Review

Specific and common genes implicated across major mental disorders: A review of meta-analysis studies

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A review of meta-analysis studies

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Major efforts have been directed at family-based association and case–control studies to identify the involvement of candidate genes in the major disorders of mental health. What remains unknown is whether candidate genes are associated with multiple disorders via pleiotropic mechanisms, and/or if other genes are specific to susceptibility for individual disorders. Here we undertook a review of genes that have been identified in prior meta-analyses examining specific genes and specific mental disorders that have core disruptions to emotional and cognitive function and contribute most to burden of illness—major depressive disorder (MDD), anxiety disorders (AD, including panic disorder and obsessive compulsive disorder), schizophrenia (SZ) and bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD). A literature review was conducted up to end-March 2013 which included a total of 1519 meta-analyses across 157 studies reporting multiple genes implicated in one or more of the five disorders studied. A total of 134 genes (206 variants) were identified as significantly associated risk variants for MDD, AD, ADHD, SZ or BD. Null genetic effects were also reported for 195 genes (426 variants). 13 genetic variants were shared in common between two or more disorders (APOE e4, ACE Ins/Del, BDNF Val66Met, COMT Val158Met, DAOA G72/G30 rs3918342, DAT1 40-bp, DRD4 48-bp, SLC6A4 5-HTTLPR, HTR1A C1019G, MTHR C677T, MTHFR C677T, MTHFR A1298C, SLC6A4 VNTR and TPH1 218A/C) demonstrating evidence for pleiotropy. Another 12 meta-analyses of GWAS studies of the same disorders were identified, with no overlap in genetic variants reported. This review highlights the progress that is being made in identifying shared and unique genetic mechanisms that contribute to the risk of developing several major psychiatric disorders, and identifies further steps for progress.

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predicted to have a potential role in the illness and examined via a case-control or family-based association study. Many genetic variants have been identified and examined; some with consistency, but more often than not, with only small effects that fail replication (Chanock et al., 2007; Sullivan, 2007). This is unlike other medical conditions such as Parkinson’s disease for which, despite its lower heritability, clear monogenic (single gene) causal risk factors have been clearly established (Burmeister et al., 2008). Therefore, there is a need to provide a synthesis of this data to guide future research activity.

What remains unknown is whether common genes via pleiotropic mechanisms are associated with psychiatric disorders that share similar symptomatology such as unipolar and bipolar affective disorders, or that are more prevalent during adulthood or childhood, or whether other genes are specific to susceptibility for individual disorders. Serious mental disorders are currently diagnosed and differentiated based on clinical symptoms, yet the genetic aetiology of these disorders is a topic of active debate. Genetic association and genome-wide association studies (GWAS) (Huang et al., 2010; Liu et al., 2011; Purcell et al., 2009; Smoller et al., 2013) suggest there is some degree of genetic overlap among specific disorders such as affective disorders and psychosis, but also specific genetic diversity. Genetic pleiotropy, or the impact of one gene on multiple phenotypes, has been reported to account for 17% of the genes or 5% of the single nucleotide polymorphisms (SNPs) associated with complex traits (Serretti and Fabbri, 2013; Sivakumaran et al., 2011). Identification of such genes between disorders can help identify shared molecular pathways between the disorders.

Here, we provide a summary of all meta-analyses conducted to date of genetic association studies of the serious mental disorders contributing a large proportion of the burden of illness in adults and children, unipolar (MDD) and bipolar depression (BD), schizophrenia (SZ), anxiety disorder (AD) and attention-deficit hyperactivity disorder (ADHD). We have chosen this approach, a review of meta-analyses, as it provides an aggregate view of the strength of genetic findings to date, with analyses based on multiple original data sets, and the opportunity to compare information from older studies and combine them with newer, larger studies. Our review includes a focus on SNPs so that we can develop an understanding of the underlying molecular pathways (such as serotonergic, dopaminergic and glutamatergic pathways) in contributing to common and unique clinical symptoms. This is because SNPs are defined by specific changes to the nucleotide base and can be localized to a specific region within a single gene. We have not targeted other elements of genetic modulation such as CNVs or linkage variation because the information provided by these measures is often representative of more pervasive changes across multiple regions or genes and to date, there have been very few studies. For instance, copy-number variations (CNVs) involve changes to larger regions of the genome, ranging from 1000 nucleotide bases to several megabases in size, and linkage studies identify chromosomal regions that can span multiple genes cosegregating within a family. We did also however target meta-analyses of GWAS studies of these same disorders as a comparison. To date the focus has been on increasing sample size and power, and thus there are fewer independent GWAS studies that have been the subject of meta-analysis. The p value of GWAS is also usually very conservative due to multiple testing, which could potentially inflate the false-negative rate of variants with smaller effects due to reduced power.

2. Methods

We searched MEDLINE for all publications available up to end-March 2013 examining meta-analyses of genotypes in the five serious mental disorders. These meta-analyses determined significance at the p < .05 threshold. Our search terms were meta-analysis, association study, gene, depression, depressive disorder, major depression, anxiety disorder, panic disorder, generalized anxiety disorder, phobic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, attention deficit disorder with hyperactivity, schizophrenia, bipolar disorder, bipolar affective disorder, manic-depressive disorder, psychosis, psychotic disorders or manic depression. A supplementary search for additional publications was performed using PUBMED using the same search terms with the limit of ‘meta-analysis’. Meta-analytical studies included in our review were based on the following criteria: (a) published in a peer-reviewed journal in English; (b) reported on effects at the allelic or genotypic level; (c) provided unique estimates for unipolar major depression, anxiety disorder, ADHD, schizophrenia or bipolar disorder; (d) based on case-control or family-based studies; (e) based on two or more studies; (f) reported the risk allele and gene name; and (g) published before end-March 2013. Meta-analyses of GWAS data were also reviewed separately. We identified 12 GWAS meta-analyses studies to date, including 4 studies in MDD (Lee et al., 2012; Lewis et al., 2010; Shyn et al., 2011; Wray et al., 2012), 3 studies in SZ (Jia et al., 2012; Shi et al., 2009; Wang et al., 2012), 2 in ADHD (Ebejer et al., 2013; Neale et al., 2010), 1 in BD (Goes et al., 2012) and 1 in AD (Otowa et al., 2012). We also identified one other study that conducted a meta-analysis across GWAS data of SZ and BD patients combined (Wang et al., 2010).

3. Results

3.1. Distribution of genetic variants

A total of 157 studies or 1519 meta-analyses of multiple genes and/or multiple disorders were included in this review; of these, 378 meta-analyses confirmed significant effects for 134 genes (206 variants) across the range of disorders. Supplementary Table 1 summarizes genetic variants that were included in meta-analyses and contributed a significant effect (p < .05) to these meta-analyses. Information on sample ethnicity is provided as some studies reported multiple meta-analyses (sometimes with different results) when stratified by ethnic origin. As some meta-analyses included the same studies reported in other meta-analyses, this table includes a column called ‘independent study’ to reflect the largest and most recent independent meta-analysis study to date (indicated by ‘+’), with the other meta-analyses that include overlapping studies indicated by a dash (–) for the same genetic variant comparison, in the same ethnic group. The genetic variants that did not survive significance (p > .05) in the meta-analyses are reported in Supplementary Table 2. Null effects were found for 75% of total studies (1141 meta-analyses). Five percent of these null effects conflicted with significant effects reported in Supplementary Table 1 (53 out of 378 confirmed meta-analyses reported in Supplementary Table 1). Supplementary Table 3 provides a direct comparison of the significant findings with the studies showing a conflicting null result, and possible reasons for these discrepancies.

Of the total 1519 meta-analyses reviewed, the majority (63%, n = 966) focused on identifying genes in schizophrenia, of which 199 meta-analyses confirmed a significant gene effect for 50 genes (97 variants). The next disorder of focus was bipolar disorder at 17% (n = 259 meta-analyses) with 98 meta-analyses confirming 46 genes (65 variants); then MDD at 12% (n = 177 meta-analyses) with 43 meta-analyses confirming 27 genes (27 variants); then ADHD at 5% (n = 81) with 25 meta-analyses confirming 8 genes (11 variants); and finally anxiety disorders at 3% (n = 36) with 13 meta-analyses confirming 3 genes (6 variants).
In terms of ethnic distribution, 47% of the significant effects were based in Caucasian samples, then mixed ethnic groups (39%), Asians (12%), South Americans (2%) or in unreported ethnic groups (1.8%). With the exclusion of meta-analyses that contained overlapping studies, Caucasians dominated in studies of BD (78%) and MDD (48%), whereas mixed ethnic groups dominated in ADHD (72%), AD (55%) and SZ (40%). Fig. 1 presents the distribution of the largest and most recent significant independent meta-analyses according to psychiatric disorder and ethnicity.

3.2. Common genetic variants

Fig. 2 summarises the significant common and specific genetic variants across the disorders. Thirteen genetic variants were common to two or more disorders, which may be indicative of genetic pleiotropy. The molecular pathways of these shared variants were mapped to help derive potential underlying mechanisms that may account for shared symptomatology. Identified pathways included serotonergic (SLC6A4 5-HTTLPR, HTR1A C1019G, SLC6A4 VNTR, TPH1 218 A/C), dopaminergic (DAT1 40-bp, DRD4 48-bp, COMT Val158Met), vascular (APOE ε4, ACE Ins/Del, MTHFR C677T, MTHFR A1298C), glutamatergic (DABA G72/G30 rs3918342) and neurotrophic (BDNF Val66Met) pathways.

3.2.1. Serotonergic system

Four polymorphisms within genes that encode for receptors or proteins involved in the serotonergic system were observed across the disorders. The serotonin transporter removes serotonin from the synapse, returning it to the presynaptic neuron where the neurotransmitter can be degraded or released at a later time. The 5-HTTLPR polymorphism in the serotonin transporter gene modulates transcription, with the Short allele shown to have reduced transcriptional efficiency, decreased serotonin uptake and expression, and therefore higher levels of synaptic 5-HT, compared to the Long allele (Karg et al., 2011). Here, the Long 5-HTTLPR variant was implicated as a risk marker in both ADHD and AD (obsessive compulsive disorder; OCD) in mixed and Caucasian cohorts. This suggests that higher levels of serotonin expression (but reduced available synaptic 5-HT) may be underlying symptoms that are common to OCD and ADHD, in particular impaired inhibition of unwanted actions and impulsivity (Sheppard et al., 1999). In contrast, the 5-HTTLPR Short variant was shared between AD (OCD), MDD and BD, highlighting a differential pathway that underlies shared symptomatology between OCD, MDD and BD that is not evident in ADHD and that is impacted by reduced serotonin expression and increased available synaptic 5-HT, such as mood lability (Young and Leyton, 2002).

The serotonin receptor 1A HTR1A C1019G polymorphism was shared across MDD and BD. HTR1A is a G protein-coupled receptor that mediates negative feedback inhibition of serotonergic neurons and signalling in limbic brain regions, including the amygdala. HTR1A C1019G blocks transcriptional repression, thereby increasing autoreceptor expression, with the G variant showing increased negative feedback and reduced serotonin signalling at postsynaptic sites (Fakra et al., 2009). As the G variant was common in both MDD and BD, it may be another gene that contributes to the negative affect and mood liability that defines these disorders.

The serotonergic variants in the Serotonin Transporter SLC6A4 STin2 VNTR and Tryptophan Hydroxylase TPH1 218 A/C were common to BD and SZ. The STin2 VNTR is a transcriptional regulator of serotonin (MacKenzie and Quinn, 1999), with the 12 repeat variant being a more potent regulator of gene expression (Fiskerstrand et al., 1999). TPH1 is the rate-limiting enzyme which catalyses the biosynthesis of serotonin. It is mostly expressed in the cortex and limbic regions and modulates serotonin in neuron growth. The function of the 218 A/C is not yet known (Saetre et al., 2009); however, like the STin2 VNTR, it is possible that the A variant is associated with increased biosynthesis of serotonin in these disorders.

3.2.2. Dopaminergic system

Commonalities in three dopaminergic genes were evident across the disorders. The Val allele of the Catechol-O-methyl transferase COMT Val158Met SNP was found in common across SZ and AD (PD in Caucasians), whereas the Met allele was in common across BD and AD (OCD in particular). COMT inactivates extraneuronal dopamine in the brain, particularly in the amygdala and prefrontal cortex (Hong et al., 1998). The Met allele of the Val158Met polymorphism is associated with a 3- to 4-fold reduction in activity of the COMT enzyme, and increased

Fig. 1. A summary of the number of the largest and most recent significant independent meta-analytical studies of genotype association studies conducted to date (end-March 2013) in major depressive disorder (MDD), anxiety disorder (AD), attention deficit hyperactivity disorder (ADHD), schizophrenia (SZ) and bipolar disorder (BD) according to psychiatric disorder and sample ethnicity. Percentage distributions of each ethnic group per disorder were: MDD (Asian – 10%, Caucasian – 48%, South American – 0%, Mixed – 40%, not reported – 2%); AD (Asian – 9%, Caucasian – 36%, South American – 0%, Mixed – 55%, not reported – 0%); ADHD (Asian – 0%, Caucasian – 22%, South American – 6%, Mixed – 72%, not reported – 0%); SZ (Asian – 20%, Caucasian – 38%, South American – 0%, Mixed – 40%, not reported – 2%); and BD (Asian – 9%, Caucasian – 78%, South American – 0%, Mixed – 13%, not reported – 0%).
dopaminergic activity at synapses (Lachman et al., 1996), suggesting reduced dopamine in corticolimbic pathways may be a risk factor for symptoms common to SZ and PD, but elevated dopamine in the same pathways for symptoms common to BD and OCD.

The 10-repeat variant of the dopamine transporter DAT1 40-bp VNTR (SLC6A3) was commonly implicated across ADHD and MDD. DAT1 has an important role in dopaminergic neurotransmission by mediating the active re-uptake of synaptic dopamine back into the neurons. The VNTR alters the function of DAT1 by regulating gene expression (Michaelhaugh et al., 2001). The 10-repeat allele is abnormally efficient at the re-uptake process (Mill et al., 2002) and underactive in the dopaminergic mesocorticolimbic and nigrostriatal pathways, suggesting reduced dopamine in mesolimbic and striatal pathways is implicated as a risk factor for symptoms common to MDD and ADHD.

The DRD4 48-bp VNTR variant was also implicated across ADHD, MDD, BD and SZ, yet the risk variant was specific to the disorder: the 2-repeat was implicated in MDD and BD, the 4-, 5- and 7-repeats in ADHD, and the 6-repeat in SZ. DRD4 is a G-protein coupled receptor that inhibits adenylyl cyclase and is responsible for neuronal signalling in the mesolimbic system of the brain. This gene contains a polymorphic number (2–10 copies) of tandem nt repeats, with the more common 2- and 7-repeats having a reduced potency for coupling dopamine receptors to adenylyl cyclase compared to 4-repeat alleles (Reist et al., 2007). The relative function of the other alleles (5- and 6-repeats) is not yet known. This suggests reduced dopamine in mesolimbic pathways may contribute towards symptoms that are common to MDD and BD, although the differential impact of the other alleles on ADHD and SZ remains to be verified.

3.2.3. Vascular system

We identified the T allele variant of 5-10-methyltetrahydrofolate reductase MTHR C677T polymorphism to be common across SZ, BD and MDD, and the C allele variant of the MTHR A1298C polymorphism across SZ and BD. MTHR is an enzyme crucial to one-carbon metabolism, a folate-mediated pathway essential for purine and thymidylate biosynthesis, the methylation of DNA and amino acids, and is integral to some neurotransmitter functions (Sugden, 2006). It plays a key role in regulation of one-carbon units between the DNA (nucleotide

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\[\text{footnote}{The term ‘vascular’ is a very broad term used to describe the potential links between these three genes, however we acknowledge that these genes may actually function within different and independent systems which may be more readily appropriate that are presently unknown.}\]
synthesis) and methylation cycle (Frankenburg, 2007; Krebs et al., 2009), with dysfunction of this cycle linked to neural tube defects and the pathogenesis of various disorders including autism, dementia and cardiovascular disease (Kim et al., 2008; Kronenberg et al., 2009; Pasca et al., 2009; Smulders and Stehouwer, 2005; van der Put et al., 2001; Zhang et al., 2008). For the C677T polymorphism, the T variant causes a 35% reduction of enzyme activity relative to the C variant (Froist et al., 1995). Similarly, for the A1298C polymorphism, the C allele is associated with reduced enzyme activity relative to the A variant (van der Put et al., 1998). The DD genotype of the Angiotensin-converting enzyme ACE Insertion/Deletion polymorphism was another variant in common across MDD and BD. ACE is part of the renin-angiotensin system and is involved in the conversion of angiotensin I into angiotensin II, a peptide hormone which stimulates proinflammatory cytokines and interferes with the HPA activation to stress (Wu et al., 2012). The homozygote D allele has been associated with highest levels of the enzyme relative to the homozygote I allele (Zintzaras et al., 2008), suggesting an overactivity of this enzyme may pose as a risk factor for mood disorders such as MDD and BD in responses to stress.

Apolipoprotein E APOE was another gene involved in vascular regulation in common across MDD and SZ. In this case however, the ε4 variant was implicated in SZ versus the ε3 variant in MDD. Apolipoprotein E is a major lipid-binding protein in the brain, with its primary function being to transport lipids between receptors and proteins (Xu et al., 2006). Individuals with the APOE ε4 variant have higher plasma and neuronal levels of cholesterol than carriers of the ε2 or ε3 alleles (Xu et al., 2006). The role of the ε4 variant may therefore implicate a role of elevated cholesterol in risk for SZ; however the relevance of the more common or ‘neutral’ ε3 variant in MDD as a risk indicator is less clear.

3.2.4. Glutamatergic system

The T variant of the d-amino acid oxidase activator DAOA (rs3918342) polymorphism involved in glutamatergic transmission was found in common between SZ and BD. DAOA (also known as G72/G30) encodes a protein that activates d-amino acid oxidase, which in turn degrades the glio transmitter D-serine, an activator of NMDA type glutamate receptors. More recent studies suggest it also modulates DAO function as a negative effector, deaminating D-ε4 variant was implicated in SZ versus the ε3 variant in MDD. Apolipoprotein E is a major lipid-binding protein in the brain, with its primary function being to transport lipids between receptors and proteins (Xu et al., 2006). Individuals with the APOE ε4 variant have higher plasma and neuronal levels of cholesterol than carriers of the ε2 or ε3 alleles (Xu et al., 2006). The role of the ε4 variant may therefore implicate a role of elevated cholesterol in risk for SZ; however the relevance of the more common or ‘neutral’ ε3 variant in MDD as a risk indicator is less clear.

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3.2.5. Neurotrophic system

The Val allele of the brain derived neurotrophic factor BDNF Val66Met variant was commonly implicated in SZ and BD. BDNF has a direct impact on neuronal growth and plasticity in frontal, hippocampal and amygdala networks (Conner et al., 1997; Rattiner et al., 2004), with the Met allele associated with a functional decrease in activity-dependent secretion of BDNF, and the Val allele associated with increased synaptic plasticity and growth (Egan et al., 2003). In SZ and BD, the Val allele could therefore promote increased synaptic connections between certain brain regions that underpin common symptoms. For instance, white matter integrity has been found to be increased in schizophrenia in specific areas such as the superior longitudinal fasciculus and corpus callosum, consistent with a role of positive symptoms of schizophrenia such as delusions (Alba-Ferrara and De Erausquin, 2013), which are also a symptom of BD.

3.3. Specific genetic variants

3.3.1. Major depressive disorder (MDD)

We identified 27 significant genetic variants implicated in MDD (Fig. 2 and Supplementary Table 1), two of which conflicted with null effects, namely MTHFR C677T and 5-HTTLPR (Supplementary Table 3). For MTHFR C677T, three studies confirmed the T allele or CT/TT genotypes in MDD in mixed ethnic cohorts (Gilbody et al., 2006; Lewis et al., 2006; Lopez-Leon et al., 2008) (Supplementary Table 1), but one study reported conflicting null effects in mixed ethnic samples for the T allele and TT genotype (Zintzaras, 2006), albeit in much smaller cohorts relative to the significant studies suggesting that the conflicting results may be due to reduced power in the null studies (Supplementary Table 3). Two studies also reported null effects for these same alleles and genotypes but in Asian and Caucasian samples (Gaysina et al., 2008; Zintzaras, 2006) (Supplementary Table 2), suggesting the effect is only apparent in mixed ethnic groups. For 5-HTTLPR, three studies confirmed the S allele or SS genotype in MDD in mixed (Lopez-Leon et al., 2008) and Caucasian samples (Furlong et al., 1998; Kiyohara and Yoshimasu, 2010). Three studies reported a conflicting null effect of the S allele in mixed and Caucasian samples (Supplementary Table 3), but which may be ascribed to differences in sample effects such as a smaller cohort (Lasky-Su et al., 2005), a smaller proportion of MDD participants (Risch et al., 2009), and a mixture of case-controls with family participants over case–control alone (Lotrich and Pollock, 2004). Two studies also reported a conflicting null effect for the SS genotype in Caucasian samples, but both within smaller cohorts (Furlong et al., 1998; Lotrich and Pollock, 2004) than the confirmed studies (Supplementary Table 3). Null allelic and genotype effects were reported when considering Asian samples (Kiyohara and Yoshimasu, 2010; Lotrich and Pollock, 2004), or SL vs LL genotype effects in mixed cohorts (Lopez-Leon et al., 2008) (Supplementary Table 2), suggesting the effects of 5-HTTLPR in MDD are specific to mixed or Caucasian cohorts, and for the S allele and SS genotype alone.

The strongest gene effects (p < .001) were reported for 18 variants, with no conflicting studies identified. The biological pathways implicated included serotonin synthesis (e.g., TPH2), dopamine and drug metabolism (e.g., DRD4, UGT2A1), calcium signalling, binding and salivary secretion (e.g., ADcy9, TPR1, PCLO), embryonic development (e.g., CHST11, PTPRR), cellular stress response and blood coagulation (e.g., DNAJ2, EHD3), heart function (e.g., ACE) and other cellular regulatory pathways (e.g., FREM3, KLHL29, PHACTR3). Other significant genetic variants identified at p < .01 or 0.05 are listed in Supplementary Table 1, and include APOE, GN13, HS6ST3, HTR1A, LPHPL2, MAOA, SLC6A3 (DAT1), SLC25A21 and VGL14.

3.3.2. Anxiety disorder (AD)

We identified 6 genetic variants involved in AD (Supplementary Table 1), with two conflicting null effects for COMT Val158Met in OCD and PD in particular. Two meta-analyses confirmed the role of the Met allele in OCD in mixed case–control cohorts when considering males and females together (Azzam and Mathews, 2003), or males alone (Pooley et al., 2007) (Supplementary Table 1). However, this effect was conflicting with a null finding from the same study when considering family association studies, and not case-controls (Azzam and Mathews, 2003) (Supplementary Table 3). This effect was also not apparent when considering females alone (Pooley et al., 2007) (Supplementary Table 2). The COMT Met allele was also implicated in Panic Disorder (PD) in Asian females (Domschke et al., 2007), but not in mixed or Asian males and females combined (Zintzaras and Sakelaridis, 2007). In contrast, the opposing Val allele was
implicated in male/female and female-only Caucasians (Domschke et al., 2007). The male/female effect was however conflicted by a null finding in a separate study of Caucasians (Zintzaras and Sakelaridis, 2007), although this may have been due to the latter study defining PD as the presence of agoraphobia rather than PD per se (Supplementary Table 3).

Strong gene effects (p < .001) were also identified for 2 variants of the 10-repeat allele in predicting PD in mixed/Caucasians (Erhardt et al., 2012). The function of 10-repeat still remains to be confirmed but there is some suggestion of its involvement in neuronal sprouting and brain connectivity (Erhardt et al., 2012). Significant effects at p < .05 were also identified for the 5-HTTLPR genetic variant in OCD as listed in Supplementary Table 1.

### 3.3.3. Attention deficit-hyperactivity disorder (ADHD)

We identified 11 significant genetic variants in ADHD, with conflicting effects found for the variant (SLC6A3 DAT1 40-bp 10 repeat) (Supplementary Tables 1 and 3). The 10-repeat allele is associated with a dopamine transporter that is abnormally efficient at the re-uptake process (Mill et al., 2002), producing underactivity in the dopaminergic mesocorticolimbic and nigrostriatal pathways. For this variant, two studies suggested a significant role of the 10-repeat allele in mixed ethnic cohorts (Gizer et al., 2009; Yang et al., 2007), but four studies reported a conflicting null effect in mixed ethnic cohorts (Curran et al., 2001; Maher et al., 2002; Yang et al., 2007). Three of these four studies however used either smaller cohorts (Li et al., 2006b) and/or samples based on family associations rather than case-controls (Curran et al., 2001; Maher et al., 2002), suggesting the lack of effects may be due to limitations in sample characteristics. However, the fourth conflicting study was derived from one of the same papers that reported a significant effect in 1373 family-based cohort (Yang et al., 2007), but in this case, the conflicting effect was reported when considering a larger (n = 3594) cohort of case-controls. Three other studies also reported null effects for this same allele in Asian or Caucasian (or unreported ethnic) cohorts (Li et al., 2006b; Purper-Ouakil et al., 2005) (Supplementary Table 2).

Other variants of focus in ADHD with strongest effects (p < .001) were the DRD4 48-bp VNTR dopamine transporter and the DRD5 dinucleotide repeat, both involved in dopamine regulation (Supplementary Table 1). Six studies confirmed the role of the 4-, 5- and 7-repeats of the DRD4 48-bp VNTR in ADHD (Faraone et al., 2001; Gizer et al., 2009; Li et al., 2006b; Maher et al., 2002; Nikolaidis and Gray, 2010; Smith, 2010), but not in Asians alone (Li et al., 2006b), and not for the 2- or 3-repeats (Li et al., 2006b). Four studies reported the impact of the DRD5 148-bp allele in ADHD (Gizer et al., 2009; Li et al., 2006b; Lowe et al., 2004; Maher et al., 2002), with no conflicting findings. Other significant genetic variants implicated in ADHD at p < .01 or .05 included DIRAS2, DRD4 5217/C, HTR1B, SLC6A3 30-bp VNTR, rs27072 and rs40184, 5-HTTLPR and SNAP-25, as listed in Supplementary Table 1.

### 3.3.4. Schizophrenia (SZ)

We identified 97 genetic variants in SZ (Supplementary Table 1), with conflicting null effects found for 27 of these variants (Supplementary Table 3). The main genetic variants of focus from multiple studies were MTHFR C677T, MTHFR A1298C, BDNF Val66-Met and COMT Val158Met.

For MTHFR C677T (rs1801133), seven studies supported the T allele, TT or TT/CT genotype in SZ in either mixed ethnic cohorts (Allen et al., 2008; Gilbody et al., 2006; Kim et al., 2011; Muntjewerff et al., 2006; Shi et al., 2008b; Yoshimi et al., 2010; Zintzaras, 2006), Asian (Kim et al., 2011; Shi et al., 2008b; Yoshimi et al., 2010; Zintzaras, 2006), or Caucasian samples (Shi et al., 2008b; Yoshimi et al., 2010) (Supplementary Table 1). The T allele effect in Asian and Caucasian samples in particular was however conflicted by null effects reported by two studies (Kim et al., 2011; Zintzaras, 2006) (Supplementary Table 3). As sample size was not reported for some of these studies (Kim et al., 2011; Yoshimi et al., 2010), a direct comparison of significant and conflicting effects is not feasible and therefore it is not definitive whether these null effects are representative of limitations in sample size and/or composition, or whether they are due to a weak effect of this particular variant.

For the other MTHFR variant (A1298C), five studies supported the role of the C allele or CC genotype in SZ in mixed (Shi et al., 2008b; Zintzaras, 2006), Asian (Kim et al., 2011), or Caucasian cohorts (Allen et al., 2008; Gilbody et al., 2006; Shi et al., 2008b) (Supplementary Table 1). The role of the C allele in mixed ethnic cohorts was conflicted by null effects reported by three studies (Supplementary Table 3), one of which was in a larger cohort (Peerbooms et al., 2011) than the confirmed study (Shi et al., 2008b); the other two conflicting studies did not report total sample size (Kim et al., 2011; Yoshimi et al., 2010), so the reasons for the discrepancy is not definitive. The role of C allele was also conflicted by null effects reported by three studies in Caucasian cohorts (Supplementary Table 3); in this case, the conflicting null study used a smaller cohort (Zintzaras, 2006) than the confirmed study (Shi et al., 2008b), and the other two studies again failed to report total sample size (Kim et al., 2011; Yoshimi et al., 2010) so the reason for the discrepancy is unclear. The CC genotype effects in the mixed ethnic group (Zintzaras, 2006) was conflicted by null effects in a much larger study (Peerbooms et al., 2011), suggesting this former effect may be rather small and/or due to false positive variability. The CC genotype effect in the Caucasian cohort (Gilbody et al., 2006) on the other hand was conflicted by a null study with a slightly smaller cohort (Zintzaras, 2006), suggesting that this significant effect may be more robust.

BDNF Val66-Met was another genetic variant of focus in a large number of SZ studies. One study suggested homozygosity (VV or MM) as the risk variant in mixed and Caucasian samples (Jonsson et al., 2006), whereas another study instead reported a preference for heterozygotes over homozygotes in risk for SZ in mixed ethnic groups, as well as VV over MM genotypes in particular (Gratacos et al., 2007) (Supplementary Table 1). Homozygosity risk did not hold in Asian cohorts (Jonsson et al., 2006), nor for Val vs Met allelic comparisons in mixed, Asian or Caucasian cohorts (Allen et al., 2008; Jonsson et al., 2006; Kanazawa et al., 2007; Kawashima et al., 2009; Naoe et al., 2007; Qian et al., 2007; van Schijndel et al., 2009; Xu et al., 2007) (Supplementary Table 2). No conflicting null effects were reported for the BDNF Val66-Met variant (Supplementary Table 3).

The other gene of focus in multiple SZ studies was COMT Val158Met. One study supported homozygosity as the risk variant in both mixed and Caucasian cohorts (Costas et al., 2011), whereas a second study identified the Val over the Met allele as the risk variant in Caucasians (Glatt et al., 2003) (Supplementary Table 1). This latter effect in Caucasians was conflicted by null findings from six studies (Fan et al., 2005; Glatt et al., 2003; Munafò et al., 2005; Okochi et al., 2009; Shi et al., 2008b; van Schijndel et al., 2009), each of which were based in larger samples than the original confirmed study (Glatt et al., 2003) suggesting that this significant effect may be small and/or due to false positive variability (Supplementary Table 3). The Val vs Met comparisons was also negated when considering mixed or Asian samples (Allen et al., 2008; Costas et al., 2011; Fan et al., 2005; Glatt et al., 2003;
Munafo et al., 2005; Okochi et al., 2009; Shi et al., 2008b) (Supplementary Table 2).

Of the total 97 variants identified in SZ, the strongest gene effects (p < .001) were reported for 30 variants. The biological pathways that were implicated included modulation of dopamine and anti-psychotic drug metabolism (e.g., COMT Val158Met, DRD2 S311C and P1319P, DRD3 Bal 1, DRD4 48-bp VNTR, HTRA2 T102C, IL1B CS1T), glutamate (e.g., DAOA rs1421292, rs778293 and rs947267, GABRB2 rs1816072, NR1N1 SNPN8GR241930, 478B8-848 and 420M9-1395 microsatellites), neuronal development and function (e.g., AH1 rs1154801, rs1475069, rs7739635, rs7750586, rs9321501, rs9494332 and rs9647635, ERG3 rs35201266, MTHFR C677T, NR1G, RELN rs7341475, TRKA C1848T, 2NF80A rs1344706), serotonint (TPI1 218 A/C) or epigenetic mechanisms (BRD1 rs4468). The function of other genes in the central nervous system still remains unclear (e.g., CMYA5 rs10043986 and rs4704591, SLC6A4 Stin2 VNTR). Of these, conflicting null effects were identified for only two variants. For the DAOA rs947267 variant, the A vs C allele was considered a risk variant in SZ in Asian cohorts in one study (Shi et al., 2008a), but not in another (Müller et al., 2011). Similarly, for the NR1G SNPN8GR241930 variant, the G allele was considered a risk marker in Caucasian samples in one study (Li et al., 2006a), but not in another (van Schijndel et al., 2009). In both sample characteristics were not reported by all studies, it is unclear whether or not these effects are the result of Type I error (Supplementary Table 3). Yet, as both of the conflicting studies were published later (and therefore more likely in larger cohorts than the initial confirmed studies), then there is a possibility that these significant effects were potentially due to small and/or false positive variability.

Other significant genetic variants implicated in SZ at p < .01 or .05 included AKTI, APOE, BAR01, BDNF 270C/T, COMT rs165599 and rs173685, CHE3L1, DAOA rs2391191, rs3916866 and rs3918342, DAO, DISC1, DKK2, DR1, DRD2 rs1801028, DRD3 rs8280, DTPB1, EML5, GRIN2B, HP, LAMAS, NET01, NOD2, PCMI, PLXNA2, PPP3CC, PTPN21, SAP97, SIGMAR1, SOX10, TP53, TNFα and UHMK1 (Supplementary Table 1). Of these, conflicting null effects were found for the variants APOE (Schurhoff et al., 2003), DTPB1 rs3213207 (Li and He, 2007a), HTRA2 rs63131 (Abdolmaleky et al., 2004), PPP3CC (Kyogoku et al., 2011) and SIGMAR1 (Uchida et al., 2003) but each in smaller cohorts suggesting the initial significant effects may not be due to false positive error but robust effects (Supplementary Table 3). In contrast, conflicting null effects were found for other variants – AKTI in mixed cohorts (Lee et al., 2010), BDNF 270 C/T in mixed (Kawahima et al., 2009; Wantanabe et al., 2007; Xu et al., 2007) and Asian samples (Kawahima et al., 2009; Xu et al., 2007), COMT rs165599 in mixed cohorts (Okochi et al., 2009; Shi et al., 2008b), COMT rs737865 in Caucasian samples (Shi et al., 2008b), DAOA rs2391191 (Allen et al., 2008), variants of the DNTBPI gene in mixed (Shi et al., 2008b) and Caucasian samples (Shi et al., 2008b), NR1G SNPN8GR221533 in mixed (Munafò et al., 2008; Munafò et al., 2006) and Caucasian samples (Munafò et al., 2006), and TPH1 in Asian cohorts (Shirouwa et al., 2010) – but each in larger cohorts relative to the initial significant studies suggesting potential for small effects and/or false positive error in the significant studies (Supplementary Table 3). For the remaining conflicting null effects for the variants DAOA rs3916865 (Allen et al., 2008), DAOA rs3918342 (Allen et al., 2008), DRD2 S311C (Shi et al., 2008b), DRD3 rs8280 (Jonnson et al., 2003), GRIN2B rs7301328 (Li and He, 2007b), NR1G SNPN8GR221132 (van Schijndel et al., 2009) and NR1G SNPN8GR221939 (van Schijndel et al., 2009). In both cases, sample characteristics were not completely specified, or were derived from samples that differed in familial distribution (case-control vs. family-based association), so whether or not these genetic effects are due to error or robust variance is not definitive.

3.3.5. Bipolar disorder (BD)

We identified 65 genetic variants in BD (Supplementary Table 1), with conflicting null effects found for five variants (BDNF Val166Met, DAOA rs3918342, MTHFR C677T, PDLIMS rs2433230 and SLC6A4 5-HTTLPR) (Supplementary Table 3). The main variants of focus in multiple BD studies were MAOA CA repeat Intron 2, MAOA T941C and MTHFR C677T.

MAOA is a gene that encodes monoamine oxidase A, an enzyme that degrades neurotransmitters such as dopamine, noradrenaline and serotonin. Two studies confirmed the role of MAOA CA repeat a5 allele in BD in Caucasian cohorts (Furlong et al., 1999; Rubinstein et al., 1996), particularly in Caucasian females (Fan et al., 2010; Furlong et al., 1999; Preisig et al., 2000; Rubinstein et al., 1996) (Supplementary Table 1). Similarly, the MAOA CA repeat a6 allele has been implicated as a risk variant in BD in Caucasian cohorts (Fan et al., 2010; Preisig et al., 2000; Rubinstein et al., 1996), particularly in Caucasian females (Fan et al., 2010; Furlong et al., 1999; Preisig et al., 2000; Rubinstein et al., 1996), but also in Japanese males and females (Furlong et al., 1999). There were no conflicting null studies identified to refute these effects (Supplementary Table 3), but null effects of these alleles were reported when considering Caucasian males or Asian males/females (Fan et al., 2010; Preisig et al., 2000; Rubinstein et al., 1996) (Supplementary Table 2).

For the MAOA T941C genetic variant, three studies confirmed the role of T variant (or r1) in BD in Caucasians (Fan et al., 2010; Preisig et al., 2000; Rubinstein et al., 1996), particularly in Caucasian females (Fan et al., 2010; Furlong et al., 1999; Preisig et al., 2000; Rubinstein et al., 1996) (Supplementary Table 1). This latter effect was confirmed by one study in 517 Caucasian females (Preisig et al., 2000), which was larger than one of the confirmed studies (Rubinstein et al., 1996) but smaller than the other two (Fan et al., 2010; Furlong et al., 1999) suggesting the significant effect is most likely a robust effect. This effect was not apparent in Caucasian males (Fan et al., 2010; Furlong et al., 1999; Preisig et al., 2000; Rubinstein et al., 1996) or Asians (Fan et al., 2010).

Many studies also focused on the role of the MTHFR C677T variant in BD. One study supported the role of the T allele in mixed cohorts (Rai, 2011), and in another, the TT genotype in Asian cohorts (Zintzaras, 2006). The T allele effect in mixed cohorts was confirmed by three other studies (Supplementary Table 3): two of which were in smaller cohorts (Seifuddin et al., 2012; Zintzaras, 2006) but one in a larger sample (Cohen-Woods et al., 2010). Null effects for the T allele effect were also reported in an Asian sample (Zintzaras, 2006) and in mixed, Asian or Caucasian samples when considering TT or CT comparisons to the CC genotype (Chen et al., 2009; Cohen-Woods et al., 2010; Lewis et al., 2006; Zintzaras, 2006) (Supplementary Table 2).

The strongest gene effects (p < .001) for BD were reported for 21 genetic variants. The biological pathways implicated included cell activation and proliferation and signal transduction (e.g., ANK3 rs8044190 and rs10994336, FGFI2 rs7379297, NTR3 rs7279122), apoptosis and chromatin modification (e.g., BRE rs6547829), chemokine signalling (e.g., GNG4 rs508208 and rs2774339), glutamate signalling and regulation (e.g., GRIN3A rs4743473), immunological response (e.g., ICAM3 rs281413), cell adhesion and migration (e.g., NCAN rs1064395), neurotransmitter degradation (e.g., MAOA CA repeat) and tumour suppression (e.g., PALB2 rs420259). There were no conflicting null findings to refute these effects. Other significant genetic variants implicated in BD at p < .01 or .05 included ACE Ins/ Del, ANK3 rs1208575, ASMT, BDNF Val166Met, BRD1, BRD1/ZBED4, CAMTA1, CDDC132, CHE3L, COMT Val158Met, DAOA, DGKH, DRD4, HTR1A C1019G, HTR2B, KLHL3, LYPD5, MAOA T941C, MTHFR A1298C and C677T, PARD6B, PDLIMS, SLC6A4 5-HTTLPR and Stin2 VNTR, STAB1, TPH1 and WNK2 (Supplementary Table 1). Conflicting null
effects were found for BDNF Val66Met (Kanazawa et al., 2007; Seifuddin et al., 2012), but both studies were in smaller cohorts relative to the confirmed study suggesting the null findings may be due to sample characteristics rather than a lack of genetic effects (Supplementary Table 3). Null conflicting effects were also found for DAOA (Seifuddin et al., 2012) and PDLIM5 (Shi et al., 2008) in mixed ethnic groups, and for SLC6A4 5-HTTLPR in Caucasian samples (Lotrich and Pollock, 2004), each of these in larger cohorts than the original confirmed studies suggesting these confirmed effects may be small and/or due to false positive variability.

3.4. A comparison of individual gene meta-analyses and GWAS meta-analyses

In addition to the individual gene meta-analyses reported above, we also identified another 12 meta-analyses of GWAS studies for the same disorders (see Supplementary Table 4). Of these studies, four focused on MDD (Lee et al., 2012; Lewis et al., 2010; Shyn et al., 2011; Wray et al., 2012), 3 on SZ (Jia et al., 2012; Shi et al., 2009; Wang et al., 2012), 2 on ADHD (Ebejer et al., 2013; Neale et al., 2010), 1 on BD (Goes et al., 2012) and 1 on AD (Otowa et al., 2012). We also identified one other study that conducted a meta-analysis across GWAS of genetic markers and BD phenotype-combined (Wang et al., 2010). With the exception of several variants identified for SZ (including known variants HIST1H2BJ rs913660 and TRNAI20 rs13194053 (Shi et al., 2009) which achieved a p value less than 5 x 10^-8) no other variants from these GWAS studies reached genome-wide significance. Supplementary Table 4 lists the top genes (with known names) reported by these GWAS meta-analyses at GWAS or sub-threshold significance. None of the specific variants identified in these 12 GWAS meta-analyses (Supplementary Table 4) were the same variants identified in the individual gene meta-analyses (Supplementary Tables 1 and 2). Only two variants (but different genes) showed some overlap. The NOTCH4 rs2071278 variant was confirmed by the GWAS meta-analysis for SZ (Jia et al., 2012), but different variants of this same gene were reported as null effects by the individual gene meta-analyses for SZ, including rs367398 and rs3877071 (Allen et al., 2008), rs520692 and rs1892591 (van Schijndel et al., 2011), and (CTG)n, (TAA)n, including rs367398 and rs3877071 (Allen et al., 2008), rs520692 reported as null effects by the individual gene meta-analyses for SZ, and for the variants rs9804190, rs10994336 and rs1938528 which were different to the variant implicated in the prior GWAS (rs10994397).

4. Discussion

4.1. Positive findings: common vs specific genetic variants

We identified 1519 meta-analyses that have examined genetic polymorphisms across the five disorders MDD, AD, ADHD, SZ and BD. Approximately 25% of the studies confirmed an effect for 206 variants. Most studies focused on variants in SZ, with the least focused on variants in AD. This could arguably reflect the amount of genetic variance reflected in these disorders, in that researchers may have focused their studies on disorders with higher heritability (Burmeister et al., 2008) or it may reflect lower effect sizes of genetic contributors to the disorders. Of the genetic variants identified, over half were significant at p < 0.01 for MDD (67%) and AD (50%), versus 32% for SZ, 28% for BD, and 18% for ADHD. 13 variants (7%) showed common pleiotropic effects between two or more disorders. The underlying molecular pathways of these shared variants spanned neurotransmitter systems of serotonin, dopamine, and glutamate, as well as neurotrophic and vascular regulatory pathways. For brevity, Fig. 2 illustrates the pattern of positive associations identified in common across the disorders and does not include variations in results due to effect size, ethnicity or null findings. This pattern suggests however that there are common variants that may underlie vulnerability to psychopathology across multiple traditional diagnostic boundaries. Further, while only a small percentage of total variants were identified, this finding is consistent with recent evidence suggesting shared genetic aetiology between these disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), for which pleiotropic effects can be expected for up to 17% of genes in complex disease (Sivakumaran et al., 2011). In a similar vein, a recent large-scale GWAS across the five disorders — MDD, BD, SZ, ADHD and autism — identified SNPs at four loci that accounted for some of the shared variation across the disorders at p < 5 x 10^-8 (Smoller et al., 2013). The SNPs included genes ITIH3, AS3MT and CACNB2. They also reported other variants evident in smaller pleiotropic models (MR137, CCDC68, CACNA1C, CNMNM2, PGCGEM1, TC4F), or that were disorder specific for BD (SYNE1, ANK3, OD24) or SZ (MHC, MMP16, CSMD1, ST3A). In our study, we also noted a significant association of the ANK3 gene in specific risk for BD, but for the variants rs9804190, rs10994336 and rs1938528 which were different to the variant implicated in the prior GWAS (rs10994397).

4.2. Negative findings: conflicting studies and total null results

Of the total meta-analyses reviewed, 75% reported null effects (Supplementary Table 2). Of these total null effects, 5% conflicted with the significant findings reported in Supplementary Table 1 (Supplementary Table 3).

The possible reasons for the 5% ‘conflicting’ null results were highlighted in Supplementary Table 3. For some variants (38%), the conflicting null study was in a larger cohort than the study reporting significant effects, suggesting the latter studies may have reflected small effects and/or false positive results due to increased variability in smaller cohorts. This was clearly evident for the variants AKT1 rs2494732, BDNF 270CT, COMT rs165599, COMT Val158Met, COMT rs737865, DAOA rs2391191, DTNBPI rs1018381, DTNBPI rs2005976, DTNBPI rs2619522, DTNBPI rs2691528, and TPH1 rs1800532 in SZ; and for the variants DAOA rs3918342, PDLIM5 rs2433320 and SLC6A4 5-HTTLPR in BD. For another 9% of the conflicting variants, null studies were based on smaller cohorts suggesting the significant studies had more power to detect robust genetic effects than the null studies. This was clearly evident for the variants MTHFR rs1801133 in MDD, APOE, PPP3CC rs2461491 and SIGMAR1 rs1800866 in SZ, and BDNF Val66Met in BD. We could not make a more definitive suggestion for the remaining conflicting variants (53%) as they were either (i) based in samples that differed in composition including clinical diagnostic criteria (e.g., COMT Val158Met in AD) or case–control and/or family-based compositions (e.g., DRD2 rs1801028, DRD3 rs6280, DTNBPI rs3213207, HTRA2A rs6313 in SZ), (ii) insufficient information was reported to enable direct comparison of the samples (e.g., DAOA rs3919685, rs3918342 and rs947267, GRIN2B rs7301328, NR1G1 SNP8NRG221132 and SNP8NRG241930 in SZ), or (iii) the null studies showed a mixture of smaller and/or larger cohorts and/or non-definitive sample characteristics for the same variant in the same disorder (e.g., for SLC6A4 5-HTTLPR in MDD; SLC6A4 40-bp VNTR in ADHD; MTHFR rs1801131 and rs1801133, and NR1G1 SNP8NRG221533 in SZ; and MTHFR rs1801133 in BD). For instance, studies that used case–control over family-association samples may have more power to detect effects. This is because homoygous parents decrease the power of family-based studies, and chi-square tests are simply more powerful in case–control studies than the family-based transmission-disease-queuestudy-test. This may also be due to an increased false-positive rate for case–control studies.
due to ethnic stratification and an inability to completely control for these differences between cases and controls (Azzam and Mathews, 2003).

Possible explanations for the null effects (over and above conflicting findings above) may include variation at the genotype/phenotype level, ethnicity of the cohorts, and/or age and sex differences between the cohorts. At the genotype level, high genotyping error rates could produce false negative (or false positive) results. Complexity at the phenotype level could also account for disparities where symptom heterogeneity due to subtyping and symptom comorbidity may dilute specific gene effects.

Variations in sample ethnicity could account for some null findings as some effects may be just specific to certain ethnic groups. Notably, 36% of studies reported effects in mixed ethnic groups, many of which failed to consider sub-analyses of ethnic-specific effects. Previous studies have highlighted that treating Asian and Caucasian populations as homogeneous populations is problematic due to population stratification effects (Nikolaidis and Gray, 2010; Ohi et al., 2010), although others have argued that ancestry-specific effects are possible but probably uncommon (Ioannidis et al., 2004).

Few studies reported the distribution of males and females that comprised the total population despite known sexual dimorphism effects in genes and symptoms. Most psychiatric disorders show sex differences in either incidence, clinical symptoms, or outcome (Aleman et al., 2003; Piccinni and Wilkinson, 2000), differences usually ascribed to sex chromosomes (Davies and Wilkinson, 2006; Vawter et al., 2004), autosomal genes (Holmans et al., 2004), sex hormones (Collaer and Hines, 1995; Kelly et al., 1999; Rubinow and Schmidt, 1996; Seeman, 1997), or sex differences in epigenetic mechanisms (Kaminsky et al., 2006). There are also genes known to display sexual dimorphism effects such as COMT (Harrison and Tunbridge, 2008), with levels in the prefrontal cortex shown to be higher in males than females in both human (Chen et al., 2004) and rodent brains (Gogos et al., 1998), or other X-linked genes such as MAOA (Pinsonneault et al., 2006) where the gene is located on the X-chromosome.

Age was another factor not examined in the previous meta-analyses. There is a clear relationship between age and disorder onset. The median age of onset in ADHD and specific phobia is 7 years, increasing to 23–24 years for panic disorder and OCD, and 30 years for mood disorders (Kessler et al., 2005). There is also a clear understanding that genetic variance, or heritability, is not static; substantial changes in genetic effects may occur at any point in the life span (Carlson and Iacono, 2006). Therefore, it is plausible that the effects of some genes may not be triggered at certain points in the lifespan. It is also possible that the correlated effects of genetics with environment may accentuate the impact of some genes in younger or older ages (Nestler, 2009).

4.3. Comparing individual gene meta-analyses to GWAS meta-analyses

GWAS is rapidly becoming the method of choice for gene discovery with very large samples (Cantor et al., 2010). Unlike the candidate gene approach, GWAS provides an unbiased method to identifying risk alleles with frequencies larger than 1%. This approach together with the new high-throughput genetic technologies also implicates the need to consider multiple gene–gene and gene–environment interactions. However, results from recent studies have often only identified a small number of risk variants once multiple testing is considered, and so more advanced approaches include combining GWAS with large-scale sequencing to target both common and rare risk variants in complex disorders (Cantor et al., 2010). These studies require very large samples and so it is likely that cohorts will need to be gathered collaboratively in order to yield robust findings. To achieve large sample sizes, cohorts from previous studies have been combined in GWAS analyses. A disadvantage of this approach is that it limits the number of meta-analyses available.

A comparison of the individual gene meta-analyses results to that of the 12 single-disorder GWAS meta-analyses suggested no overlap in significant genetic variants identified from the different studies. This lack of overlap does not necessarily imply that the impact of the individual variants is negligible in comparison to the SNPs identified from the GWAS, but may be due to other reasons. One of the reasons is a lack of statistical power: under the GWAS model, many variants do not reach significance due to the large penalties on significance thresholds imposed on such models due to multiple testing, in combination with the smaller effects often identified by candidate gene studies. Another possible reason for the lack of overlap is that the GWAS meta-analyses focused solely on SNPs, whereas the individual meta-analyses sometimes included VNTRs, insertion/deletions and microsatellites amongst these variations. An alternative approach to overcome some of the shortcomings of both candidate gene and GWAS studies is the polygenic score method which draws on information derived from GWAS studies and combines multiple variants into a single cumulative index of risk (Purcell et al., 2009). When combined, more variance is accounted for in the phenotype than individual SNPs alone (Terwisscha van Scheltinga et al., 2013), and the sample sizes required to run this analysis are not as large as required for a discovery cohort.

4.4. Limitations

Meta-analyses have their own sources of bias that should be considered when evaluating these results (Levinson, 2005). Publication bias is the main source which occurs when investigators intentionally combine multiple datasets in light of their positive results. This bias has the potential to limit genetic variants that are targeted in meta-analyses by virtue of the possible limitation of such studies only targeting attractive or functional genes. The considerable number of meta-analytical studies with negative data reported here however suggests that negative findings were not disproportionally represented. The potential for publication bias in candidate gene studies in general however warrants discussion. Given the large number of genes and polymorphisms in the genome, the chance of any given polymorphism demonstrating a true association is actually quite small, and is something that readers need to be vigilant of, particularly when the study was conducted using under-powered samples and when there was insufficient correction for multiple testing within and across studies. In these cases, many published findings may actually reflect false positive effects rather than true associations (Hart et al., 2013; Thomas and Witte, 2002). Too often, major published findings of significant SNP associations were the result of exploratory and repeated testing of many SNPs within the same study, and of the same dataset across different studies, but without statistical adjustment and without acknowledgement of such analyses being conducted, thereby inflating the type 1 error rate of the findings (Hart et al., 2013; Hattersley and McCarthy, 2005). To overcome these issues, we are increasingly encouraged towards better standards for reporting prior analyses, to use extremely conservative significance levels and to demonstrate replicated associations in an independent sample (Hart et al., 2013; Thomas and Witte, 2002). A review of meta-analyses conducted to date provides a timely overview of the strength of some of these SNP associations in independent cohorts.
Combining results from meta-analyses also has the potential problem of overlap in control subjects between studies and therefore a potential overlap in genetic variants, although this is unlikely when considering pleiotropic mechanisms as most of the candidate studies will have been done by groups working on just one disorder. A recent study from the Psychiatric Genetics Consortium provides independent support for the shared etiology of these disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), yet it would be important to confirm these particular SNPs in an independent GWAS.

This review focused on common and specific variation in SNPs from candidate and GWAS studies; it did not target other genetic variants such as CNVs for which there is less available data. Future reviews may also consider these variations.

5. Conclusions

Here we review meta-analyses of genotypes implicated in serious mental disorders that have varying levels of reported heritability. Most significant advances have been made for schizophrenia with 50 genes identified, comparable to only 3 genes for anxiety disorder. With significant advances in genotyping technologies, the issue of multiple comparisons is paramount, as is finding an optimal solution to identify risk variants. Meta-analysis is one key method to prioritize primary research results and identify the genes to target in resequencing projects. Future studies should consider meta-analysis of studies focused on CNVs and GWAS results to prioritize further gene targets.

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Author contributions

JMG developed the conceptual idea of the paper, conducted the main literature search and wrote the first draft of the paper. KLOB assisted with the literature review and text editing. LMW and PRS contributed to the data interpretation. All authors approved the final version of the manuscript.

Conflicts of interest

The Brain Resource Ltd. (BR) was the industry partner on the ARC-linkage grant which funded this study, but had no further role in design or implementation of the project. JMG was a postdoctoral fellow on the ARC-linkage grant which funded this project, has previously received consultancy fees from Brain Resource Ltd, and is a stock holder in Freedomsway Corp. Pte Ltd. LMW is a stock holder in BR, has stock options in BR, has received fees from BR for consultancies unrelated to this study. CLOB and PRS report no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.09.014.

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