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The genetic architecture of schizophrenia, bipolar disorder, obsessive-compulsive disorder and autism spectrum disorder

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ABSTRACT

Considerable evidence suggests that autism spectrum disorders (ASD), schizophrenia (SCZ), bipolar disorder (BD) and obsessive-compulsive disorder (OCD) share a common molecular aetiology, despite their unique clinical diagnostic criteria. The aim of this study was therefore to determine and characterise the common and unique molecular architecture of ASD, SCZ, BD and OCD. Gene lists were obtained from previously published studies for ASD, BD, SCZ and for OCD. Genes identified to be common to all disorders, or unique to one specific disorder, were included for enrichment analyses using the web-server tool Enrichr. Ten genes were identified to be commonly associated with the aetiology of ASD, SCZ, BD and OCD. Enrichment analyses determined that these genes are predominantly involved in the dopaminergic and serotonergic pathways, the voltage-gated calcium ion channel gene network, folate metabolism, regulation of the hippo signaling pathway, and the regulation of gene silencing and expression. In addition to well-characterised and previously described pathways, regulation of the hippo signaling pathway was commonly associated with ASD, SCZ, BD and OCD, implicating neural development and neuronal maintenance as key in neuropsychiatric disorders. In contrast, a large number of previously associated genes were shown to be disorder-specific. And unique disorder-specific pathways and biological processes were presented for ASD, BD, SCZ and OCD aetiology. Considering the current global incidence and prevalence rates of mental health disorders, focus should be placed on cross-disorder commonalities in order to realise actionable and translatable results to combat mental health disorders.

1. Introduction

Clinically autism spectrum disorders (ASD), schizophrenia (SCZ), bipolar disorder (BD) and obsessive-compulsive disorder (OCD) differ substantially in that they not only fall into different categories of the DSM (American Psychiatric Association, 2013), but also differ in age of onset, neurocognitive profiles and neuroimaging (American Psychiatric Association, 2013). Genetically, however, they might be more similar in a broader sense (psychiatric disorders) whereby common symptom overlap might be somewhat attributable to common underlying molecular mechanisms (Carroll and Owen, 2009; Khanzada et al., 2017). Research supports this theory in that a number of independent single disorder genome-wide association studies (GWAS) have identified the same significant loci regardless of disorder (Consortium et al., 2013), and a number of cross-disorder case-control GWAS association studies have yielded significant results (Carroll and Owen, 2009). Similar behavioural, social, cognitive and perceptual disturbances are observed in individuals suffering from ASD, SCZ, BD and OCD (American Psychiatric Association, 2013; Vannucchi et al., 2014), while molecular overlap, at both genetic and transcriptomic levels, has been identified for the aetiology of SCZ, BD and ASD (Carroll and Owen, 2009; Gandal et al., 2016; Khanzada et al., 2017), and suggested for ASD and OCD (Jacob et al., 2009). Considering the latter, the exact molecular mechanisms that OCD may share with ASD have not been described, while unpublished results suggest molecular overlap between OCD, SCZ and BD (Anttila et al., 2017).

In addition to the molecular overlap described above, clinical evidence further suggests common aetiology for neuropsychiatric disorders. Individuals affected by OCD and SCZ show similar age-related reductions in white matter connectivity, with overlapping spatial pattern deficits, suggesting common neurobiology (Hawco et al., 2016). Obsessive-compulsive behaviors are present in some ASD affected

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individuals (Cath et al., 2008), while individuals suffering from OCD have increased comorbid diagnoses of both SCZ and BD (Cederlöf et al., 2015), as well as ASD traits (Ivarsson and Melin, 2008), further suggesting common aetiology for these neuropsychiatric disorders. Despite evidence to suggest common aetiology for these neuropsychiatric disorders they present with distinct clinical profiles, suggesting that each must have a corresponding unique genetic architecture.

This study aims to characterise the common and unique molecular architecture of ASD, SCZ, BD and OCD by analysing previously identified associations with the aforementioned neuropsychiatric disorders.

2. Materials and methods

Gene lists were obtained from previously published studies for ASD (number of genes, $n = 792$) (Butler et al., 2015), BD (number of genes, $n = 291$) (Douglas et al., 2016), SCZ (number of genes, $n = 560$) (Butler et al., 2016), and OCD (number of genes, $n = 153$; OCDB) (http://alpha.dmi.unict.it/ocdb/; accessed 31 May 2017) (Privitera et al., 2015). These disorders were selected for investigation due to the evidence outlined in the introduction above and the public availability of the gene datasets listed.

Genes identified to be common to all disorders, or unique to one specific disorder, were included for enrichment analyses using Enrichr (http://amp.pharm.mssm.edu/Enrichr) (Kuleshov et al., 2016). Enrichr computes enrichment by assessing 35 gene-set libraries (including KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways and GO (gene ontology) biological processes) and calculates *p*-values, adjusted *p*-values, Z-scores and combined scores representative of Fisher exact and Z-score statistics. The *p*-values are calculated using the Fisher's exact test and the adjusted *p*-values are then obtained using the Benjamini-Hochberg method for correction for multiple hypotheses testing. The Z-score is computed for deviation from an expected rank using a modification to Fisher's exact test. Finally, the combined score is a combination of the *p*-value and z-score calculated by multiplying the two scores (combined score = $\log(p\text{-value} * \text{Z-score})$) (Kuleshov et al., 2016).

STRING v10 (http://version10.string-db.org) was used to produce a network diagram of the genes common to ASD, BD, SCZ and OCD (Szklarczyk et al., 2015). Default interaction sources and scores were used. No more than 50 s shell interactions (software generated secondary genes) were required in order to connect all first shell interactions (target input genes; 10 common genes identified for ASD, BD, SCZ and OCD).

3. Results

3.1. Gene list summary statistics

Ten genes were identified to be commonly associated with the aetiology of ASD, SCZ, BD and OCD (*BDNF*, *CACNA1C*, *CHRNA7*, *DRD2*, *HTR2A*, *MAOA*, *MTHFR*, *NOS1AP*, *SLC6A3* and *TPH2*). In contrast, a large number of previously associated genes were shown to be disorder-specific with 620 (78%), 183 (63%), 365 (65%) and 56 (37%) genes unique to ASD, BD, SCZ and OCD, respectively. These results, as well as the results of two- and three-disorder gene overlap, are presented in Fig. 1.

A network diagram showing the 10 genes commonly associated with the aetiology of ASD, SCZ, BD and OCD, as well as other genes with which they interact is presented in Fig. 2. The majority of these genes were clustered in recognisable networks and pathways (dopaminergic and serotonergic pathways, the voltage-gated calcium ion channel gene network and folate metabolism), except for a gene cluster surrounding *NOS1AP* (*AJUBA*, *FBLIM1*, *LIMD1*, *LPP*, *NOS1AP*, *TRIP6*, *WTIP*, *ZYX*), which was further individually investigated using enrichment analyses.

3.2. Enrichment analyses – KEGG pathways

The top 10 KEGG pathway results were determined for the 10 genes commonly associated with the aetiology of ASD, SCZ, BD and OCD (Table 1), as well as for genes unique to ASD, BD, SCZ and OCD aetiology (Supplementary Tables 1–4), respectively. Four KEGG pathways were associated with the identified gene cluster surrounding *NOS1AP* (Table 2).

3.3. Enrichment analyses – biological processes

The top 10 results for biological processes were determined for the 10 genes commonly associated with the aetiology of ASD, SCZ, BD and OCD (Table 3), as well as for the unique genes to ASD, BD, SCZ and OCD aetiology (Supplementary Tables 5–8), respectively. Additionally, the top 10 results for biological processes were determined for the identified gene cluster surrounding *NOS1AP* (Table 4).

4. Discussion

4.1. Genetic overlap

Ten genes were identified as commonly associated with the aetiology of ASD, BD, SCZ, and OCD; namely *BDNF*, *CACNA1C*, *CHRNA7*, *DRD2*, *HTR2A*, *MAOA*, *MTHFR*, *NOS1AP*, *SLC6A3* and *TPH2* (Fig. 1). These genes are predominantly involved in substance abuse and addiction, the dopaminergic and serotonergic pathways, the voltage-gated calcium ion channel gene network and folate metabolism (Tables 1 and 3).

Considering each disorder independently this is not too surprising since substance abuse (alcoholism, amphetamine abuse and cocaine addiction) and dopaminergic involvement are ‘repeat offenders’ in terms of comorbidities, covariates and risk factors in association studies (Walker and Druss, 2017). The novelty presented here, however, is that a molecular argument can be made for cross-disorder investigations in support of genetic overlap for these factors. This has the potential to go a long way in terms of not only understanding the molecular aetiology of mental disorders, but also comorbidity and treatment outcome. Supporting this is the fact that dopamine and serotonin neurotransmitters have been implicated in neuropsychiatric disorder aetiology for a number of decades (Carlsson, 1977). The evidence for their involvement in the aetiologies of ASD, BD, SCZ, and OCD has been extensively reviewed and includes neuroimaging, pharmacological and genetic studies (Bokor and Anderson, 2014; Grünblatt et al., 2014; Muneer, 2016; Sumiyoshi et al., 2014). Similarly, neuroimaging, pharmacological and genetic studies have also implicated voltage-gated calcium ion channels (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Heyes et al., 2015) and folate (one-carbon) metabolism (Esnafoğlu and Yaman, 2017; Gatt et al., 2015; Siscoe and Lohr, 2017) in neuropsychiatric disorder aetiology.

In addition to these well-characterised networks and pathways a small gene cluster (*AJUBA*, *FBLIM1*, *LIMD1*, *LPP*, *NOS1AP*, *TRIP6*, *WTIP*, *ZYX*) was also identified surrounding the commonly associated *NOS1AP* gene (Fig. 2). Enrichment analyses showed that this cluster is involved in the regulation of the hippo signaling pathway, as well as, the regulation of gene silencing and expression (Tables 2 and 4).

4.2. The hippo signaling pathway

The hippo signaling pathway was initially identified as the major regulator of organ size, by modulating cell proliferation and migration (Harvey et al., 2003; Pan, 2007), however it is also known to play a role in regulating dendritic maintenance (Emoto et al., 2006; Emoto, 2012; Ultanir et al., 2012). Dendritic maintenance is the process by which dendritic coverage is maintained over the receptive field for the lifespan of a neuron (Grutzendler et al., 2002; Mizrahi and Katz, 2003). SCZ and

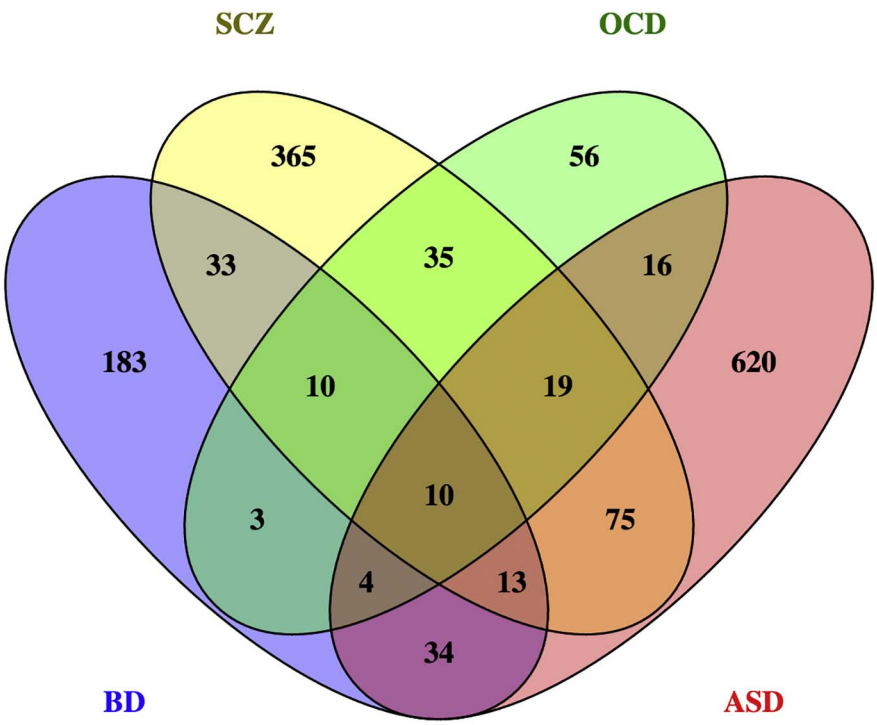

Fig. 1. A Venn-diagram demonstrating the overlap of investigated genes in the aetiology of autism spectrum disorder (ASD), bipolar disorder (BD), schizophrenia (SCZ) and obsessive-compulsive disorder (OCD).

BD are characterised by disrupted dendritic maintenance and reduced coverage (Konopaske et al., 2014; Moyer et al., 2015; Penzes et al., 2013), while dendritic abnormalities were also recently described for ASD (Martínez-Cerdeño, 2017) and OCD (van de Vondervoort et al., 2016). It may be hypothesised that dysregulation of this signaling pathway, by genetic variation within core pathway genes, may therefore result in aberrant dendritic maintenance and disease progression. Overexpression of *NOS1AP* has been shown to modulate hippo

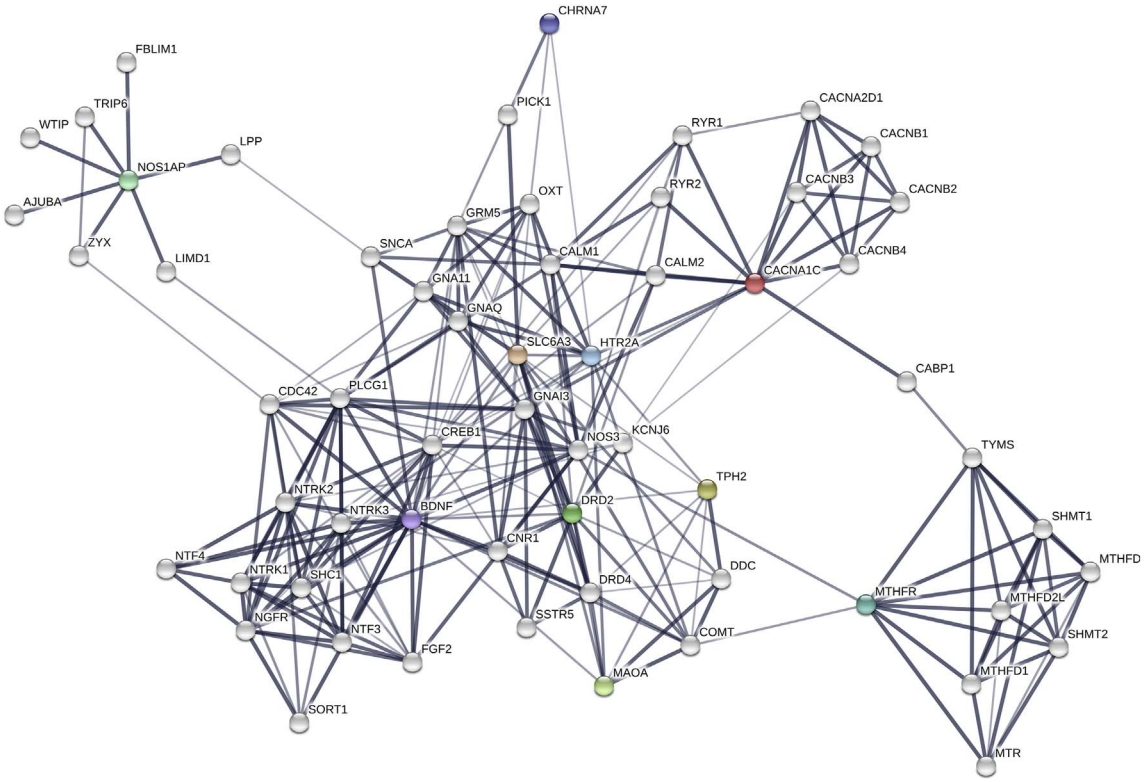

Fig. 2. A network diagram generated in STRING v10 demonstrating the 10 genes commonly associated with the aetiology of ASD, SCZ, BD and OCD (*BDNF*, *CACNA1C*, *CHRNA7*, *DRD2*, *HTR2A*, *MAOA*, *MTHFR*, *NOS1AP*, *SLC6A3* and *TPH2*) (coloured), as well as the genes with which they interact. No more than 50 interactions were required in order to connect all 10 initial genes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
KEGG pathways associated with the 10 genes commonly associated with the aetiology of ASD, BD, SCZ and OCD.

Rank	KEGG pathway (accession number)	*p*-Value	Adjusted *p*-value	Z-score	Combined score
1	Cocaine addiction (hsa05030)	6.604×10^{-09}	3.170×10^{-07}	−1.89	28.33
2	Serotonergic synapse (hsa04726)	1.907×10^{-07}	4.576×10^{-06}	−1.86	22.82
3	Dopaminergic synapse (hsa04728)	3.366×10^{-07}	5.386×10^{-06}	−1.84	22.34
4	Alcoholism (hsa05034)	1.249×10^{-06}	1.499×10^{-05}	−1.83	20.30
5	Amphetamine addiction (hsa05031)	4.240×10^{-06}	4.071×10^{-05}	−1.87	18.91
6	Calcium signaling pathway (hsa04020)	8.213×10^{-05}	6.570×10^{-04}	−1.83	13.42
7	cAMP signaling pathway (hsa04024)	1.106×10^{-04}	7.584×10^{-04}	−1.79	12.86
8	Tryptophan metabolism (hsa00380)	1.737×10^{-04}	0.001	−1.61	11.09
9	Neuroactive ligand-receptor interaction (hsa04080)	2.935×10^{-04}	0.002	−1.70	10.98
10	Cholinergic synapse (hsa04725)	0.001	0.005	−1.75	9.14

Table 2
KEGG pathways associated with the identified gene cluster surrounding *NOS1AP* (*AJUBA*, *FBLIM1*, *LIMD1*, *LPP*, *NOS1AP*, *TRIP6*, *WTIP*, *ZYX*).

Rank	KEGG pathway (accession number)	*p*-Value	Adjusted *p*-value	Z-score	Combined score
1	Hippo signaling pathway (hsa04390)	2.390×10^{-05}	9.561×10^{-05}	−1.74	16.07
2	Circadian entrainment (hsa04713)	0.037	0.050	−1.89	5.67
3	NOD-like receptor signaling pathway (hsa04621)	0.023	0.045	−1.77	5.48
4	Focal adhesion (hsa04510)	0.078	0.078	−1.85	4.71

Table 3
Biological processes for the 10 genes commonly associated with the aetiology of ASD, BD, SCZ and OCD.

Rank	Biological process (GO accession number)	*p*-Value	Adjusted *p*-value	Z-score	Combined score
1	Dopamine metabolic process (GO:0042417)	6.414×10^{-10}	1.886×10^{-7}	−2.65	41.05
2	Phenol-containing compound metabolic process (GO:0018958)	2.384×10^{-10}	1.402×10^{-7}	−2.14	33.71
3	Catechol-containing compound metabolic process (GO:0009712)	3.852×10^{-9}	5.663×10^{-7}	−2.30	33.14
4	Catecholamine metabolic process (GO:0006584)	3.852×10^{-9}	5.663×10^{-7}	−2.30	33.09
5	Synaptic transmission (GO:0007268)	1.968×10^{-8}	2.145×10^{-6}	−2.34	30.57
6	Behaviour (GO:0007610)	4.254×10^{-8}	3.187×10^{-6}	−2.40	30.34
7	Learning or memory (GO:0007611)	2.189×10^{-8}	2.145×10^{-6}	−2.30	29.98
8	Cognition (GO:0050890)	4.337×10^{-8}	3.187×10^{-6}	−2.31	29.19
9	Phenol-containing compound biosynthetic process (GO:0046189)	4.016×10^{-7}	2.147×10^{-5}	−2.56	27.48
10	Response to drug (GO:0042493)	3.957×10^{-7}	2.147×10^{-5}	−2.44	26.24

GO, gene ontology.

Table 4
Biological processes for the identified gene cluster surrounding *NOS1AP* (*AJUBA*, *FBLIM1*, *LIMD1*, *LPP*, *NOS1AP*, *TRIP6*, *WTIP*, *ZYX*).

Rank	Biological process (GO accession number)	*p*-Value	Adjusted *p*-value	Z-score	Combined score
1	Regulation of posttranscriptional gene silencing (GO:0060147)	3.525×10^{-09}	1.049×10^{-07}	−2.42	38.88
2	Regulation of gene silencing by miRNA (GO:0060964)	3.525×10^{-09}	1.049×10^{-07}	−2.41	38.78
3	Regulation of gene silencing by RNA (GO:0060966)	3.525×10^{-09}	1.049×10^{-07}	−2.37	38.07
4	Regulation of hippo signaling (GO:0035330)	3.525×10^{-09}	1.049×10^{-07}	−2.34	37.53
5	Regulation of gene silencing (GO:0060968)	7.411×10^{-08}	1.764×10^{-06}	−2.55	33.81
6	Gene silencing by RNA (GO:0031047)	2.733×10^{-07}	5.420×10^{-06}	−2.43	29.45
7	Gene silencing (GO:0016458)	1.571×10^{-06}	2.671×10^{-05}	−2.30	24.21
8	Cell-substrate adherens junction assembly (GO:0007045)	3.527×10^{-05}	3.816×10^{-04}	−2.50	19.68
9	Focal adhesion assembly (GO:0048041)	3.527×10^{-05}	3.816×10^{-04}	−2.49	19.62
10	Regulation of gene expression, epigenetic (GO:0040029)	1.213×10^{-05}	1.804×10^{-04}	−2.27	19.59

GO, gene ontology.

signaling by promoting phosphorylation of the key hippo signaling protein (yes-associated protein, YAP) resulting in reduced transcriptional activity of YAP-target genes, ultimately restricting cellular proliferation and migration (Clattenburg et al., 2015). This has been shown to alter neuronal migration during cortical development resulting in reduced numbers of cells in the cortical plate (Carrel et al., 2015). Furthermore, *NOS1AP* overexpression has been shown to alter dendritic maintenance (Richier et al., 2010), in a similar manner to that observed in ASD (Martínez-Cerdeño, 2017), BD (Penzes et al., 2013), SCZ (Konopaske et al., 2014; Moyer et al., 2015), and OCD (van de Vondervoort et al., 2016) patients as described above. Moreover, an investigation of transcriptomic overlap between neuropsychiatric disorders provides additional validation of these results by identifying downregulation of genes involved in neuronal and synaptic processes in ASD, BP and SCZ (Gandal et al., 2016). These studies support the association of *NOS1AP* variation with neuropsychiatric disorder aetiologies by providing evidence of potential mechanisms through which disease progression may be modulated.

Interestingly, *AJUBA*, *LIMD1* and *WTIP* were identified by *NOS1AP* enrichment analyses. These genes encode for proteins that inhibit LATS1/2 resulting in reduced phosphorylation of the key hippo signaling protein YAP and corresponding increased transcriptional activity of YAP target genes, cell proliferation and migration (Keyvani Chahi et al., 2016; Reddy and Irvine, 2013; Sun and Irvine, 2013). The effect

that changes in the expression of these genes may have on dendritic maintenance has not been investigated to date. These genes do, however, exhibit opposite effects on the hippo signaling pathway as those identified for increased *NOS1AP* expression (Keyvani Chahi et al., 2016; Reddy and Irvine, 2013; Sun and Irvine, 2013). Reduced expression of these genes, resulting in increased LATS1/2 activity and corresponding increased YAP phosphorylation, may therefore result in restricted cell proliferation and migration, and aberrant dendritic maintenance similar to that observed when *NOS1AP* is overexpressed. Future studies should investigate these genes as candidates in the pathophysiology of neuropsychiatric disorders due to their probable roles in altered neuronal migration during cortical development and aberrant dendritic maintenance (Keyvani Chahi et al., 2016; Reddy and Irvine, 2013; Sun and Irvine, 2013). Furthermore, functional variation within these genes, and others in the hippo signaling pathway, should be assessed for association with neuropsychiatric disorders. This may provide targets for novel drug development in the treatment and/or prevention of these disorders.

4.3. miRNA mediated gene silencing

In addition to their role in the hippo signaling pathway, *AJUBA*, *LIMD1* and *WTIP* are also implicated in miRNA mediated gene silencing (James et al., 2010). The proteins encoded by these genes interact with the Ago1/2 proteins in miRNA induced silencing complexes (miRISC), as well as eukaryotic translation initiation factor 4E (eIF4E) and the 7-methyl-guanosine (m^7GTP) cap structure (James et al., 2010). The eIF4E protein is responsible for directing ribosomes to the m^7GTP cap at the 5′ region of mRNA molecules in order for translation to occur (Sonenberg et al., 1979). The AJUBA, LIMD1 and WTIP proteins inhibit eIF4E-m^7GTP translation and instead direct this complex to Ago1/2 in the miRISC complex where the mRNA is cleaved (James et al., 2010). Atypical expression of specific genes due to miRNA mediated gene silencing, as a result of variation within the *AJUBA*, *LIMD1* and *WTIP* genes, may contribute to the aetiology of neuropsychiatric disorders and requires future investigation.

4.4. Disorder-specific genetics

The majority of previously associated genes were shown to be disorder-specific for ASD (78%), BD (63%) and SCZ (65%), while only 37% of genes previously associated with OCD aetiology were unique to that disorder (Fig. 1).

4.5. Autism spectrum disorder

Chromatin modifications, changes to the genomic DNA and/or associated nuclear proteins, were the most notable biological processes identified when genes unique to ASD were investigated (Supplementary Table 5). Evidence for the role of chromatin modification in the aetiology of ASD has been previously described (LaSalle, 2013; Vogel Ciernia and LaSalle, 2016). In addition to variant associations, mutations within histone demethylase genes have been identified in patients with ASD (Adegbola et al., 2008; Jensen et al., 2005). Furthermore, chromatin itself influences genomic locations of *de novo* mutations, specifically hyper-mutability of open active chromatin in ASD patients (Michaelson et al., 2012), as well as DNA methylation levels in the form of partially methylated domains (PMDs) (Lister et al., 2009). These domains are characterised by lower levels of methylation (40–70%), compared to methylation observed in the rest of the genome (> 70%) (Lister et al., 2009), and are often observed in genes involved in neuronal development, immune response and synaptic transmission (Schroeder et al., 2011, 2013). Genes shown to be mutated in patients with ASD are also highly enriched for PMDs when compared to the other parts of the genome (Schroeder et al., 2011). Further complicating the role of chromatin modification in ASD aetiology is that a number of factors have been shown to influence chromatin, including genetic variability, gender, environmental toxins, nutrition and metabolism, and immune response (LaSalle, 2013). Understanding the complex nature of chromatin modelling, as well as the factors that affect it, is key in characterising gene networks and pathways contributing to ASD aetiology.

4.6. Bipolar disorder

One of the main biological processes identified for the genes uniquely associated with bipolar disorder is the regulation of sodium ion transmembrane transporter activity (Supplementary Table 6). The sodium- and potassium-activated adenosine triphosphatase pump (Na, K-ATPase) hypothesis for bipolar disorder, initially proposed by Singh (1970) and expanded on later by el-Mallakh (1983), suggests that a reduction in Na-K-ATPase activity may lead to mania and depression by increasing membrane excitability and decreasing neurotransmitter release. Subsequently, reduced Na-K-ATPase activity has been identified in the neural tissue of *Myshkin* mice displaying mania-like behaviour (Kirshenbaum et al., 2011) and in the erythrocyte membranes of BD patients (Banerjee et al., 2012). Despite the aforementioned literature, as well as the enrichment results of this study, highlighting the importance of Na-K-ATPase in the aetiology and treatment of BD, the exact mechanism(s) by which lithium regulates Na-K-ATPase remains unknown (Banerjee et al., 2016).

4.7. Schizophrenia

When the genes unique to SCZ aetiology were investigated using enrichment analyses a number of substance abuse-related pathways were identified; including nicotine, amphetamine and cocaine addiction, as well as alcoholism (Supplementary Table 3). The prevalence of substance abuse in schizophrenic patients is known to be high (Toftdahl et al., 2016), and a number of studies implicate substance abuse in the aetiology of SCZ (Callaghan et al., 2012; Jordaan and Emsley, 2014; Kuepper et al., 2011; Nielsen et al., 2017). In addition to this, recent studies have identified shared genetic liability between SCZ and nicotine dependence (Bhavsar et al., 2017; Chen et al., 2016). The results of this study further contribute to the concept of shared molecular and genetic liability between risk for substance abuse and SCZ. These results challenge the current clinical and diagnostic boundaries separating substance abuse and neuropsychiatric disorders, such as schizophrenia (American Psychiatric Association, 2013), and should be considered for improved understanding going forward.

4.8. Obsessive-compulsive disorder

Considering the genes unique to OCD, neuroactive ligand-receptor interactions and G-protein coupled receptor (GPCR) signaling pathways were among the top enrichment results (Supplementary Tables 4 and 8). Further analysis of the known human neuroactive ligand-receptor interactions revealed that all eight genes (*ADRB1*, *BDKRB2*, *CCKBR*, *CHRM4*, *CRHR2*, *HTR2B*, *MTNR1A* and *MTNR1B*) associated with these interactions encode for GPCRs, and interact with a number of molecules including epinephrine, bradykinin, cholecystokinin, acetylcholine, corticotropin releasing hormone, 5-hydroxytryptamine and melatonin, respectively (http://www.genome.jp/kegg/pathway/hsa/hsa04080.html). Interestingly, neuroactive ligand-receptor interactions have previously been associated with SCZ treatment response (Adkins et al., 2012) and Parkinson's disease aetiology (Kong et al., 2015). Considering the much smaller subset of genes uniquely associated with OCD aetiology and the identification of overlapping KEGG pathways and biological processes, these results highlight the neuroactive ligand-receptor interactions as excellent candidates for investigation to better understand the aetiology of OCD.

4.9. Study limitations

The analyses performed in this study are limited by the availability of published literature and the maintenance and accuracy of curated databases (Knottnerus and Tugwell, 2013; Matosin et al., 2014). Furthermore, it is not known if all genes specific to each disorder gene set have been investigated in any/all disorders due to the bias of not publishing negative findings (Matosin et al., 2014), as well as the possibility of unpublished positive results (Knottnerus and Tugwell, 2013). A limited number of input genes may explain the lack of additional enriched KEGG pathways (Table 2) for the identified small gene cluster (*AJUBA*, *FBLIM1*, *LIMD1*, *LPP*, *NOS1AP*, *TRIP6*, *WTIP*, *ZYX*) and further studies examining additional genes that interact with this cluster may help to identify additional significant pathways that could be investigated in the aetiology of neuropsychiatric disorders. Additionally, although outside the scope of this publication, very relevant traction in support of epigenetic factors and shared environment as a contributing factor to mental health disorders has been proposed (Nestler et al., 2016). Despite these limitations, these analyses provide relevant insight into pathways and biological processes that may be explored to better understand the common underlying aetiologies of the investigated neuropsychiatric disorders. Moreover, key pathways and biological processes were highlighted for further investigation for their contribution to the disorder-specific progression of the aforementioned disorders.

5. Conclusions

Neuropsychiatric disorders are complex in nature and consequently variation within many genes is expected to contribute to their aetiology (Visscher et al., 2012). Genetic overlap between ASD, BD, SCZ and OCD suggests common pathways, as well as pathways unique to each disorder. Here genetic overlap between ASD, BD, SCZ and OCD was found to be enriched for the well-characterised dopaminergic and serotonergic pathways, voltage-gated calcium ion channel gene network, and folate metabolism biological networks. The novel finding of regulation of the hippo signaling pathway was found to be commonly associated with these neuropsychiatric disorders, implicating neural development and neuronal maintenance as key in disorder psychopathology. In addition to the commonalities, unique disorder-specific pathways and biological processes were identified for ASD, BD, SCZ and OCD. These results highlight new prospects to be explored for the improved understanding of the complex aetiologies across neuropsychiatric disorders. Considering the current global incidence and prevalence rates of mental health disorders (Kessler et al., 2007; "WHO | Global status report on noncommunicable diseases 2010", 2011), it might be best to focus on cross-disorder commonalities in an attempt to realise actionable and translatable results to combat mental health disorders.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mcn.2018.02.010.

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