecture of behavioural phenotypes with those that would qualify as endophenotypes: for instance measures of electrophysiology, biochemistry, haematology and immunology. The drawback is that mouse models of psychiatric disease are imperfect, so that inferences drawn from the mouse data may be misleading. Nevertheless, we have no reason to expect the relationship between endophenotypes and behavioural phenotypes to be different in rodents and humans.

Reviews of the distribution of locus effect sizes show no difference between physiological and behavioural phenotypes (Flint *et al.* 2005). Moreover, in the most detailed analysis to date of the genetic architecture of complex traits in the mouse, among phenotypes there was no significant difference in the number or effect size of loci detected (Valdar *et al.* 2006). Intriguingly, regardless of the phenotype, the genetic effects that were detected explained about the same proportion of the additive variance, suggesting considerable similarity in the genetic architecture of many phenotypes (Valdar *et al.* 2006). Fig. 4 shows the effect sizes of 843 quantitative trait loci (QTL). The phenotypes include measures of anxiety and learning and memory, as well as haematology, immunology, biochemistry, physiology and anatomy. A full description is given in Valdar *et al.* (2006) and on a website (http://gscan.well.ox.ac.uk). Fig. 4 shows that preponderance of small effects. For each of the 100 phenotypes analysed, many loci contribute a small proportion to the variance. Large effect QTL are rare: only ten account for greater than 5% of phenotypic variance, and the mean is 2·2%.

The mouse data indicate that we would not have obtained a simpler genetic architecture by working with any of the physiological, immunological, biochemical or haematological phenotypes in place of the behavioural phenotypes. We would still face the currently demanding challenge of having to identify the molecular basis of many small genetic effects.

The second example addresses the question of the relationship between genetic variants and phenotypes at an extremely immediate level, namely the correlation between DNA sequence variants and variation in the relative abundance of mRNA. Variation in transcript abundance is heritable and it is reasonable to expect that the variation in expression of some genes may correlate with psychiatric disease. Thus a gene expression profile could act as an endophenotype, although currently we do not know which genes show expression patterns correlated with psychiatric disease. Compared to any of the endophenotypes so far analysed (Table 1), variation in the amount of transcript is more

proximal to DNA sequence variation and, if the assumptions about the nature of an endophenotype are correct, the genetic architecture of transcript variation should be relatively simple.

Analyses of gene expression variation in yeast, rodents and humans concur in finding that the genetic architecture of gene expression is polygenic and that the genetic effects are relatively small (Morley *et al*. 2004; Brem & Kruglyak, 2005; Chesler *et al*. 2005; Hubner *et al*. 2005). In yeast, where we have the most reliable estimates, relatively few transcripts have large effects: the median effect size was equivalent to 27% of variation in transcript level, only 16% of loci accounted for more than 60% of variation, and a quarter explained less than 10% (Brem & Kruglyak, 2005). Although estimates of effect size are not as robust in rodents, the available data indicate that the effect sizes are comparable to those found in yeast (Morley *et al*. 2004; Chesler *et al*. 2005; Hubner *et al*. 2005).

Although the effect sizes of loci contributing to variation in mRNA transcript abundance are larger than the effects found in complex traits (which explain less than 1% of the phenotypic variance) effect sizes are relative to the population in which they are measured. A reasonable comparison for the rodent mRNA data is with the effect sizes of QTL found in crosses between inbred strains of mice. Remarkably, the median effect size of QTL is 12% (Flint *et al*. 2005), just under half that of the expression phenotypes. Therefore, even when we consider a phenotype that is directly linked to the genetic constitution of the organism, genetic architecture is not radically different from complex phenotypes.

We have reviewed what is known about the genetic basis of endophenotypes and shown that their genetic architecture may be as complex as that of psychiatric disease. This does not mean there is no advantage to the use of endophenotypes for genetic studies. We have pointed out that the robust, quantitative measures that are typical of many endophenotypes means that they may be suitable for collecting the large samples needed for genetic analysis of complex traits, and may afford more statistically reliable data. We suggest that, along with the frequency and penetrance of a disease-causing allele given in Table 3, the ease and reliability of phenotyping should be factored into power calculations.

There are important limitations to our analysis. First, we have little reliable data about the genetic basis of complex traits in general and psychiatric endophenotypes in particular. Assumptions about the genetic architecture of complex traits depend so far largely on negative findings: our inability to detect robust linkage and association signals is due to lack of power and we have not sufficiently appreciated the genetic complexity. It is possible that, with the completion of the first whole genome association studies when estimates of effect size across the genome are available, a different picture will emerge. A second important limitation is that our review has concentrated on the effect of *COMT* on endophenotypes. Unfortunately there are no other examples where sufficient data have accumulated to be included in meta-analyses. Again, the availability of additional data might alter our results.

However, we think that our conclusions are unlikely to change much: first, studies in genetically more tractable organisms, such as yeast, flies and rodents, confirm the finding of genetic complexity for all phenotypes. The results are not here based on negative results: we have definite evidence of complexity. Second, as we have shown in the example of the genetic analysis of transcriptional abundance, there is no indication that alternative phenotypes will be any easier to deal with. Thus, while endophenotypes may be useful for many reasons, such as providing trait markers of susceptibility to psychiatric illness, for providing biological markers of disease and models for investigating disease process, we do not think they are likely to be any easier to dissect at a genetic level than the disorders to which they are related.

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enabled inclusion in the meta-analyses we report.

Declaration of Interest

None.

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