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Genetic dissection of neurocognitive phenotypes : implications for psychopathological susceptibility

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Genetic dissection of neurocognitive phenotypes: Implications for psychopathological susceptibility

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Abstract

This thesis aimed to uncover some of the more precise mechanisms by which genetic loci may influence neuropsychiatric susceptibility. I aim to identify genetic susceptibility for neuropsychiatric disorders using quantitative traits such as behaviour and neuroimaging parameters, which may help to index subclinical components present across several neuropsychiatric classifications. I probe specific neural networks/parameters of neurocognition; hypothesising to witness larger and more specific effects than assaying global parameters such as IQ and brain volume. I aim to uncover novel mechanisms by which some of the most intriguing genetic polymorphisms identified from recent genetic discoveries may modulate susceptibility.

The first study provides evidence suggesting that a common genetic variant hypothesized to modulate dopamine levels *(COMT),* may account for individual differences in the brain's global valuation system, which may then mediate susceptibility to a host of neuropsychiatric illness characterised by deficits in reward processing.

The second study provides evidence that genes identified by agnostic approaches (genome-wide association studies) may have a role in neurobiological pathways mechanistically linked to disorders such as schizophrenia/psychosis. I show a component of the working memory network for emotional faces is modulated by a variant on the *ZNF804A* gene in a manner that mirrors the disruptions seen in patients with schizophrenia.

The third study demonstrates that a variant on the *CLU* gene may modulate susceptibility to Alzheimer's disease in a similar functional manner to well-established genetic variants such as *APOE*. The study contributes to a body of knowledge suggesting that using neuroimaging, it is possible to

witness the association between genetic susceptibility to Alzheimer's disease and compensatory neurobiological changes, decades before the manifestation of clinical symptoms.

Based on the progression in the field of behavioural/imaging genetics and the discoveries within this thesis, I conclude by discussing the efficacy of tools such as behaviour/neuroimaging measures in the processes of linking genetic variance to neurobiological pathways to behaviour. I also show how the experimental studies in this thesis embed in present literature and replicate/converge with independent data. We must identify appropriate techniques to understand the nature of genetic susceptibility and classify specific neurobiological specific domains of heritable neurocognition. Once we can reliably link gene variants to specific domains of neurocognition, we can identify mechanistic links between genetic suspect ability and symptomology. These developments will help us consider therapeutic interventions for neuropsychiatric symptoms/states and develop risk prediction/reduction strategies.

Declaration

This work has not previously been accepted in substance for any degree and is not being currently submitted in candidature for any degree.

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Statement One.

This dissertation is the result of my own independent work/investigation, except where otherwise stated. A bibliography is appended.

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Statement Two.

I hereby give consent for my dissertation, if accepted, to be available for photocopying and inter-library loan, and for the title/summary to be made available for outside organisations.

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First, I acknowledge my close friends, whose passion and determination in their respective fields' inspired motivation and enthusiasm to work to the best of my ability.

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Most importantly, I offer my most sincere appreciation to Professor David Linden. His insight and expertise, coupled with his passion and enthusiasm are having a visibly positive impact on the research field. The methods by which we approach questions /interpret results in neuropsychiatry are now enhanced owing to Prof Linden's contributions. It has been both an honour and pleasure to work for him, and I aim to inspire thought and insight in the field in the same way. This investigation would not have been possible without him.

Last, I dedicate this thesis to my family. The skills you taught and the advice you gave have prepared me for what will hopefully be an exciting and rewarding career in science. Thank you for your constant love and support.

Abbreviations

5F	coagulation factor V
5HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled
5HTTLPR	neurotransmitter transporter (serotonin)
ABCA7	ATP-binding cassette, sub-family A (ABC1), member 7
AD	Alzheimer's disease
AdGWAS	Alzheimer's disease genome wide association study
ADHD	attention deficit hyperactivity disorder
ANK3	ankyrin 3, node of Ranvier (ankyrin G)
APOE	apolipoprotein E
APP	amyloid beta (A4) precursor protein
ARHGAP18	Rho GTPase activating protein 18
ARPP-21	cAMP-regulated phosphoprotein, 21kDa
ASDs	autism spectrum disorders
ASTN2	astrotactin 2
ATK	v-akt murine thymoma viral oncogene homolog 1
ATP5G2	TP synthase, H+ transporting, mitochondrial Fo complex
BDNF	brain-derived neurotrophic factor
BIMLP	biologically informed multi-locus profiles
BIN1	bridging integrator 1
BOLD	blood oxygen level dependency
BP	bipolar Disorder
BpGWAS	bipolar genome wide association study
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit
CD2AP	CD2-associated protein
CDH13	alanyl (membrane) aminopeptidase
CFG	convergent functional genomics
cIP	connectomic intermediate phenotype
CLU	clusterin
CNV	copy number variation
COMT	catechol-O-methyltransferase
CR1	complement component (3b/4b) receptor 1
CRHR1	corticotropin releasing hormone receptor 1

Abbreviations

CT	cortical thickness analysis
CTXN3	cortexin 3
DAAO	D-amino-acid oxidase
DARPP32	dopamine and cAMP regulated phosphoprotein
DAT1	neurotransmitter transporter (dopamine)
DCM	dynamic causal modelling
DD	delay discounting
DDR2	discoidin domain receptor tyrosine kinase 2
DGKH	diacylglycerol kinase, eta
DISC1	disrupted in schizophrenia 1
DLPFC	dorsolateral prefrontal cortex
DPP4	dipeptidyl-peptidase 4
DRD2/4	dopamine receptor D2/D4
DTI	diffusion tensor imaging
DTNBP	dystrobrevin binding protein 1
DWI	diffusion weight imaging
EPHA4	EPH receptor A4
eQTL	expression quantitative trait locus
ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4
FA	fractional anisotropy
FAD	familial Alzheimer's disease
FBXW8	F-box and WD repeat domain containing 8
FHR	familial high risk
fMRI	functional magnetic resonance imaging
GAD1	glutamate decarboxylase 1
GCA	granger causality analysis
GCFC2	GC-rich sequence DNA-binding factor 2
GPC1	glypican 1
GPCPD1	glycerophosphocholine phosphodiesterase GDE1 homolog
GPR6	G protein-coupled receptor 6
GR	glucocorticoid receptor
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B
GRS	genetic risk score

Abbreviations

GWAS	genome wide association study
HMGA2	high mobility group AT-hook 2
HRK	harakiri, BCL2 interacting protein
IP	Intermediate phenotype
IQ	intelligence quotient
KMO	kynurenine 3-monooxygenase
LD	linakge disequilibrium
LHFP	lipoma HMGIC fusion partner
MAOA	monoamine oxidase A
MCI	mild cognitive impairment
MD	major depression
MSRB3	methionine sulfoxide reductase B3
MTHFR	methylenetetrahydrofolate reductase
NCE	Neurocognitive endophenotype
NCIP	Neurocognitive intermediate phenotype
NOS1	nitric oxide synthase 1 (neuronal)
NRG1	neuregulin 1
NRGN	neurogranin (protein kinase C substrate, RC3)
NTRK2	neurotrophic tyrosine kinase, receptor, type 2
NTSR	neurotensin receptor 1
NXPH1	neurexophilin 1
OPRM1	opioid receptor, mu 1
PDE8B	phosphodiesterase 8B
PICALM	phosphatidylinositol binding clathrin assembly protein
POU3F2	POU class 3 homeobox 2
PSEN1/2	presenilin 1
RELN	presenilin 2
RGDM	reward guided decision making
ROBO1-ROBO2	roundabout, axon guidance receptor, homolog 1/2
RSRC1	arginine/serine-rich coiled-coil 1
SCN1A	sodium channel, voltage-gated, type I, alpha subunit
SELP	selectin P (granule membrane protein 140kDa, antigen CD62)

Abbreviations

SHROOM2	shroom family member 2
SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporters)
SLC9A7	solute carrier family 9, subfamily A
sMRI	structural magnetic resonance imaging
SNAP25	synaptosomal-associated protein, 25kDa
SNP	single nucleotide polymorphism
SORL1	sortilin-related receptor, L(DLR class) A repeats containing
SYNPR	synaptoporin
SZ	schizophrenia
SzGWAS	Schizophrenia genome wide association study
TBSS	Tract based spatial statistics
TCF4	transcription factor 4
TNIK	TRAF2 and NCK interacting kinase
TOMM40	translocase of outer mitochondrial membrane 40 homolog
TP63	tumor protein p63
TTC27	tetratricopeptide repeat domain 27
VBM	voxel based morphometry
VNTR	variable number tandem repeat
WDR41	WD repeat domain 41
WIF1	WNT inhibitory factor 1
WM	working memory
ZNF292	zinc finger protein 292
ZNF673	zinc finger family member 673
ZNF804A	zinc finger protein 804A
ε2, ε3, ε4	predominant *APOE* genotype isoforms

Preface

This thesis will investigate associations between genetic variance, the brain and behaviour in healthy individuals. I will take into account recent genetic discoveries and applications of these novel findings within behavioural genetic neuroimaging research, aiming to test novel associations that will help to mechanistically link genetic polymorphisms to the neurobiological traits that characterise some of the most debilitating neuropsychiatric disorders. It is not within the scope of this thesis to produce/contribute to an exhaustive list of associations between gene variance and behavioural/imaging phenotypes. However, a lot of this information is incorporated together for the first time in this thesis.

On a stage where genomics and phenomics are rapidly evolving, we are expected to identify and report the relationships that link genes and phenotypes with precise specificity and sensitivity. Once the specific mechanisms by which genes account for susceptibility are captured, we can start to take advantage of this knowledge and begin to develop treatment strategies based on our understanding of the underlying neurobiology. This thesis aims to investigate how some of the most intriguing hypothesized susceptibility SNPs (single nucleotide polymorphisms) may influence specific domains of neurocognition. Each of the experimental studies will determine effects of specific genetic variants using novel parameters of neurocognition designed to measure fundamental features of neuropsychiatric susceptibility.

By exploring hypothesized links between genetic variants and their putative functional consequences, it may be possible to reconceptualise ‘how’ and ‘to what extent’ genetic effects/contributions modulate neuropsychiatric susceptibility. The precise mechanisms by which these loci modulate

susceptibility may also offer neurobiological insights with novel therapeutic implications.

1. General Introduction

One of the most challenging tasks in psychiatric research is the identification of biological mechanisms that underlie clinical symptomology (Meyer-Lindenberg & Weinberger, 2006). Many psychiatric traits/symptoms have unknown aetiology and are hypothesized to be influenced by a complex host of biological factors, environmental exposure and interactions between the two (Sullivan, Daly & O'Donovan, 2012). Many of the psychiatric disorders that burden health care providers today are characterised by high rates of heritability. At present, we have the ability to capture components of the genome that contribute to the genetic risk underlying many of these conditions (Sullivan, 2010). One of the most substantial advances during the time of this thesis was the development of GWAS (genome wide association studies). Many GWAS have identified/replicated SNPs (single nucleotide polymorphisms), where a nucleotide variant (allele) may have increased/decreased incidence in patient groups compared to healthy controls. This approach has been used to identify gene variants that confer risk to schizophrenia (SZ) (O'Donovan, Craddock & Owen, 2009), bipolar disorder (BP) (Liu et al., 2011), Alzheimer's disease (AD) (Seshadri et al., 2010), major depression (MD) (Wray et al., 2012) and attention-deficit hyperactivity disorder (ADHD) (Stergiakouli et al., 2012). As genotyping becomes increasingly accessible and phenotypic data became readily available through multisite collaboration, the GWAS application was expanded to association of SNPs with dissected clinical phenotypes (Craddock et al., 2010; Hamshere et al., 2011), sub-clinical phenotypes (Terracciano et al., 2010), parameters of cognition (Papassotiropoulos et al., 2011a) and cortical morphology (Stein et al., 2012) at a population level. However, these vast

databases have yielded little information that can be utilized for clinical applications, contrary to widespread hopes (Sullivan & 96 Psychiatric Genetics Investigators, 2012). However, many of the single variant GWAS are identifying novel biological pathways by which these risk variants confer risk. This thesis aims to contribute original knowledge to this expanding field by quantifying the biological effects by which significant GWAS 'hits' contribute to the genetic architecture of the brain and increase susceptibility to clinical phenotypes.

The thesis will consider cognitive processes and biological pathways that are significantly disrupted in psychiatric/neurodegenerative disorders and measure the impact that susceptibility loci contribute towards total genetic risk. Parameters of cognition/neurobiological pathway and disruptions herein are selected based on specific criteria that will be discussed in Chapter 2.
It is hypothesized that large regulatory gene networks underpin neurobiological deficits associated with psychiatric disorders (Manolio et al., 2009). Furthermore, the genetic variation implicated in neuropsychiatric susceptibility from GWAS appears to extend far beyond protein-coding sequences and is likely to influence proximal regulatory elements in non-coding regions (ENCODE Project Consortium et al., 2012). It is likely that genetic susceptibility contributes to a large component of these disorders (Eichler et al., 2010). Preliminary studies used either genetic linkage analysis (coinheritance of genetic markers & phenotype) or candidate genotyping (association between phenotype and polymorphic markers on a gene of interest) to identify novel risk variants, based on understanding of the biological pathophysiology. Since the turn of the millennium, the advent of

1. General Introduction

GWAS has permitted the exploration of genetic variance, using hypothesis-free data exploration. Although the effect sizes of these SNPs are modest, it is estimated that their additive effects may explain ~23% of the variance in heritable neuropsychiatric disorders (Lee et al., 2012). McCarthy (McCarthy et al., 2008) posits a model in which genetic variance can contribute to a phenotype based on frequency and penetrance (impact of a gene on a phenotype) (Figure 1a). Genetic variants may be characterised by the manner in which they affect a phenotype. First, highly frequent variants contribute modestly to complex disorders. Second, intermediate proportion of genetic variance contributes with a moderate impact on phenotypic variance and third, infrequent variants may have significantly larger impact (penetrance) on a phenotype. Much of the genetic variance identified to date in the field of neuropsychiatric genetics abides to this model (Rucker & McGuffin, 2010) (Figure 1b/c), suggesting that neuropsychiatric disorders are characterised by complexity (Perlis, 2010) and heterogeneity (Labbe et al., 2012).

These findings also adhere to the polygenic model suggesting that genetic susceptibility is moderated by genetic variance ranging from low impact and high frequency to high impact and low frequency (McCarthy et al., 2008; Manolio et al., 2009). Taking into account the recent advances in genotyping (high power GWAS, whole-exome/deep-sequencing) one must also consider the possibility of finding genetic variance of high frequency and high penetrance. There may also be a degree of common/overlapping genetic variance for neuropsychiatric disorders (Schulze et al., 2012). It is suggested that genetic factors contribute to biological pathways that can increase susceptibility to several disorders that exist on a clinical spectrum. The main

themes of this thesis include investigating the role of functional polymorphisms (i.e. genetic variants that may affect the expression of a gene or the structure/function of the gene product) and GWAS variants, which are significantly associated with neuropsychiatric illness, but contribute modestly to the disease risk by relatively unknown mechanisms.

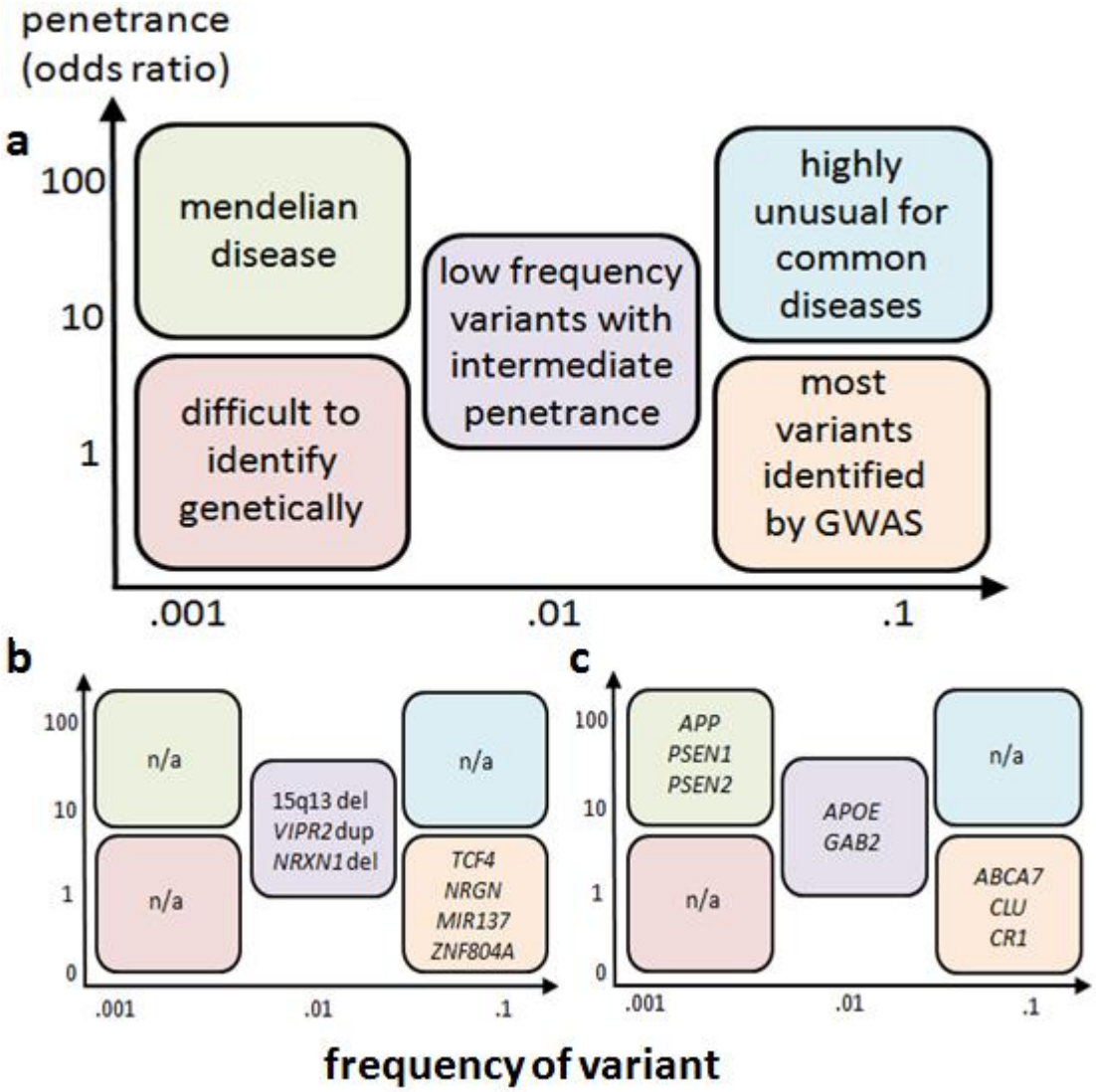

Figure 1 | Adapted from McCarthy (McCarthy et al., 2008). Figure (a) Model by which genetic variance may influence disease susceptibility. Figures (b) and (c) show the basic (non-exhaustive) inverse relationship between allele frequency and effect size for SZ (b) and AD (c). (del; deletion, dup; duplication).

2. Quantifying Mechanistic Pathways in Neuropsychiatric Genetics

2.1. The Biomarker Strategy

Several parameters are used when observing phenotypes in neuropsychiatric disorders, with varying criteria. One of the central questions is whether a measurement is a state or trait marker (Almasy & Blangero, 2001). State markers index the extent of clinical manifestation, whereas trait markers play an antecedent role in disorder pathophysiology, independent of clinical status. Early attempts to quantify the biological dysfunction in neuropsychiatric illness use the definition 'biomarker' to describe the presence or extent to which a neurobiological process linked to some manifestation or outcome of the illness. It was suggested that the biomarkers would robustly indicate pathological process, aid in the diagnostic classification of neuropsychiatric illness (Henley, Bates & Tabrizi, 2005; Schwarz & Bahn, 2008) and predict pharmacological response (Shaw et al., 2007). However, this hope, with the possible exception for some of the dementias (Zetzsche et al., 2010), has not been fulfilled. One reason may be the heterogeneity present in patient groups. Most neuropsychiatric disorders may have a multifaceted aetiology and biomarkers may thus not serve as a reliable and valid measure of diagnostic status (Ritsner, 2009). In order to further understand the aetiology of mental disorders, investigators sought to identify the biological pathways that exist on a causal pathway between putative aetiology and phenotype. Considering the large component of heritability underlying many neuropsychiatric illnesses, it was suggested that variation at multiple genetic loci contributed to disease complexity and heterogeneity (Cannon & Keller, 2006). Twin studies demonstrated that many cognitive parameters where largely driven by genetic factors (Wright et al., 2001). Many

of these cognitive parameters were disrupted in neuropsychiatric disorders. It was hypothesized that the genetics variants associated with disruptions in heritable domains of cognition would underpin components of neuropsychiatric susceptibility.

2.2. The Endophenotype Strategy

The endophenotype concept was an important development in neuropsychiatry as it specifically explored heritable traits associated with a disorder, rather than all observable pathogenic entities. Endophenotypes were defined as measurements with the ability to detect fundamental features of a disorder, independent of state-associated psychopathology and driven by genetic factors (Gottesman & Gould, 2003). The concept was introduced to minimize the heterogeneity of complex genetically influenced disorders (Cannon & Keller, 2006) by offering a series of quantitative, heritable trait-related deficits that reflected a particular subcomponent/s of a psychiatric disorder/s (Braff et al., 2008). The inception of the endophenotype criteria prompted the investigation of genetic susceptibility rather than phenotypes most associated with the clinical phenotype. The criteria, proposed by Gottesman (Gottesman & Gould, 2003) specified that an endophenotype must be a biologically anchored heritable state with the ability to co-segregate between patient groups and must also be present in unaffected biological relatives (Gottesman & Gould, 2003). It is suggested that these defects are more sensitive to genetic variance compared to complex clinical traits (Almasy & Blangero, 2001; Almasy et al., 2008; Gur et al., 2007). As biomarkers are not limited in scope by the requirement for genetic factors, a biomarker may or may not be an endophenotype, and endophenotypes may also serve as

biomarkers if they are reliably associated with a neuropsychiatric disorder (pp42-51; Volume 1 (Ritsner, 2009). Endophenotypes were hypothesized to serve as an approach to reducing the complexity and heterogeneity of neuropsychiatric disorders, offering alternatives and/or complementary objective traits to symptom/diagnostic based phenotypes.

The endophenotype strategy may help to delineate neurobiological disorder subcomponents and in doing so, may help to characterise psychiatric subgroups (Thaker, 2012). Broadening the scope of knowledge for psychiatric subclinical neurocognitive traits may also aid in the development of clinical classification and/or treatment strategies (Avila et al., 2003; Deutsch et al., 2005; Javitt et al., 2008; Thaker, 2008) and the identification of individuals with high levels of risk (Thaker, 2000; Thaker & Avila, 2003; Walters & Owen, 2007) . Many neuropsychiatric disorders are explored using endophenotypes, as they may be specific to a disorder and replicable across patient groups (Gottesman & Gould, 2003; Hasler et al., 2006). Endophenotypes include neurocognitive traits, biochemical/immunological altercations, physiological anomalies, neurodevelopmental or neuroanatomical/neuroimaging traits (Review: pp12-13 (Ritsner, 2009). This thesis will explore the association between gene variants and endophenotypes derived from behaviour and/or neuroimaging. Specifically, this work will consider the impact of genetic influence on a selection of promising candidate endophenotypes designed to recruit specialised and domain specific neural resources, compared to conventional biomarkers, which are not sufficiently heritable. Although, many candidate endophenotypes meet the necessary criteria as genetic trait markers, it is not fully understood how these endophenotypes mechanistically

link risk genes to disease pathophysiology. Endophenotypes do not necessarily clarify different mechanisms of susceptibility between disease subgroups and often reflect combinations of deficits highly heterogeneous in form and distribution for a clinical disorder. For example, brain structure deficits (a popular SZ endophenotype candidate) differ between SZ patient subgroups suggesting that several different neurobiological disease entities independently modulate regional structural abnormalities across diagnostic subcategories (Nenadic, Gaser & Sauer, 2012). It is also not established whether the genetic factors underlying heritability of an endophenotype are the same as the genetic susceptibility that confers vulnerability to neuropsychiatric illness. Furthermore, the assumptions underlying endophenotypes suggest that the disease entity is concealed, however, owing to recent advances in neuroimaging we are able to measure the parameters of specific neurobiological systems, particularly those implicating in neuropsychiatric disease.

2.3. The Intermediate Phenotype Strategy

The intermediate phenotype approach provided an alternative link between gene and psychopathology. Rather than relying on measuring the genetic effects on heritable states of neurocognition, the strategy aims to quantify neurobiological entities that mechanistically linked genetic susceptibility and neuropsychiatric vulnerability. Endophenotypes served to add predictive value to the genetic weighting underlying neuropsychiatric susceptibility, using components of neurocognition that recruited global/unspecific neural networks. Using this approach, it is difficult to specifically identify the pathogenic processes underlying susceptibility. The

intermediate phenotype strategy takes into account specific neurobiological deficits observed in a disorder and makes predictions about which genetic contributions confer susceptibility based upon how the gene modulates the pathogenic disease entity. The intermediate phenotype method is now used to describe measurements that aim to predict both gene-neurobiology and neurobiology-behaviour associations, mechanistically linking gene and behaviour in the process. The decomposition of psychiatric diagnosis into alterations in biological-pathway based entities was primarily achieved using neuroimaging methods. Although the heritability components of functional/structural imaging parameters are not as explicitly understood as neurocognitive endophenotypes (Rasetti & Weinberger, 2011), intermediate phenotypes appear to measure the principal mechanisms influenced by genetic variance and antecedent to behaviour.

Recent evidence suggests that functional activation/connectivity measures serve as heritable components of cognitive neurophysiology (Blokland et al., 2011; Fornito et al., 2011; Fornito et al., 2012), although it remains uncertain to what extent genetic variance may affect these functional/connective imaging parameters. It is hypothesized that at a system level, the effects of genetic variance may be observed in individuals who do not display overt symptomology/behavioural deficits. Functional neuroimaging parameters are attractive measures as they employ tasks independently moderated by heritability (Ando, Ono & Wright, 2001; Carter et al., 2009; Eack et al., 2010; Hansell et al., 2005; Mathersul et al., 2009; Wright et al., 2001). There have been several neural circuits proposed as potential intermediate phenotypes, many of which probe either cortical regions previously implicated

in neuropsychiatric pathogenesis, cortical regions that robustly activated during a neurocognitive task or a combination of the two. For example, the dorsolateral prefrontal cortex (DLPFC) is routinely implicated in the molecular pathogenesis of neuropsychiatric disorders (Glahn et al., 2010b; Potkin et al., 2009b) and recruited during robust neuroimaging endophenotypes such as working memory (WM). Thus, mechanisms of neural circuitry in WM may provide insight into the putative effects of genetic risk variants (Linden & Thome, 2011; Linden, 2012). Genetic neuroimaging is an attractive approach towards the eludification of genetically driven pathogenic endomechanisms that confer susceptibility to neuropsychiatric symptomology. Parameters of behaviour may also act as intermediate phenotypes if they characterise a domain specific neurobiological system with enough neurobiological specificity to observe effects of a hypothesized gene variant. As understanding of the neurobiological processes underlying pathogenic neural networks increases, it could be suggested that we are now quantifying genetic contributions to ‘exophenotypes’ (Meyer-Lindenberg & Weinberger, 2006) as we have access to information detailing the mechanisms by which neural networks are disrupted.

3. Genotype Phenotype Associations: A General Hypothesis

Although each of the studies presented in this thesis has a specific hypothesis regarding how genetic variants influence a specific trait or behaviour, there is a principal hypothesis that will be carried throughout the investigations. The experimental studies in this thesis support a polygenic model for neuropsychiatric disorders. That is, complex neuropsychiatric disorders manifest as combinations of genetic variants that modulate susceptibility based on specific biological entities (International Schizophrenia Consortium et al., 2009). It is suggested that these gene variants operate through a number of biological pathways (Greenwood et al., 2011). Within this model, one genetic variant may contribute to more than one neurobiological pathway and more than one disorder (genetic pleiotropy), as supported by evidence of genetic overlap between disorders (Williams et al., 2011a). Pathogenic alleles that contribute to these pathways may also influence general transdiagnostic phenotypes, deficits that can be observed in many neuropsychiatric disorders (Arguello & Gogos, 2012). It may also be apparent that several genetic variants may evoke broad susceptibility to neuropsychiatric disorders based on the specific neurobiological pathway that the variant alters (Burdick et al., 2009) (Figure 2).

3. Genotype Phenotype Associations: A General Hypothesis

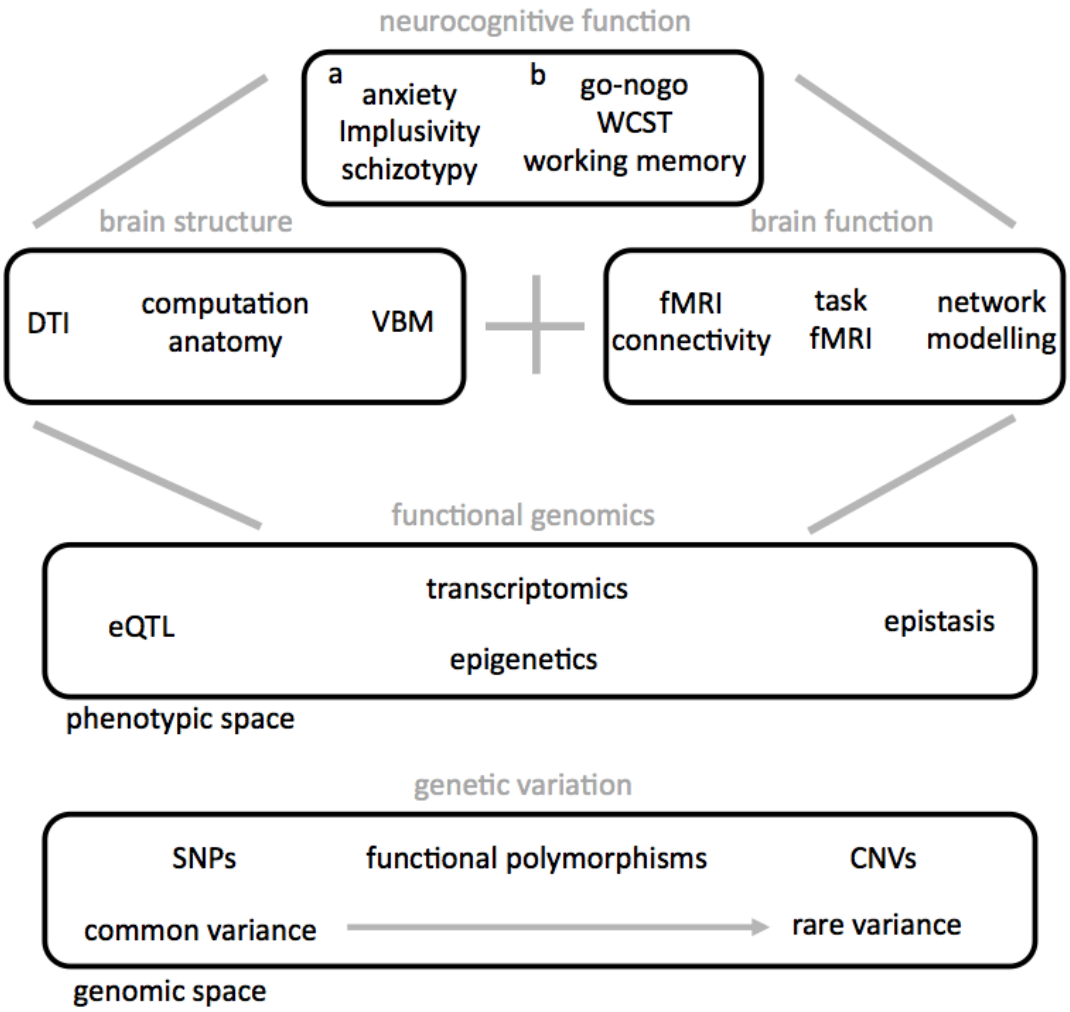

Figure 2 | Adapted from Congdon (Congdon, Poldrack & Freimer, 2010) . A prototypical model demonstrating how parameters of genetic variance may contribute to phenotypic landscape. Four (non-exhaustive) biomarker/intermediate/endophenotype subcomponents commonly probed for function effects of genetic variance, with documented association with specific phenotypes (such as neuropsychiatric disorder symptomology). NB. In the neurocognitive function component (a) refers to personality dimensions and (b) refers to various parameters of neurocognitive performance. (DTI: diffusion tensor imaging; eQTL (expression quantitative trait loci); VBM (voxel based morphometry); WCST (Wisconsin card sorting task); SNPs (single nucleotide polymorphism); CNVs (copy number variations).

4. Neurocognitive Phenotypes: A General Hypothesis

There are many components of physiology that are described as intermediate/endophenotypes, ranging from molecular level (genomic, transcriptomics, intracellular) and peripheral (proteomic, metabolic) to 'neurocognitive' (measuring brain structure, neurophysiology and/or behaviour) (Gottesman & Gould, 2003). Establishing the links between neurocognitive intermediate/endophenotypes and genetic variance may further the understanding of how genetic variance may contribute to neurobiological process at a systems level (Buckholtz & Meyer-Lindenberg, 2012). Indeed, understanding the mechanisms by which genes/gene networks contribute to system level intermediate/endophenotypes will further the understanding of neuropsychiatric symptomology and nosology (Linden, 2012) and may aid in the prediction of risk status (Whalley et al., 2012). Although there are too many candidate neurocognitive endophenotypes (NCEs) to exhaustively list in this thesis, some of the NCEs used to disambiguate the role and function of candidate/GWAS risk variants will be discussed (Chapter 5.Working Memory; Chapter 6.Emotion Processing). As these experimental paradigms have not been mapped for heritability estimates, I will refer to the experimental procedures in this thesis as 'neurocognitive intermediate phenotypes' (NCIPs) (a definition that avoids the assumption that the phenotypes are either heritable or 'hidden'). Furthermore, the thesis will discuss novel NCIPs and how they may contribute in the understanding of genetic susceptibility (Chapter 7.Reward-Processing). This thesis will evaluate the impact/usefulness that NCIP (Chapters; 5-7) have had on quantifying genetic susceptibility. Furthermore, I will consider experimental approaches that dissect NCIPs into smaller 'domain-specific' entities and

probe for potential effects of genetic susceptibility on these specific neurocognitive pathways.

5. Working Memory

5.1. Working Memory As A Neurocognitive Endophenotype

Working memory (WM) is described as a limited-capacity storage system for the temporary maintenance and manipulation of information (Cowan et al., 2005). Deficits in WM have been extensively documented in a broad range of neuropsychiatric illness across a wide range of WM based tasks. WM disruptions in psychiatric populations become more prevalent at higher WM demands (Gold et al., 2010). These deficits appear to be independent of clinical status changes such as disease progression, medication effects or positive symptom (delusions/hallucinations) severity. WM disturbances are present in clinically unaffected biological relatives of SZ and BP patients (Cannon, 2005), suggesting that WM disruptions are not manifestations of the disorder, but rather reflect underlying biological disruptions that contribute to the vulnerability for illness (Heaton et al., 2001; Liu et al., 2006; Niendam et al., 2007; Nopoulos et al., 1994; Rodriguez-Sanchez et al., 2008; Sponheim et al., 2010; Zanello et al., 2009). The heritability of WM is moderate (estimates range between .36 and .49) (Ando, Ono & Wright, 2001; Hansell et al., 2005). The neural networks underlying WM are also well characterised in healthy individuals, unaffected biological relatives and psychiatric populations. First-degree relatives and neuropsychiatric populations show aberrant patterns of activation and connectivity during WM tasks (Glahn et al., 2005).

As WM seems to be influenced by genetic factors (Hansell et al., 2005; Wright et al., 2001), many studies have sought to characterise the specific genetic contributions that modulate performance in WM (See Table 1). It is suggested that detecting genetic variants that influence WM ability may help

to identify biological pathways to that increase susceptibility to psychiatric illness with disruptions in WM such as SZ, for which treatments strategies can be modelled upon (Apud & Weinberger, 2007; Giakoumaki, Roussos & Bitsios, 2008; Roussos, Giakoumaki & Bitsios, 2009). Genetic influences over WM will be more detectable as WM reflects a subcomponent of several complex psychiatric phenotypes, which are modulated a more specific genetic network, reducing the complexity of the genetic analysis required to identify genetic susceptibility (Rasetti & Weinberger, 2011). Although much of this works uses WM as an endophenotype for neuropsychiatric illness in younger populations (SZ, BP, MD etc.), there is also a large body of working implicating WM as a component of cognition that is vulnerable to disruption during the aging process, mild cognitive impairments and during neurodegenerative diseases (Huntley & Howard, 2010; Rentz et al., 2010; Saunders & Summers, 2010).

5.2. Genetic Contributions To Working Memory Performance

Over the last fifteen years, researchers have sought to identify the genetic variants that contribute to variability in WM performance. Several studies have studied the effects of single gene variants, epistatic relationships and multi-locus contributions to WM performance (Greenwood et al., 2011; Markett, Montag & Reuter, 2010). It is now suggested that WM heritability reflects a complex network of genetic contributions that modulate performance via several neurobiological pathways. There is also a degree of selectivity, where genetic variants may influence specific sub-components of WM, suggesting specific neurobiological roles within a WM network (Stelzel et al., 2009). As cognitive processes are incorporated into WM (numbers,

scenes, faces, words, shapes) and WM measures vary in task-complexity (maintenance vs. maintenance & manipulation) the range of genetic variants that contribute to cognitive processes may diversify further.

Neuroimaging studies have also identified that genetic modulation of WM can be divided via temporal sub-processes; where selective genetic variants modulate the attentional/encoding process, the maintenance period or during retrieval suggesting that contributions from neurobiological pathways may affect WM independently (Tan et al., 2007a).

A review of the genetic variants associated with WM, organised via WM task and biological pathway (Table 1) demonstrates the complexity of WM neurobiology. This review includes variants from both candidate genes and those identified via genome wide association studies (GWAS). The review incorporates gene variants that show variability at a behavioural level, all GWAS genes associated with neural activity during WM are documented later (See 9. GWAS and Magnetic Resonance Imaging). This analysis suggests that the neurobiology that facilitates WM is derived from many molecular processes, which may all affect susceptibility to many neuropsychiatric disorders such as SZ (*ZNF804A*, *DISC1*), BP (*CACNA1C*), MD (GR, *BDNF*) and AD (SCN1A, *APOE*).

It is difficult to estimate the proportion of variance or size of effect for a single gene locus on WM performance partly due task differences (for example; COMT (rs4680) explained 4% of variance in one WM task and 11% in another (pp199 (Goldberg & Weinberger, 2009)). At a population level, single loci appear to have modest effects on WM performance. Individual genetic contributions (identified via candidate gene studies or GWAS) to WM

disrupt different components of the WM process, which all ultimately lead to a WM deficit. WM may be a global disruption, and may be indicative that one of many gene-neurobiological disruptions has occurred. This has implications when determining the underlying cause and treatment for neuropsychiatric disorders characterised by WM deficits. WM may also vary as a function of epistasis (A gene loci-WM association is modulated by other gene loci and/or environmental stimuli). There appear to be many routes to WM disruption so understanding the nature/transmission of WM deficits in healthy controls/patient groups may help to contextualize the specific neurobiological mechanisms that drive neuropsychiatric susceptibility (Karlsgodt et al., 2011).

5. Working Memory

Neurobiological Pathway	Gene/s	Studies
axon guidance/axonogenesis	*RELN CACNA1C BDNF DRD2*	Gong et al., 2009 Markett, Montag & Reuter, 2010 Richter-Schmidinger et al., 2011 Wedenoja et al., 2008
neuron differentiation/migration	*RELN GAD1 DRD2*	Markett, Montag & Reuter, 2010 Straub et al., 2007 Wedenoja et al., 2010
transcription factor binding	*GR ZNF804A*	Kumsta et al., 2010 Walters et al., 2010
cell migration	*DISC1 DTNBP1*	Alfimova et al., 2009 Alfimova et al., 2010 Carless et al., 2011 Hashimoto et al., 2010
protein binding	*GR DISC1 NOS1 NRG1 DTNBP1*	Alfimova et al., 2009 Alfimova et al., 2010 Carless et al., 2011 Donohoe et al., 2009 Hashimoto et al., 2010
cell proliferation	*ERBB4 AKT1 NRG1*	Alfimova et al., 2011 Stefanis et al., 2007
nervous system development	*DISC1 NRG RELN BDNF*	Carless et al., 2011 Gong et al., 2009 Richter-Schmidinger et al., 2011
synaptic transmission	*SNAP25 NTSR DTNBP1 DAT1*	Hashimoto et al., 2010 Hashimoto et al., 2011 Li et al., 2010 Soderqvist et al., 2010
dendritic development	*BDNF ZNF804A*	Gong et al., 2009 Walters et al., 2010
cell adhesion molecule	*NRG1 RELN*	Alfimova et al., 2011 Wedenoja et al., 2010
ion channel transport	*CACNA1C SCN1A*	Papassotiropoulos et al., 2011a Zhang et al., 2012
lipid metabolism	*CDH13 APOE*	Arias-Vasquez et al., 2011 Greenwood et al., 2005 Gong et al., 2011a
glutamate signaling pathway	*SNAP25 BDNF GAD1 DAAO*	Gong et al., 2009 Jansen et al., 2009a Jansen et al., 2009b
amino acid metabolism	*KMO MTHFR*	Roffman et al., 2008 Tsai et al., 2011 Wonodi et al., 2011
anti-apoptotic	*ERBB4 NOS1 AKT1 BDNF GAD1*	Donohoe et al., 2009 Rose et al., 2012a Wonodi et al., 2011
glutamate signaling pathway	*DTNBP1 GAD1*	Alfimova et al., 2009 Alfimova et al., 2010

		Wolf et al., 2011
dopamine signaling pathway	*COMT DAT1 DRD4 NTSR*	Barnett et al., 2011 Froehlich et al., 2007 Li et al., 2011 Zilles et al., 2012
serotonin signaling pathway	*5HTT 5HT2A MAOA*	Barnett et al., 2011 Enge et al., 2011 Gong et al., 2011a Zilles et al., 2012

Table 1 | Working memory performance, as modulated by gene variants and the neurobiological pathways to which they contribute. For this review, each of the gene-WM associations documented have been replicated in at least one independent sample (healthy controls (HC) x 2 or HC and one neuropsychiatric patient group). All pathways considered are modulated by at least two genes.

6. Social Cognition and Emotion Processing

6.1. Emotion Processing As A Neurocognitive Phenotype

The complexity of a cognitive process may affect its construct validity as a candidate endophenotype. Broad endophenotypes are likely to be supported by large regulatory gene networks, as argued in the previous chapter on WM. Genetic components of cognition with specific neurobiological substrates will be easier to identify than cognitive processes that recruit complex and diverse neurobiological mechanisms. Many endophenotypes do not specifically distinguish between biological systems and may be as complex as symptoms/diagnosis and recruit a wide platform of neural resources that are difficult to disentangle at a genetic level (Butcher, Kennedy & Plomin, 2006; Kovas & Plomin, 2006; Plomin, Haworth & Davis, 2009). Social cognition has been extensively studied within neuropsychiatry and some of the most dramatic deficits occur in emotion regulation/processing (Derntl & Habel, 2011; Taylor, MacDonald & Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, 2012). Many of these deficits appear to have genetic determinants (Bevilacqua & Goldman, 2011). Meta-analysis suggests that genetic variance may account for a small proportion of the variance in affect-related traits (Munafo et al., 2009b) and a moderate proportion of variance in emotion processing (Pergamin-Hight et al., 2012). The latter suggests that biased attention for emotional information is a notable parameter (medium effect size). These domains may be useful in capturing novel components of heritable susceptibility, compared to conventional measures of cognition that yield smaller effects (Barnett et al., 2007; Barnett, Scoriels & Munafo, 2008). Evidence suggests a robust link between neurobiological substrates of emotion processing (*5HTTLPR* and

amygdala activation for example; (Murphy et al., 2012b)) although this effect size is most likely due to the sensitivity of functional neuroimaging (Linden, 2012) showing evidence for proximal links between emotion modulating pathways and genetic variance of the serotonergic system.

The multifaceted interaction between phenotypes, genetics and the environment (Meyer-Lindenberg & Tost, 2012; Tost & Meyer-Lindenberg, 2012) should also be taken into consideration when exploring social cognition. Social processing parameters are relatively dynamic and vary according to exposure from environmental stimuli. The interplay between gene and environment allows researchers to observe the effect a gene variant can potentially have, for example on individuals exposed to environmental stressors (Munafo et al., 2009a). The networks of social cognition and emotion processing are likely mediated by environmental stimuli. The impact of the environment may exaggerate the effects of genetic predisposition in accordance with conventional diathesis-stress models. It may be apparent that components of social cognition and emotion processing yield greater individual differences as a function of environmental experience combined with genetic predisposition. Although the effect of a single variant on behavioural phenotypes may be relatively modest, genotypes may have a significantly larger effect on individuals exposed to different stressors (van Ijzendoorn, Belsky & Bakermans-Kranenburg, 2012). This may also explain the discrepancy in effect sizes between patients and controls. Several studies using behavioural and neuroimaging measures support the notion of gene × environment interactions where gene effect sizes are larger for those who face social stressors (European Network of Schizophrenia Networks for the

Study of Gene-Environment Interactions, 2008; Stefanis et al., 2007; van Os, Rutten & Poulton, 2008; van Os & Rutten, 2009). To this end, convergent genomic, molecular, neural and behavioural phenotypes suggest that genetic variance, environmental stimuli and gene × environment interactions are implicated in specific neurobiological systems, which contribute to selective components of emotion processing and stress responses (Mickey et al., 2011; Zhou et al., 2008;). One component of emotion processing that has drawn considerable attention is the processing of face identity and expression. This component of social cognition is of considerable importance, as it is likely to be a conserved, specialised neurobiological system in humans.

Research notes that accuracy of facial affect recognition and/or processing is a significantly heritable and dynamic process (Greenwood et al., 2007) and also a robust trait marker of transmitted states such as SZ (Calkins et al., 2010) and BP (Glahn et al., 2010a). The identification of facial affect in patients is considered a relatively stable trait as deficits in emotion recognition persist in patients despite improvement of symptom severity (Bediou et al., 2007a; Bediou et al., 2007b). Face processing deficits have also been shown in relatives of SZ patients with intermediate accuracy between patients and healthy controls (Leppanen et al., 2008a; Leppanen et al., 2008b). These findings suggest that deficits in face processing may be selective to faces due to the emotional expression of the face. This finding supports previous theories that the heritable component of emotion recognition may be derived from the emotional valence of social cues (Toomey et al., 1999). Neurophysiological parameters measuring early visual processing components identify restricted visual-scan paths in both patients and first-

degree relatives, suggesting an element of genetic susceptibility (Loughland, Williams & Harris, 2004; Loughland, Williams & Gordon, 2002; Morris, Weickert & Loughland, 2009; Wolwer et al., 2005). Unlike WM, the genetic/neurobiological factors underpinning emotion processing/facial affect recognition appears to be more precise and resolute. An emerging body of behavioural/neuroimaging research implicates specific gene-pathways with these processes, limiting the scope of susceptibility to serotinergic (Munafo et al., 2009a; Munafo et al., 2009b; Murphy et al., 2012b), catecholominergic (Drabant et al., 2006), stress–axis (Hsu et al., 2012; Mickey et al., 2011; Zhou et al., 2008;) or neurotrophic gene pathways (Pezawas et al., 2004) and interactions between these systems (Review; (Bevilacqua & Goldman, 2011)). One notable body of evidence also implicates a functional (mRNA expression mediating) *DTNBP1* variant with dissociable emotion-memory networks (Wolf et al., 2011a). The gene in this study has previously been linked to SZ (Owen, Williams & O'Donovan, 2004), cognitive endophenotypes (Burdick et al., 2007) and molecular-level dysfunction (Weickert et al., 2004) and is suggested that *DTNBP1* may pleiotropically mediate heritable susceptibility states through dopamine-glutamate mediated signalling pathways (Wolf et al., 2011a). Although the specific cortical pathways that mediate emotional content-effects in face processing vary between studies, the deficits provide evidence that genetic variance associated with facial affect recognition/processing may serve as neuropsychiatric susceptibility. There is also considerable interest in this pathway as a neurocognitive endophenotype due to its heritability and specificity compared to ‘global’ parameters such as IQ or global attention (Zhu et al., 2010).

6. Social Cognition and Emotion Processing

6.2. GWAS SNPs & Emotion Processing

Emotion processing has been identified as a domain of cognition strongly influenced by genetic factors. It is also a notable endophenotype for neuropsychiatric disorders (Greenwood et al., 2007). There have been consistencies in neuropsychiatric genetics studies at a genome-wide level, which may help to distinguish between patients, relatives and healthy controls. This is especially reassuring, as neurocognitive domains such as emotion processing seem to be modulated by different genetic networks between families (Wiener et al., 2012).

One of the most consistent findings from GWAS implicates *CACNA1C* in the pathophysiology of neuropsychiatric illness (Ferreira et al., 2008; Sklar et al., 2008). Although initially associated with BP it has been repeatedly linked with a broad spectrum of neuropsychiatric illnesses (Green et al., 2010; Hamshere et al., 2012; Nyegaard et al., 2010; Ripke et al., 2011; Sklar et al., 2008) . A significant risk variant on the *CACNA1C* gene (rs1006737) is also associated with a host of candidate endophenotypes with converging findings implicating the variant in the emotion/face regulation process (Bigos et al., 2010; Jogia et al., 2011; Radua et al., 2012; Soeiro-de-Souza et al., 2012). Considering the success of this paradigm at identifying the effects of a SNP with a modest effect size (rs1006737; OR=1.18) the use of emotion/face processing in genetic imaging/behavioural genetics for SZ susceptibility may also identify effects of SZ genes with modest susceptibility such as *ZNF804A* (See Chapter; 17.1-17.5.).

6. Social Cognition and Emotion Processing

6.3. Face Memory, Heritability & Susceptibility

Memory and emotion processing remain two of the most robust heritable traits (Barch et al., 2009b; Mathersul et al., 2009) and well-established endophenotypes within neuropsychiatric subfields (Calkins et al., 2010; Eack et al., 2010; Greenwood et al., 2007). Many genetic associations studies have attempted to provide neurobiological mechanisms that facilitate heritability and susceptibility in these domains. However, meta-analysis suggests that many penetrant functional polymorphisms yield no/little effects on these parameters (Barnett, Scoriels & Munafo, 2008; Frustaci et al., 2008; Munafo et al., 2009b) . Although these candidate endophenotypes' are certainly transmitted in families (Savage et al., 2012), it is suggested that the heritability for these states reflects a broad and unspecific genetic weighting (which explains the small contribution from genetic variants) and may differ between populations (Wiener et al., 2012). Rather than attempt to establish how each genetic variant contributes to broad cognitive domains such as IQ, researchers are now attempting to establish the genetic contributions towards specific cognitive domains. One such domain is memory for faces, showed to be disrupted in SZ patients/relatives (Calkins et al., 2010) and BP patients /relatives (Glahn et al., 2010a) with larger penetrance than WM and similar to that of emotion processing. Using face memory as a candidate endophenotype has identified significant effects of the SZ risk gene *RSG4* in large samples, even after strict Bonferonni corrected adjustments for verbal/spatial memory tests and multi-variant analysis (Prasad et al., 2010), but not other candidate variants with similar clinical associations (Jansen et

al., 2010), suggesting the quantitative trait has domain specific neurobiological underpinnings rather than generalised function.

There have been relatively few explorations into pathophysiological characteristics of emotion-cognition interactions in neuropsychiatric populations, considering the contribution of WM and emotion processing towards susceptibility. It has been suggested that negative emotion attribution disrupts the allocation of task relevant resources in SZ (Premkumar et al., 2008). The association of negative stimuli with WM exaggerates the reallocation of cortical resources from WM relevant regions to neural substrates associated with emotion processing in patients with SZ (Pauly et al., 2008). Furthermore, SZ patients and familial high-risk (FHR) populations have reduced efficiency of emotional processing during WM (Phillips et al., 2011). Studies within our lab characterised the nature of this dysfunction using functional neuroimaging. BOLD signal intensity differences were calculated for healthy controls > SZ patients (matched for education, age, sex etc.) when performing WM task using emotional faces. The cortical regions activated by WM load (1-4 faces) and emotional face valence (angry, neutral & happy) were replicated from previous studies (Jackson et al., 2008), but group differences suggested a specific dysfunction for WM for faces. Patients showed aberrant activation in the dorsolateral prefrontal regions (DLPFC). The right DLPFC failed to recruit the adequate neural resources and left DLPFC showed hyper-activation, presumably acting as a contralateral homologue to compensate for the dysfunction of the right DLPFC (Wolf et al., 2011b). The DLPFC performs guided maintenance of task relevant information (Cowan, 2001) and is recruited for WM in a load dependent

manner (Linden et al., 2003). Neural activation in prefrontal regions has been found to correlate positively with performance (Jackson et al., 2008). It is also widely implicated in the processing of facial affect and dysfunctional in neuropsychiatric disorders (Leitman et al., 2011; Robinson et al., 2008; Ursu et al., 2011; Yoon et al., 2008).

It could be suggested that dysfunctional DLPFC activation during WM for emotional faces may be a phenotype that characterizes the deficits in emotional and/or face memory that are observed in neuropsychiatric populations (Becerril & Barch, 2011; Yoon et al., 2008;). Preliminary use of this emotional face WM as a neurocognitive phenotype identified effects of a functional *DTNBP1* variant on widespread WM and face processing networks (Wolf et al., 2011a).

7. Neuroeconomics

Neuroeconomics (decision-making regarding value and utility (Sharp, Monterosso & Montague, 2012)) is considered a 'high-level' cognitive process that moderates how we interpret potential outcomes based on preferential choice selection (Ernst & Paulus, 2005) . It is modulated by a host of intrinsic/extrinsic factors and governed by well-defined parameters of neurobiology (Doya, 2008). Although there are well-established deficits implicating the reward guided learning process in several neuropsychiatric disorder (Der-Avakian & Markou, 2012; Deco et al., 2012), reward guided learning is seldom considered an endophenotype as its heritability remains largely unexplored (Sharp, Monterosso & Montague, 2012) . There are a host of studies implicating genetic variability in the dopaminergic and serotoninergic (Aarts et al., 2010; Aarts, van Holstein & Cools, 2011; Frank & Fossella, 2011) as well as preliminary evidence suggesting potential roles of the opioid system (Lee et al., 2011; Perkins et al., 2008; Ramchandani et al., 2011; Troisi et al., 2011) in reward/learning processes. Interestingly, there is a host of empirical *in vivo* evidence from animal studies considering the neurobiology of reward processing (Chang, Barack & Platt, 2012), much of which can be considered when exploring mechanisms of genetic susceptibility. It could be argued that genetic variance contributing to the dopaminergic, serotonergic and opioid system should be taken with special consideration. However, the recent stratification of reward processing into subcomponents may also offer researchers a unique opportunity to explore domain specific mechanisms by which genetic variance may contribute to neurocognitive systems. This next chapter will consider the heritability of reward processing subcomponents, the deficits associated with

neuropsychiatric illness and potential mechanisms by which genetic variance may modulate domains of reward processing implicated in neuropsychiatric illness.

7.1. Risk-Taking, Impulsivity & Financial Decision Making

A significant proportion of risk-taking behaviour and financial decision-making can be accounted for by genetic differences. It is estimated that between 20-60% of the variance in risk-taking can be accounted for using tasks that measure risk taking propensity (Anokhin et al., 2011; Zhong et al., 2009). There are well-defined neurobiological pathways in the brain that coordinate risk-taking propensity (Meyer-Lindenberg et al., 2006a; Whelan et al., 2012). Deficits in risk-taking may arise as a pathological phenotype in disorders of impulsivity and affect (Robbins et al., 2012). Deficits in risk-taking, impulsivity and financial decision-making have been observed in patient groups at a behavioural level (Adida et al., 2011a; Adida et al., 2011b; Cheng et al., 2012) via neuroimaging parameters (Kaladjian et al., 2007; Kaladjian et al., 2009; Kaladjian et al., 2011; Mazzola-Pomietto et al., 2009) and for candidate genes (Forbes et al., 2009a; Gizer & Waldman, 2012; Reif et al., 2010; White et al., 2009) .

Delay Discounting (DD) is a well-defined parameter of impulsivity, in which impulsive individuals underestimate the subjective value of delayed rewards and demonstrate an increased propensity to choose smaller immediate rewards (Kirby & Santiesteban, 2003; McClure et al., 2004;). Individuals who display myopic discounting (preferences for smaller immediate rewards) are largely driven by the prospects of immediate gratification rather than considering the rewards associated with long-term

pursuits. DD is mediated by distinct cortical regions compared to other measures of impulsivity such as response inhibition which require motor networks (Hariri et al., 2006; Monterosso et al., 2007), however the full neural network that moderates the choice-protocol is a subject of on-going debate (Kable & Glimcher, 2010; Marco-Pallares et al., 2009; Pine et al., 2010). Self-report measures of delay discounting suggest a heritability estimate of ~50% (Anokhin et al., 2011). Myopic DD has been observed in heritable disorders such as addiction (Mackillop et al., 2012; Miedl, Peters & Buchel, 2012), ADHD (Paloyelis et al., 2010) and SZ (Heerey et al., 2007; Wing et al., 2012). DD may also predict traits such as reward reactivity (Lempert & Pizzagalli, 2010). There are also significant gene × age interactions during DD suggesting potential epigenetic and/or environmental factors (Boettiger et al., 2007; Gianotti et al., 2012; White et al., 2009).

7.2. Reward, Motivation & Hedonic Capacity

Anhedonia is conventionally characterised as a diminished capacity to experience rewarding events with positive affect (Der-Avakian & Markou, 2012) or more recently; a cognitive impairment that negatively biases ratings of pleasure at recall (Strauss & Gold, 2012). Preliminary evidence suggests that additive genetic effects explains ~50% of self-reported introverted anhedonia (Linney et al., 2003) and laboratory-measured hedonic capacity (46%) (As measured by responsiveness to reward (Bogdan & Pizzagalli, 2009). These findings suggest that an individual's emotional attribution towards pleasurable events and the magnitude of reward based on experience may both have genetic contributions.

7. Neuroeconomics

Loss of interest, reduced reactivity to positive events, anhedonia and dysregulation of incentive motivation are core features of several neuropsychiatric disorders (Gold et al., 2012). It is suggested that symptoms associated with reward function are trait-like dysfunctions of the dopaminergic system (Tremblay et al., 2002; Tremblay et al., 2005). One theory suggests that motivation is a heritable trait capable of mediating learning strategy and style. It may be argued that genetic variance in motivation may modulate the framework of an individuals learning parameters (Frank & Fossella, 2011). The motivation salience an individual attributes to a stimulus can be measured using behavioural and imaging methods (Linke et al., 2010; Locke & Braver, 2008; Watanabe et al., 2007). These are useful tools when quantifying an individual's experience of reward and the resources they are prepared to allocate to that reward.

The brain's valuation-processing network has also been studied in SZ, MD and BP (Gold et al., 2008; Heerey, Bell-Warren & Gold, 2008; Heerey, Matveeva & Gold, 2011). These studies established that the deficits in reward-guided behaviour in patients are the result of an inability to couple a representation of reward with its expected value. This suggests that disruptions may occur in the process of reward attribution.

7.3. Dopaminergic Genes In Reward Guided Decision Making

A host of literature implicates the dopaminergic system as a key mediator in reward guided decision-making (RGDM). In recent years, researchers have sought to dissect the neurocognitive components of reward processing, reinforcement learning and motivation. These studies implicate a range of dopaminergic genes in specific subcomponents of RGDM.

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Interestingly, genetic variants could selectively influence different parameters of decision-making (Frank & Fossella, 2011). Accumulating evidence suggests that genes expressed in prefrontal regions of the brain (such as *COMT* and *DRD4*) modulate reward and learning processes in a top-down manner. Based on evidence from independent sample/multiple tasks it is suggested that *COMT* modulates the extent to which individuals can supersede reward/learned associations with behavioural inhibition and cognitive control (Frank et al., 2007; Kramer et al., 2007; Nomura, Kondo & Kashiwano, 2011) .

Genes expressed predominately in the striatum (*DRD2*, *DAT1* and *DARPP32*) appear to have specific roles in the reinforcement learning process that uses the medial and posterior components of cortico-striatal circuitry (Aarts et al., 2010; Aarts, van Holstein & Cools, 2011; Curcic-Blake et al., 2012) . Much neuroimaging evidence also supports the notion that different dopaminergic genes modulate different reward/learning-processing subcomponents (Aarts, van Holstein & Cools, 2011). Table 2 shows how different dopaminergic genes contribute based on their putative function. Evidence suggests that genes expressed in the striatal dopaminergic systems modulate variability in learning rates (Frank et al., 2007; Frank et al., 2009; Frank & Fossella, 2011), learning approaches (Frank et al., 2007; Frank & Hutchison, 2009) and reward representations (Dreher et al., 2009;Forbes et al., 2009a; Nikolova et al., 2011). Dopaminergic genes though to affect prefrontal dopamine modulate these signals via top-down mechanisms such as inhibitory control (Kramer et al., 2007), WM (Aguilera et al., 2008; Diaz-

Asper et al., 2008;), reward-value estimation (Camara et al., 2010; Marco-Pallares et al., 2009;) and uncertainty-based exploration (Frank et al., 2009).

studies	gene (variant)	putative functional consequence	reward/learning parameter
Frank et al., 2007 Frank et al., 2009	*COMT* (rs4680)	dopamine turnover (catabolism rate)	trial-trial adjustments uncertainty/exploration
Kramer et al., 2007 Fossella et al., 2002	*DRD4* (rs1800955)	transcriptional efficiency	monitoring decision conflict error related feedback
Frank & Hutchinson, 2009 Frank et al., 2007	*DRD2* (rs6277)	D2 receptor striatal mRNA expression	learning from negative PEs (avoid negative outcomes)
Marco-Pallares et al., 2009 Dreher et al, 2009	*DAT1* (40_{bp}VNTR)	DAT1 protein expression/density	cognitive flexibility striatal reward response
Doll et al., 2011 Frank et al., 2007	*DARPP32* (rs907094)	mRNA expression corticostriatal plasticity	probalistic 'Go' learning learning from positive PEs
Collins & Frank, 2012	*GPR6* (rs4354185)	basal ganglia function	reward learning rate parameter

Table 2 | Example for how functional genetic variants associated with the dopaminergic system may influence specific parameters of the learning/reward guided decision-making. PFC (prefrontal cortex); PE (prediction error).

7. Neuroeconomics

Reward guided decision-making is an extensively dissected cognitive component of human behaviour. Research in this area has yielded several important dissociations between frontal and striatal genetic contributions in human inter-individual differences. However, little of this knowledge has been explored within the field of neuropsychiatry. Emerging evidence implicates reward-guided decision making in neuropsychiatric disorders (Sharp, Monterosso & Montague, 2012; Hasler, 2012). Therefore understanding the causal roles of genetic variants in decision-making subcomponents will inform us of the pathophysiology of domain specific heritable phenotypes. Experimental Chapter 1 (15.1-15.5) will explore the potential mechanisms by which genetic variance may influence susceptibility to 1) ‘reward responsiveness’ and 2) ‘reward seeking behaviour’ and their validity as candidate endophenotype for neuropsychiatric illnesses.

8. Genetic Neuroimaging and Neuropsychiatric Disorders

8.1. Structural Biomarkers

A host of MRI techniques are used to quantify the structure of the brain, including voxel-based morphometry, cortical thickness, diffusion weighted imaging. The resulting MRI parameters index morphological and volumetric sub/components of cortical architecture and whole brain volume estimates. Studies suggest that various regions of grey matter and white matter volume are significantly heritable (Chiang et al., 2011; Peper et al., 2009; Chou et al., 2009; Hulshoff Pol et al., 2006). Furthermore, specific cortical and subcortical architecture may also be heavily influenced by genetic components (Goldman et al., 2009; Goldman et al., 2008; Siebner et al., 2009; Pell et al., 2010). There is also a large body of evidence suggesting that these methods reliably and specifically delineate between healthy controls and individuals with neuropsychiatric disorders (de Geus et al., 2007; McDonald et al., 2004; Nenadic, Gaser & Sauer, 2012; Rijsdijsk et al., 2010; Tost, Alam & Meyer-Lindenberg, 2010; van 't Ent et al., 2007; Wright et al., 2000). The structural/volumetric abnormalities associated with SZ may be seen in prodromal cases (Rapoport et al., 1999) and correlate with illness chronicity (Cahn et al., 2002) and medication protocols (Chua et al., 2007; Deng et al., 2009) suggesting that environmental susceptibility contribute largely (but are not solely attributable) to these abnormalities. Genetic variants that confer risk to these disorders also appear to be associated with reductions and/or abnormalities in both cortical and subcortical volume and/or morphology (Thompson, Martin & Wright, 2010) . Structural brain imaging can make several diagnostic discriminations with high levels of sensitivity, specificity and accuracy using multivoxel pattern analysis (Linden, 2012),

suggesting these techniques are becoming increasingly useful as biomarker detection parameters. There are several accounts suggesting that structural biomarkers are also present in unaffected relatives, suggesting their potential as endophenotypes (Knochel et al., 2012a; Knochel et al., 2012b). However, the use of structural MRI in characterising the neurobiological underpinnings by which susceptibility loci confer risk is unclear. It remains uncertain whether structural measurements of the brain probe for susceptibility-weighted genetic risk or more general parameters of heritability that do not play integral roles in the genetic susceptibility underlying neuropsychiatric disorders (Nenadic, Gaser & Sauer, 2012) . Recent evidence suggests that the genetic contributions to SZ are more likely to be predicted by functional activation during cognitive tasks rather than structural parameters (Blokland et al., 2011). Although volumetric/structural abnormality can be used as a valid imaging biomarker, investigations aiming to quantify genetically derived susceptibility should be interpreted with caution. Functional polymorphisms with established effects on neurotrophic support seem to influence macroscopic structure (Braskie et al., 2012a; Gerritsen et al., 2012; Ho et al., 2006; Montag et al., 2009; Murphy et al., 2012a; Pezawas et al., 2004) but genetic variants associated with a specific neuropsychiatric illness may not necessarily have a neurobiological impact on brain structure/volume (Allen et al., 2008; Cousijn et al., 2012). It appears that although it may be possible to characterise the proportion of genetically derived variance in brain structure, it may not help to understand the mechanisms by which neuropsychiatric genes influence susceptibility as an intermediate/endophenotype (Goldman et al., 2008; Honea et al., 2008).

8. Genetic Neuroimaging and Neuropsychiatric Disorders

8.2. BOLD Based Endophenotypes

There is a well-established body of evidence quantifying patterns of BOLD activation in healthy controls, unaffected relatives and neuropsychiatric patients during neurocognitive endophenotype testing. There are several well-characterised functional imaging candidate endophenotypes exploring the neural systems that are disrupted at a behavioural level. Recent studies serve to suggest that BOLD levels during neurocognitive endophenotype assessment are reliable trait markers for neuropsychiatric susceptibility, rather than structural biomarkers, which act principally as state markers (Owens et al., 2012; Nenadic, Gaser & Sauer, 2012). Studies suggest that patterns of activation (as measured via BOLD signal) are aberrant across a wide range of behavioural modalities (Hasler et al., 2006; Le Hellard & Hanson, 2012; Meyer-Lindenberg, 2010a; Rasetti & Weinberger, 2011). Chapter 16. Experimental Chapter 2: Preface, will address the use of BOLD during our experimental NCIP. There are several well-established cognitive domains that have been implicated in each neuropsychiatric disorder, many of which are probed for potential genetic effects (twin studies, additive genetic effects, single variant studies, gene/gene interactions, gene/environment interactions). However, in a similar manner to structural biomarkers, one must also consider the possibility that functional activation may differ as a function of state, rather than trait (Rasetti et al., 2009). Recently, the multi-institute consortium CNTRICS (Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia) formulated a battery of neurocognitive intermediate phenotypes designed to quantify the core deficits and neural substrates of schizophrenia. These imaging trait markers recruit well-defined neural

networks and are capable of robustly predicting neural dysfunction (Reviews; (Barch et al., 2009a; Butler et al., 2012; Carter et al., 2011; Carter et al., 2012; Luck et al., 2012; Ragland et al., 2009; Taylor, MacDonald & Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, 2012). WM is a robust intermediate/endophenotype that elucidates well-recognised sub-clinical features in several neuropsychiatric disorders. Altered MRI based activation/connectivity of fronto-limbic/fronto-parietal system during WM are consistently reported in patients with SZ (Callicott et al., 2003; Manoach, 2003) and BP (Thermenos et al., 2010) and AD (Peters et al., 2009). Furthermore, unaffected relatives of SZ (Broome et al., 2010; Choi et al., 2011), BP (Drapier et al., 2008; Thermenos et al., 2010; Thermenos et al., 2011) and patients with MCI (Yetkin et al., 2006) also show abnormal processing of WM in the same neural networks. WM performance is a highly genetically modulated process, suggesting that gene network govern the WM system. WM networks are frequently probed using risk loci identified via candidate and GWAS studies (Mier, Kirsch & Meyer-Lindenberg, 2010; Rasetti & Weinberger, 2011), which estimate moderate effect sizes.

This thesis will also use an experimental NCIP (neurocognitive intermediate phenotype) to quantify the genetic risk and associated preclinical neuropathological changes associated with MCI and AD. Previous work (Chapter 5.1) suggests that WM is a core dysfunction in AD and that WM dysfunction may precede any pathological changes as it can be observed in early stages (MCI (Gagnon & Belleville, 2011; Saunders & Summers, 2010)) and in individuals with genetic risk (Snowden et al., 2007). Neuroimaging studies yield robust findings implicating a network of cortical regions that are

disrupted in individuals with AD (Bokde et al., 2010; Peters et al., 2009), MCI (Yetkin et al., 2006) and those at genetic risk (Burggren et al., 2002; Meier et al., 2012). These studies demonstrate that individuals with genetic risk, MCI or AD exhibit compensatory responses during WM in hippocampal, cingulate and prefrontal regions (Bookheimer et al., 2000; Meier et al., 2012; Mondadori et al., 2006; Peters et al., 2009; Saunders & Summers, 2010; Yetkin et al., 2006). Although the genetic machinery underlying the WM networks changes associated with cognitive aging, MCI and AD are not fully understood, the functional changes in these WM networks are a suitable candidate intermediate phenotype for AD susceptibility and may help elucidate genetic predisposition.

Considering the body of evidence implicating functional imaging biomarkers as valid IPs/NCEs, these paradigms have the potential of being used in multi-site genetic imaging studies; it may be possible in the future to conduct genome-wide association studies using activation patterns from these paradigms as quantitative traits. As more is understood about the neurobiology that underlies task-performance, it may also be possible to develop data-reduction/boot-strapping techniques that pool gene variants into neurobiologically derived canonical pathways (Hibar et al., 2011a).

8.3. Connectomic Intermediate Phenotypes

Broadly considered an intermediate phenotype for neuropsychiatric disorders such as SZ, BP, MD and AD, brain connectivity may index a physiological consequence of genetic risk to a broad domain of neuropsychiatric states (Buckholtz & Meyer-Lindenberg, 2012). Conventional measures of neuroimaging phenotypes focus on anatomical or activation

associated measurements. It is likely that the major neuropsychiatric disorders are characterised by multiple neural abnormalities, most likely the result of aberrant information processing between regions rather than isolated, independent cortical disruptions (Bartzokis et al., 2004; Fornito et al., 2012; Machulda et al., 2011; Meyer-Lindenberg, 2009). As many neuropsychiatric risk genes are expressed ubiquitously throughout the brain on multiple neurobiological pathways, connectome based phenotypes provide useful indices for probing the effects of genetic susceptibility at a systems level (Hibar et al., 2011a). The use of connectomic IPs (cIPs) has thus proved a sensitive measure for which to probe the functional effects of susceptibility loci (Meyer-Lindenberg, 2009). The human connectome is studied using imaging at a structural, functional or theoretical level (Bassett & Bullmore, 2006; Buckholtz & Meyer-Lindenberg, 2012; Fornito & Bullmore, 2012). There are several approaches one can take when using imaging to define structural and functional connectivity, many of which have been used as a cIP for genetic association. There have been notable findings for each of these approaches (Table 3). Each approach has identified gene variants with putative mechanisms to influence brain connectomics.

Connectome Measurement		Gene	Study
Structural Connectivity			
T1	White matter voxel based analysis	*NRG1*	Barnes et al., 2012
	Morphometric covariance analysis	*DARPP32*	Meyer-Lindenberg et al., 2007
DWI	Voxel based analysis	*NRG1*	Winterer et al., 2008
	Tract-based spatial statistics	*NTRK2*	Murphy et al., 2012a
	Tractography	*BDNF*	Voineskos et al., 2011a
Functional Connectivity			
Function	Seeded cluster	*ZNF804A*	Esslinger et al., 2009
	Independent components analysis	*BDNF*	Meda et al., 2010
	Pairwise correlation network	*APOE*	Filippini et al., 2009
Effective	Psychophysiological interactions	*ZNF804A*	Rasetti et al., 2011
	Dynamic causal modelling	*DARPP32*	Curcic-Blake et al., 2012
	Granger causality analysis	*CACNA1C*	Radua et al., 2012

Table 3 | Overview of the neuroimaging techniques used to measure the structural and functional properties of the human connectome and notable gene associations found using each measurement.

8. Genetic Neuroimaging and Neuropsychiatric Disorders

Much work has investigated how genetic variance may modulate the integrity of the human connectome (strength, stability) in relation to neuropsychiatric disorders (review (Fornito et al., 2012)). The anatomical arrangement of the human connectome may be genetically determined (Fornito et al., 2011). The spatial architecture of neural networks is orchestrated in a manner that maximises efficiency of communication between regions (Fornito & Bullmore, 2012; Zalesky et al., 2012). Many observations suggest that anatomically, the brain is organised in a manner that optimizes the efficiency of communication between neural networks (Bullmore & Bassett, 2011). The topological properties of the human connectome may be studied using graph theoretical measures (Bassett & Bullmore, 2006; Bassett et al., 2006), in which it is assumed that the transfer of information is processed in the most efficient manner (i.e. through as few connections as possible). Preliminary twin studies suggest that neural topology is a highly heritable network (Fornito et al., 2011). Early evidence specifics that global efficiency of communication (lambda (λ)), independent of local clustering (gamma (Γ)) or total connection density (κ) metrics (van den Heuvel et al., 2012). These studies suggest that neural topology as measured using graph theoretical measures explains similar amounts of phenotypic variance as well defined behavioural and imaging endophenotypes (~42-60%).

9. Genome Wide Association Studies & Magnetic Resonance Imaging

The previous chapters (Chapters; 5-8) discuss significant risk gene variants to be associated with neuropsychiatric illness (psychosis, disorders of affect, impulse etc.). It is hypothesized that the penetrance of these variants is modest at best (Lee et al., 2012a) and exploring the function by which they confer risk is difficult, especially in smaller samples. Psychiatric symptomology is conventionally assessed using structured diagnostic interview and behavioural markers. Neuroimaging biomarkers however, may co-segregate between psychiatric patients, non-affected families members and the healthy population, showing clear genetic connection and independent of psychiatric state (Please see; Chapter 4. Neurocognitive Phenotypes).

MRI is commonly used to explore the neurobiological deficits underlying psychiatric traits and states (Linden, 2012; Meyer-Lindenberg, 2012). MRI may also help to quantify whether heritable or prodromal risk states are visible at a neurobiological level, in the absence of behavioural symptoms (Meyer-Lindenberg, 2012). MRI as a tool with the potential to explore biomarkers in neuropsychiatric states with increased sensitivity as it offers an insight into the neural correlates of a particular behavioural dysfunction. MRI is now used independently to probe for vulnerability to neuropsychiatric illness with increasing specificity, especially in cases of neurodegeneration (Abdulkadir et al., 2012).

Owing to the sensitivity of MRI, it is also possible to probe the effects of single genetic risk variants using established biomarkers, endophenotypes and/or intermediate phenotypes. The field of ‘genetic imaging’ has been of particular interest during the dramatic re-landscaping of neuropsychiatric

genetics in the post GWAS era (Meyer-Lindenberg, 2012). MRI may be a suitable tool for investigating the effects of neuropsychiatric GWAS loci in smaller samples. In imaging genetics, biomarkers/endophenotypes that reliably dissociate populations are used in either structural or functional MRI studies to establish how risk loci may confer risk to a particular neuropsychiatric illness (Talbot et al., 2006). The present chapter will provide an up-to-date summary of the most significant GWAS loci and how they confer risk to their respective disorders as revealed by the most popular MRI modalities.

9.1. GWAS Loci & Structural MRI

Structural MRI studies indicate that cortical integrity is disrupted in neuropsychiatric disorders (Goldman et al., 2009; Oertel-Knochel et al., 2012). Abnormalities in whole brain volume, gyrification, grey matter, white matter and ventricular size (Winkler et al., 2010) are considered potential biomarkers for neuropsychiatric illness. However, it is unknown whether these abnormalities reflect a genetic contribution or are state dependent (Owens et al., 2012; Rimol et al., 2010). The first studies looked at the effects of single GWAS loci, applying whole brain correction (Meyer-Lindenberg et al., 2008), however studies now study large platforms of genetic variants over every voxel independently in the brain, a methods known as ‘voxel-wise genome wide association study’ (vGWAS) (Stein et al., 2010a).

9.2. GWAS Loci & Diffusion-Weighted MRI

The brain connectome has been widely discussed as architecture vulnerable to insult from the neuropsychiatric risk loci (Buckholtz & Meyer-Landenberg, 2012)) As a result, candidate risk loci with putative influence

over myelin integrity have been used to probe for potential effects on white matter integrity. Although sometimes contested, fractional anisotropy (FA) has proved to be a reliable measure of WM tract integrity. FA correlates with performance on many psychometric assays (Linke et al., 2012; Ready et al., 2011; Voineskos et al., 2012; Yu, 2012) and is disrupted in neuropsychiatric populations, and modulated by many neuropsychiatric risk genes (Review; (Mothersill et al., 2012)).

9.3. GWAS Loci & Functional Connectivity

Another method used to test the 'disconnection hypothesis' in neuropsychiatric disorders (Buckholtz & Meyer-Lindenberg, 2012; Fornito & Bullmore, 2012; Friston & Frith, 1995; Schmitt et al., 2011;) uses the blood oxygen level dependency (BOLD) to measure the statistical dependencies between time courses in a seed voxel cluster and all the voxel clusters in the brain (Friston et al., 1996). Functional connectivity may assay resting-state (default mode networks) or map cortical regions with activity that correlates during a neuropsychological task. A key psychosis risk gene (*ZNF804A*) identified via GWAS and follow-up (O'Donovan et al., 2008; Riley et al., 2010) has been shown to modulate functional connectivity during WM supporting the notion that the locus modulates risk to psychosis via the functional connection of cortical regions during WM (Esslinger et al., 2009; Paulus et al., 2011; Rasetti et al., 2011).

9.4. GWAS Loci & Effective Connectivity

Emerging evidence now suggests that genetic loci may modulate information flow between cortical regions. This technique may offer an insight into the causal relationship between neural communications during task

processing. Effective connectivity may monitor the dynamic between regions by assaying the neural response to psychological stimulation (Psychophysiological interaction) (Friston et al., 1997), time series models (granger causality) (Goebel et al., 2003), structural equation models (Buchel & Friston, 1997) or dynamic causal modelling (Friston, Harrison & Penny, 2003). Key risk loci for SZ and BP (within *ZNF804A* and *CACNA1C*; respectively) have now been shown to modulate information flow between neural populations in a causal manner (Radua et al., 2012; Rasetti et al., 2011). These studies provide initial evidence that GWAS loci modulate interacting networks containing the cortical regions disrupted in neuropsychiatric populations and high-risk individuals.

9.5. GWAS Loci & BOLD Signal

The most conventional method used to probe for functional effects of neuropsychiatric risk loci observes the differences in task-induced neural activation between genotype groups. Many well-established NCE/IPs for neuropsychiatric illness are used to probe for aberrant task dependent patterns of neural activation, many of which may be influenced by genetic factors. Components of cognition are all thought to be significantly heritable, (Blokland et al., 2011) so it is suggested that the patterns of neural activation that underpin behaviour will also be heritable, which has held true for WM (Blokland et al., 2011). The concept is yet to be applied to other components of cognition that meet the criteria for NCE/IPs. Well-established NCE/IPs for neuropsychiatric illness are frequently used during functional neuroimaging to probe the effects of single risk loci (Please see Table 4 for full review,

considering the functional effects of GWAS identified susceptibility loci for SZ and BP).

9.6. Conclusions

The majority of recent studies use robust/well-defined structural and functional NCE/IPs when using MRI to discover potential neurobiological effects of neuropsychiatric risk variants. Although these studies are useful in guiding knowledge regarding the neurobiological impact of GWAS loci (which have unknown function), there are many limitations to this approach. One; single gene studies do not usually control for multiple comparisons (making them vulnerable to false-positive findings). GWAS loci often yield high effect sizes on imaging phenotypes; however explain little of the variance in behavioural/symptomatic phenotypes (Rose & Donohoe, 2012) . This may be due to the modest odds ratios calculated for most GWAS SNPs (O'Donovan et al., 2008). Two; large phenotype based association studies between large numbers of loci and voxel or voxel clusters 'vGWAS' (Hibar et al., 2011b) or 'vGWAS' (functional measures such as frontal activation during WM; (Potkin et al., 2009b)) allow large data-driven explorations in vulnerable cortical regions to find novel susceptibility loci. However, these approaches are limited by the methods by which they address the multiple comparison issues. VGWAS may falsely assume independence of voxel in the brain, which may produce null results (Stein et al., 2010a) (potentially due to false negatives), or using putative structural/volumetric integrity measures as heritable phenotypes. These approaches may also assume independence of gene loci, which may also reduce the power of these studies (Stein et al., 2010a). These problems are being addressed by probing imaging data using

cumulative genetic risk or ‘polygenic risk scores’ (Kohannim et al., 2012; Walton et al., 2012; Whalley et al., 2012) that aggregate risk loci with small effects together, which control for large number of testing between gene variants. However, the molecular resolution is diluted as it represents the effects of a combination of ubiquitous risk loci rather a specific biological pathway (Linden, 2012).

Study & Gene		Method	Task	Genotype Effect	Region/s (R/L)	Sample (n)	
Structural/Volumetric							
Kempton et al., 2009	*CACNA1C*	VBM	-	AA>AG>GG	GMV	HC	77
Lencz et al., 2010	*ZNF804A*	VBM	-	GG/GT > TT	L-AG, R-PHG,R-PC, R-ITG	HC	39
			-		MOG, R-AG, R-CBM, L-IFG		
Agartz et al., 2011	*MHC region*	CT	-	CC>CG>GG	VV	SZ	95
Lencz et al., 2010	*ZNF804A*	VBM	-	CC/AC > AA	R-H	SZ	70
Lencz et al., 2010	*ZNF804A*	CT	-	CC/AC > AA	L-PC, L-STG, R-AC	HC	62
Wang et al., 2010	*CACNA1C*	VBM	-	AG/AA>GG	R/L-PFC, AC, TL	HC	55
Cousijn et al., 2012	*ZNF804A*	VBM	-	No Effect	-	HC	892
Ohi et al., 2012	*NRGN*	VBM	-	CC>CT>TT	L-AC	SZ	99
Rose et al., 2012a	*NOS1*	VBM	-	AA>AG/GG	VM-PFC	HC	157
Wei et al., 2012	*ZNF804A*	VBM	-	TT/GT > GG	R-H, L-H	CO	149
				TT/GT > GG	L-PFC	SZ	80
				GG>TT/GT	L-PFC	HC	69
Diffusion-weighted MRI							
Voinekos et al, 2011	*ZNF804A*	FA/MD	-	No effect	-	HC	62
Kuswanto et al.,	*ZNF804A*	FA	-	TT>GG/GT	R-TL	HC	153
				GG/GT>TT	L-PL, R-PL, L-CG	SZ	
Genotype differences in task-related BOLD							
Walter et al., 2011	*ZNF804A*	NA	TOM	CC>AC>AA	DM-PFC, IPL, TPJ	HC	109
Rose et al., 2012a	*NOS1*	NA	SWM	AG/GG>AA	R-CAUD, PL, SFG, R-	HC	48
Roussos et al., 2012	*ANK3*	NA	WM	CC>CT/TT	I-FG, M-FG	HC	52
Thimm et al., 2011	*CACNA1C*	NA	ANT	GG>AG/AA	I-PL, M-FG	HC	80
Wessa et al., 2010	*CACNA1C*	NA	PRL	GG<AG/AA	AMYG	HC	64
Erk et al., 2010	*CACNA1C*	NA	EM	GG>AG/AA	R-H, L-H, AC	HC	110
Bigos et al., 2010	*CACNA1C*	NA	EP/WM	GG>AG/AA	R-H, L-H (EP) PFC (WM)	HC	316
Krug et al., 2010	*CACNA1C*	NA	SVF	GG<AG/AA	L-IFG, L-PRECUN	HC	63
Krug et al., 2011	*NRGN*	NA	EM	TT>CT/CC	L/R-AC, LG, L-INS, L-	HC	94
Pohlack et al., 2011	*NRGN*	NA	CFC	CT/CC>TT	R-H, L-H	HC	112
Linden et al., 2013	*ZNF804A*	NA	EWM	GG>GT>TT	RDLPFC	HC	43

Study & Gene		Method	Task	Genotype Effect	Region/s (R/L)	Sample (n)	
Functional/Effective Connectivity: Neural Networks							
Esslinger et al., 2009	*ZNF804A*	SC	WM	AA>AC>CC CC>AC>AA	RDLPFC-R/LDLPFC RDLPFC-L-H	HC	115
Erk et al, 2010	*CACNA1C*	SC	EM	GG>AG/AA	R-H-LH	HC	110
Esslinger et al., 2011	*ZNF804A*	SC	WM/EP	CC>AC>AA AA>AC>CC	RDLPFC-R/L-FG R.-DLPFC-R/L-H	HC	111
Paulus et al., 2011	*ZNF804A*	SC	WM	AA>AC>CC CC>AC>AA	RDLPFC-R/L-HF RDLPFC-R/L-DLPFC RDLPFC-RDLPFC	HC	94
Rasetti et al., 2011	*ZNF804A*	SC/PPI	WM	AA>AC>CC	RDLPFC-R/L-H RDLPFC-R-PFC	HC HC	153
Rasetti et al., 2011	*ZNF804A*	SC/PPI	WM	AA>AC/CC CC>AC>AA CC/AC>AA	RDLPFC-RDLPFC RDLPFC-L-PFC RDLPFC-R-H	FDR FDR FDR	171
Rasetti et al., 2011	*ZNF804A*	SC/PPI	WM	CC>AC>AA CC/AC>AA	RDLPFC-R/L-PFC RDLPFC-L-H	SZ SZ	78
Walter et al., 2011	*ZNF804A*	SC	TOM	AA>AC>CC CC>AC>AA	L-TPJ RDLPFC-L-MTG RDLPFC- L-CAUD	HC	109
Wang et al., 2011	*CACNA1C*	SC	EP	GG>AG/AA	AMYG-VLPFC	HC	55
Radua et al., 2012	*CACNA1C*	CGA	EP	GG>AG>AA	L-AMYG-L-PUT-MFG	HC FDR BP	60

Table 4 | Overview of all genetic imaging studies from the GWAS era for psychosis/bipolar risk variants (2008-2012). All articles studied one variant or one gene rather than the analysis of large SNP platforms like vGWAS. NB. (Linden et al., 2013 are the results are documented in 'Experimental Chapter 2; Chapter 17.1-17.5.' in this thesis).

9. Genome Wide Association Studies & Magnetic Resonance Imaging

Cohorts: n (sample size); HC (healthy controls); FDR (first-degree relatives); SZ (schizophrenia patients); BP (bipolar patients), CO (Combined HC/SZ)

MRI Methods (Structural): VBM (voxel based morphology); CT (cortical thickness); FA (fractional anisotropy); MD (mean diffusivity)

MRI Methods (Functional): NA (neural activity); SC (seeded connectivity); PPI (psychophysiological interactions); CGA (cluster granger analysis)

Cognitive Tasks: PRL (probabilistic reward learning); SVF (semantic verbal fluency); EM (episodic memory), EP (emotional processing) CFC (contextual fear conditioning); S/EWM (spatial/emotional working memory); TOM (theory of mind).

GWAS SNPs: *ZNF804A* (rs1344706); *NRGN* (rs12807809); *CACNA1C* (rs1006737); *NOS1* (rs6490121); *MHC* Region (rs2596532); *ANK3* (rs10994336).

Regions of Interests: GMV (grey matter volume); H (hippocampus); STF (superior temporal gyrus); AC (anterior cingulate), VV (ventricular volume): AG (angular gyrus); CBM (cerebellum); PHG (parahippocampal gyrus); PC (posterior cingulate); ITG (inferior temporal gyrus); MOG (medial orbital gyus); IFG (inferior frontal gyrus); PFC (prefrontal cortex); VM (ventro-medial); PL (parietal lobe); I (Inferior); LG (lingual gyrus); INS (insula); PCG (precentral gyrus); AC (anterior cingulate); CG (cingulate gyrus); TL (temporal lobe); CAUD (caudate); AMYG (amygdala); TPJ (temporal parietal junction); VL (ventro-lateral); PUT (putamen); DL (dorsolateral); PRECUN (precuneus); CUN (cuneus); MFG (medial frontal gyrus); MTG (medial temporal gyrus).

10. Agnostic/Multifocal Genotype-Phenotype Association Studies

Genome wide association studies are used in neuropsychiatric genetics to establish associations between clinical diagnosis and risk loci. However, psychiatric phenotypes span a wide and diverse symptom spectrum, which makes interpretation of the risk marker/gene and its role in the disorder difficult (Ayalew et al., 2012; Lee et al., 2012a). It may be possible that SNPs associated with psychiatric disorders capture key components of susceptibility but heterogeneous samples reduce the effect sizes of these risk markers. This would account of the modest effect size calculates from most SNPs associated with psychiatric disorders at genome-wide level. However, the cumulative total of all susceptibility captured by SNPs is hypothesized to be moderate (Lee et al., 2012a). Considering the important additive role that SNPs may play in neuropsychiatric susceptibility, it is essential to explore potential ways in which these SNPs may contribute to the pathophysiological features of neuropsychiatric disorders. In order to further investigate the role of SNPs in neuropsychiatric disorders, associations are calculated based on disease subtype, behavioural phenotype or brain structure/function. This method reduces sample heterogeneity and helps to explain the genetics that underpin core elements of neuropsychiatric pathophysiology. These studies are not hypothesis driven (like GWAS) and are designed to identify novel loci that contribute to a specific phenotype. Unlike GWAS for neuropsychiatric disorders, these methods are hypothesized to capture larger proportions of the variance in the phenotype, as the samples are more homogenous. One may also reduced multiple testing constraints by only testing SNPs on genes expressed within the central nervous system. These studies face the same multiple comparison problems as early GWAS,

but with the advantage of increased specificity. However, these studies will undoubtedly contribute towards the improving classification and nosology of neuropsychiatric illness based on novel insights from genetic architecture (Derks et al., 2012; Gladwin et al., 2012). Below are some of the methods by which sub clinical GWAS have aimed to dissect the pathophysiology of neuropsychiatric illness.

10.1. Personality Traits

As GWAS techniques became more accessible, larger samples were used to explore five conventional measures of personality (McCrae, Costa Jr & Martin, 2005) to identify genetic variance that may have strong links to psychiatric illness. The genetic substrates for personality traits have also been explored using the GWAS approach (de Moor et al., 2012; Luciano et al., 2012) owing to evidence that personality components have significant heritability (~33-65%).

The first attempts to use GWAS to identify personality related genes identified loci considered as noteworthy candidate SNPs (Terracciano et al., 2010). However, it was established that due to the complexity of the traits, the sample sizes would have to be larger (Luciano et al., 2012). Interestingly, loci identified in this study have previously been implicated in neuropsychiatric susceptibility and heritable cognition (*BDNF* and *SNAP25*). Recently larger studies have attempted to identify genetic loci associated with personality dimensions discovering *KATNAL2* as a potential modifier locus for conscientiousness (de Moor et al., 2012); a region recently associated with autism spectrum disorders (ASDs) (Neale et al., 2012). Convergent findings also implicate *NOS1* with psychosis (O'Donovan et al., 2008) and

neuropsychiatric symptomology (Luciano et al., 2012). Lastly, the BP/SZ susceptibility gene *CACNA1C*, identified by GWAS and replication (Ferreira et al., 2008; Sklar et al., 2008) shows sex-specific associations with personality traits/factors that contribute to neuropsychiatric susceptibility (Strohmaier et al., 2012). The study was conducted at a population level, but was guided by *a priori* hypothesis with specific consideration of the pathogenic variant (rs1006737).

10.2. General Cognitive Parameters

General cognitive ability is considering a high heritable trait (Davies et al., 2011) suggested to be an intrinsic factor in neuropsychiatric susceptibility, as deficits occur in relatives of patients (pp157-161, Volume 1 (Ritsner, 2009)). However, the broad and ambiguous definition of IQ (*g*) *is* a difficult parameter to measure at a genome-wide level. Nevertheless, principle components of cognition such as IQ (*g*) have been investigated in population based samples to explore the neurobiological underpinning of cognitive ability. Early studies suggest that little (>.5% of the variance in *g;* (Butcher et al., 2008)) or no common genetic variance modulated by parameters of cognitive performance (Need et al., 2009). As sample sizes increased, genetic association with *g* became more robust. It was hypothesized that the additive effects of SNPs explain between ~40-51% of the variance in crystallized/fluid intelligence (Davies et al., 2011). However meta-analysis also suggests sample sizes are too small to detect the single locus effects on *g* (Chabris et al., 2012) suggesting much larger sample sizes are needed to detect the modest effect sizes of single loci. Other, more specific parameters of cognition have also been considered at whole-genome level. The agnostic approach

has been used to identify loci associated with episodic (Kauppi et al., 2011; Wersching et al., 2011) and short-term memory (Papassotiropoulos et al., 2011b) both of which have since been implicated in AD pathophysiology (Burgess et al., 2011; Meier et al., 2012) respectively. Lastly, whole-genome approaches have also revealed the molecular pathways implicated in information processing speed, which has been implicated in a wider range of psychiatric illness (Luciano et al., 2011).

10.3. Brain Structure

Multisite neuroimaging cohorts have facilitated the expansion of sample sizes for structural brain scans. Using similar approaches as those of GWAS, these voxel wise GWAS or vGWAS allow the association genetic variance with cortical structure with candidate endophenotypes such as hippocampal volume (Bis et al., 2012), intracranial volume (Stein et al., 2012) and multiple grey matter regions/volumes (Hibar et al., 2011a; Hibar et al., 2011b; Melville et al., 2012; Stein et al., 2011) (Table 5). Voxel-based GWAS show association of AD endophenotypes with the genetic variance previously identified as risk loci for the diagnosis (*APOE* & *TOMM40*; (Vounou et al., 2012) & *PICALM*; (Melville et al., 2012)). Cortical regions susceptible to AD neurodegeneration also share the same genetic susceptibility as Alzheimer's disease, supporting the role of these genes in AD pathophysiology. Furthermore, several vGWAS are adopting multivariate approaches (hierarchal clustering), where voxels and genes are not treated independently, but rather organised into anatomically defined regions and biologically specific pathways, respectively. This strategy will permit increased power/effect sizes

whilst reducing false negatives lost during multiple comparisons thresholding (Liu et al., 2012; Meda et al., 2010).

10. Agnostic/Multifocal Genotype-Phenotype Association Studies

Study	Cohort	Quantitative Trait	Gene/s
Potkin et al., 2009a	HC, MCI, AD	Hippocampal Atrophy (VBM)	*TOMM40*
Potkin et al., 2009b	HC, SZ	fMRI (DLPFC activation)	*ROBO1-ROBO2, TNIK, TRAF*
Potkin et al., 2009c	HC, SZ	fMRI (DLPFC activation)	*CTXN3-SLC12A2 POU3F2,GPC1 RSRC1, ARHGAP18*
Stein et al., 2010	HC, MCI, AD	Temporal Lobe Volume (VBM)	*GRIN2B*
Hibar et al., 2011	HC, MCI, AD	Multiple WM (TBM)	*No significant hits*
Vounou et al., 2012	HC, MCI, AD	Multiple GM ROIs (VBM)	*APOE, TOMM40, EPHA4 TP63, NXPH1*
Furney et al., 2011	HC, MCI, AD	Multiple GM (VBM)	*ZNF292, ARPP-21, PICALM*
Bakken et al., 2011	HC, SZ BP, OTH	Multiple GM ROIs (CT)	*No significant hits*
Liu et al., 2012	HC/SZ	Independent Components Analysis	*Multiple Pathways*
Stein et al., 2011	HC, MCI, AD	Caudate Volume (VBM)	*WDR41, PDE8B*
Stein et al., 2010	HC, MCI, AD	Multiple WM ROIs (TBM)	No significant hits
Stein et al., 2012	HC	Multiple GM ROIs (VBM)	*12q24.22, HMGA2, DDR2*
Bakken et al, 2012	HC	GM ROI (CT)	*GPCPD1*
Meda et al., 2012	HC, MCI, AD	Multiple ROIs (GM/CT)	*ZNF673, VPS13, SLC9A7 ATP5G2, SHROOM2*
Melville et al., 2012	HC, MCI, AD	Multiple GM ROIs (VBM)	*APOE, F5/SELP, LHFP GCFC2, PICALM*
Melville et al., 2012	HC, MCI, AD	Total Cranial Volume (VBM)	*SYNPR*
Melville et al., 2012	HC, MCI, AD	White Matter Hyperintensities	*TTC27*
Melville et al., 2012	HC, MCI, AD	Hippocampal Volume (VBM)	*Multiple Pathways*
Ikram et al., 2012	HC	Intracranial Volume (VBM)	*17q21*
Bis et al., 2012	HC	Hippocampal Volume (VBM)	*MSRB3-WIF1, HRK-FBXW8 DPP4, ASTN2*
Kochunov et al., 2011	HC	Multiple GM & FA ROIs (VBM/TBM)	*No significant hits*

Table 5 | Review of vGWAS (2009-2012; descending from earliest to latest).

VBM (voxel based morphometry), CT (cortical thickness), GM (grey matter), TBM (tensor based morphometry), ROI (region of interest). HC (healthy controls), MCI (mild cognitive impairment), AD (Alzheimer's disease)

10. Agnostic/Multifocal Genotype-Phenotype Association Studies

10.4. Brain Function

Although these studies require replication, they offer novel insights into the genetic landscape, exploring many dimensions by which genetic variance may confer susceptibility. One potential way to expand on this work is to build genetic risk scores (GRS) (Ayalew et al., 2012; Derks et al., 2012). Based on polygenic models of genetic susceptibility, these studies aimed to capture the genetic variance previously associated with a quantitative trait or genetic variance associated with a specific biological pathway. Studies have aimed to capture larger proportions of genetic variance associated with prefrontal activation during WM (Walton et al., 2012) (a strong candidate endophenotype for SZ (Barch et al., 2009a)). This was achieved by calculating GRS based on the top hits from a SZ risk gene database (Allen et al., 2008). The correlation between GRS and endophenotype was significant, further supporting the polygenic model of complex traits, but did not infer novel insights into the pathophysiological mechanisms of WM dysfunction as the gene variance spanned a broad range of neurobiological mechanisms, some of which were unknown (*ZNF804A*, *TCF4* for example; (O'Donovan et al., 2008; Stefansson et al., 2009)).

One example of a pathway specific -quantitative trait based association study investigated the relationship between white matter integrity and common genetic variants previously associated with brain structure. Together, the genetic variants explained a higher proportion of the variance in corpus callosum fractional anisotropy (FA) than any single variant study with similar sample size (Kohannim et al., 2012). However, the study considered genetic variants based on previous associations with white matter integrity rather than

specific biological pathways. This method is only in its infancy, but as the understanding of trait based susceptibility increases, genetic models will capture larger proportions of genetic variance and create more opportunities for therapeutic interventions. Convergent functional genomics (CFG) is a recent strategy developed to capture susceptibility based on canonically derived pathways. These studies has identified and replicated key neurobiological pathways that contribute to neuropsychiatric susceptibility (Ayalew et al., 2012), however these pathways have yet to be explored using imaging phenotypes.

11. Considerations of Heterogeneity and Pleiotropy

Neuropsychiatric disorders are clinical manifestation derived from a series of neurobiological disruptions, potentially the result of genetic variance/heterogeneity, environmental stress and/or gene × environment interplay, which produce an additive and interactive series of quantitative traits (Meyer-Lindenberg & Weinberger, 2006). These quantitative traits may facilitate broad susceptibility to a host of neuropsychiatric illness (Shen et al., 2010). Considering this evidence, it may be more productive to characterise susceptibility by the quantitative measure most likely to predict genetic variance. Using this approach, susceptibility loci would not necessarily predict a specific disorder, but rather a combination of quantitative traits that may predispose to one of many diagnostic outcomes. It may be apparent that some genetic variance is more specific to a particular phenotype or conversely, display high levels of pleiotropy, influencing several quantitative traits and modulating susceptibility to many disorders (Labbe et al., 2012).

11. Considerations of Heterogeneity and Pleiotropy

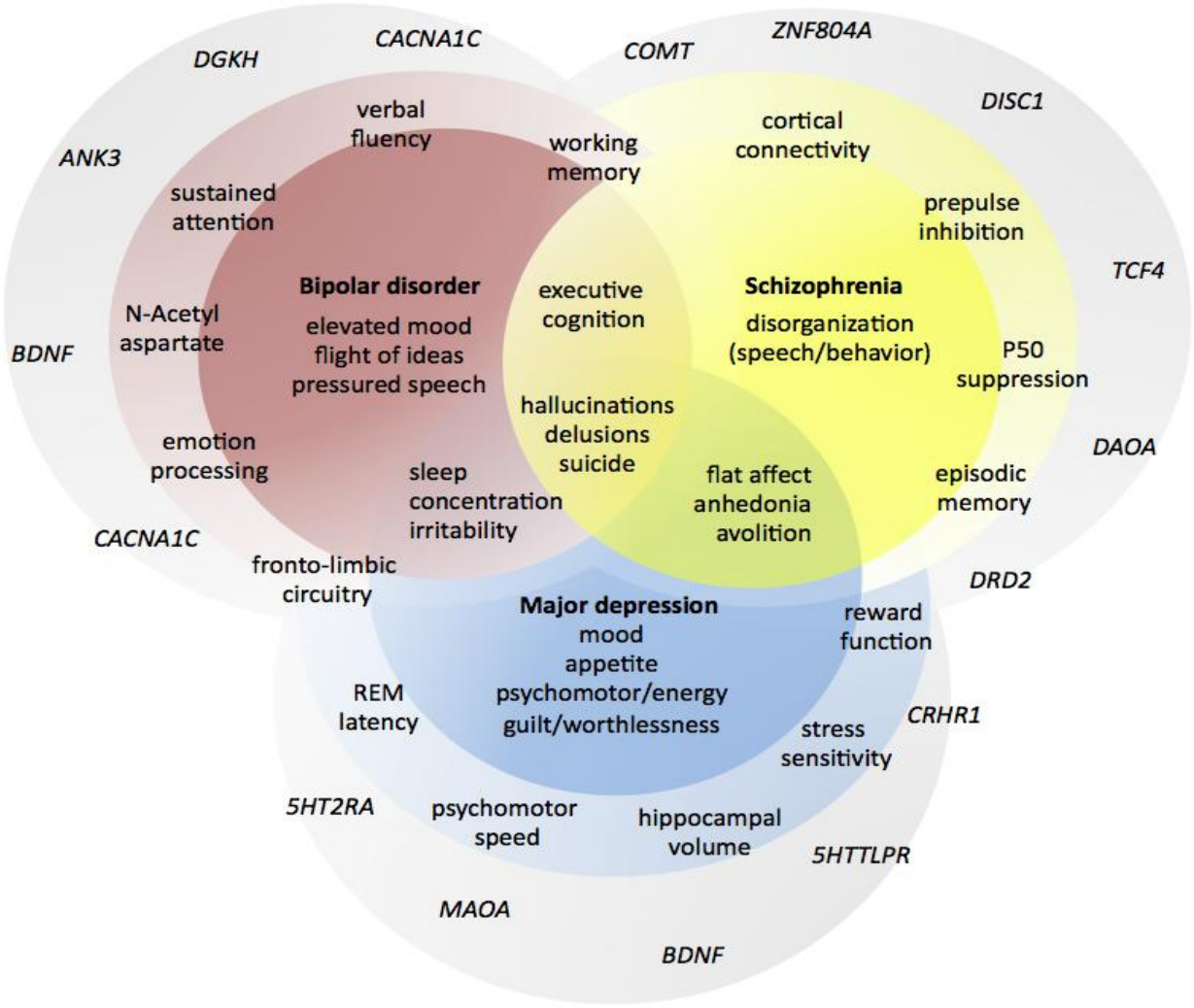

Figure 3 | A potential psychopathological interactome, adapted from (Bearden et al., 2004). (1-3, from the inner to the outer Venn diagram). 1. Symptom/traits that are distinct or share overlap for DSM-IV diagnosis for BP, SZ and MD. 2. Convergence and/or distinctions for candidate endophenotypes which may mediate the relationship between genetic susceptibility and symptomology.3. Candidate genes associated with the endophenotype/trait and/or diagnosis. The strength of association between gene, endophenotype and syndrome is not taken into consideration (for example; assumed sensitivity and/or molecular proximity: neuroimaging > behaviour). The illustration provides a model rather than being based on empirical evidence.

12. Neurocognitive Phenotype Domain Specificity

Worldwide initiatives aim to capture the specific effects and aetiology by which genetic variants contribute to neuropsychiatric disorders using imaging/behaviour (Carter et al., 2008; Carter et al., 2011; Carter, Barch & CNTRICS Executive Committee, 2012; Harvey, 2008), eQTLs (de Jong et al., 2012; Liu, 2011;) and disorder diagnosis (Greenwood et al., 2012a) as measures of phenotypic variance. Standardized measures are an essential parameter when conducting multi-site collaborations in genetic association studies. However, as sample size increases, so does the variability (and heterogeneity) which may reduce the strength of association between the quantitative trait and potential risk markers. Although many quantitative traits are designed to measure specific components of neurobiology, these parameters may assay large neural networks that are moderated by a host of candidate genes and variants herein. One potential method to overcome this issue is the use of genetic risk prediction scores (GRPS) to establish the cumulative effects of risk variants on a quantitative trait. GRPS have been relatively successful at capturing larger proportions of variance in quantitative traits, but do not improve the resolution needed to gain understanding between gene and function (Derks et al., 2012). In order to quantify the genetic architecture of the brain high-dimension phenotypic data sets have been used with success (Greenwood et al., 2011; Greenwood et al., 2012b). Another potential avenue of exploration is ‘genetic dissection of neurocognitive traits’; a method of investigation that divides cognitive processes into specific neurobiological processes and explores the genotypic variance associated with those sub-processes (Congdon, Poldrack & Freimer, 2010). This approach has been employed in genetic imaging, where phases

of a task (for example; WM) are sub-divided according to the neurobiological process as separate processes (e.g. visual processing > encoding > maintenance > retrieval) to establish how genetic variants affect the components of the cognitive process (Karlsgodt et al., 2010; Karlsgodt et al., 2011). Similarly, genetic variability may contribute to specific components of reward processing such as anticipation and magnitude (Camara et al., 2010; Schmack et al., 2008). Considering the endophenotype approach is an initiative to unify cognitive processes with the neurobiological parameters with significant genetic influence (Congdon, Poldrack & Freimer, 2010) characterising specific components of cognitive processes may yield significant associations with more specific components of neurobiology and smaller gene networks.

13. Optimizing Neurocognitive Traits For Genetic Association

It has been widely acknowledged that neuroimaging is a powerful tool to quantify effects of genetic variance (Rasetti & Weinberger, 2011) because of the proximal association between gene and neurobiological pathway. The field of neuroimaging has resonated strongly in psychiatry for its role in conceptualising psychopathological entities at a neurobiological level. Imaging genetics may facilitate the dissection of pathophysiological entities into tractable biological subprocesses and bridge the gap between genetic variance and pathological behaviour. Many genes considered to be significantly associated with neuropsychiatric diagnosis do not have large effects or penetrance on clinical phenotypes (Gill, Donohoe & Corvin, 2010) . For these variants, imaging phenotypes would appear to be a more sensitive tool for characterising potential biological function than neurocognitive assays measuring behaviour.

Behaviour-based neurocognitive measurements appear to be useful for finding novel associations between gene and phenotype as they may now be studied at a population level (Papassotiropoulos et al., 2011a), which are tested using neuroimaging with *a priori* hypotheses regarding the functional nature of the genetic variance (Meier et al., 2012), abiding to the intermediate phenotype strategy. This technique is useful when the molecular consequence of a novel locus is unknown, as it may give insights into potential mechanisms of pathophysiological susceptibility. This knowledge can then be used in intermediate phenotypes strategies such as neuroimaging to elucidate neurobiological underpinnings. Most behavioural neurocognitive phenotypes remain at present; largely complex, polygenic traits and any genetic variance associated with such parameters have only

yielded modest association. For example, (Mier, Kirsch & Meyer-Lindenberg, 2010) constructed large meta-analysis to demonstrate that variants associated with cognition (example in this case is *COMT* val158met) account for variance ranging from .01% to .5% for some of the most robust endophenotypes to date, and do not actually offer closer biological proximity/penetrance than disorder diagnosis (Flint & Munafo, 2007). One potential method to overcome this issue is to increase specificity of the cognitive sub-component. Using this strategy, it may be possible to capture the contribution of gene/s to a specific neural network/process. By delineating the function of genes in these specific domains, we may capture a more robust association between genetic variance and its neurobiological consequence; however this method requires *a priori* knowledge regarding the functional nature of the genetic variant.

14. Experimental Chapter 1: Preface

Early candidate gene variants were investigated as they had hypothesized physiological effects on the neurobiological pathways implicated in the pathogenesis of the disorder (Meyer-Lindenberg & Zink, 2007). These genetic variants were considered 'functional polymorphisms'. To satisfy the criteria for a function polymorphism, there must be direct evidence that the genetic variant affects the expression, structure or function of the gene transcript and/or protein product (pp12-13 (Goldberg & Weinberger, 2009)). Functional variants may occur on genes that encode transporter proteins, receptors, metabolizing enzymes, and post-synaptic proteins. These variants may influence neuronal integrity and neurotransmission and modulate their respective signalling pathways. Many attempts to quantify the relationship between these gene variants and phenotypes have been made (Greenwood et al., 2012b). Many early associations studies suggest that the variants were associated with neuropsychiatric illness (*COMT*, *DISC1*, *DRD2*, *NRG1* etc.) however through meta-analysis, many of these associations appear to be non-significant (Barnett, Scoriels & Munafo, 2008; Flint & Munafo, 2007; Mathieson, Munafo & Flint, 2012; Munafo, Matheson & Flint, 2007; Munafo, Attwood & Flint, 2008). Nevertheless, many of the associations between functional variants and behaviour/imaging phenotypes have remained significant (Mier, Kirsch & Meyer-Lindenberg, 2010; Murphy et al., 2012b). This suggests that functional variants do not increase risk to neuropsychiatric illness per se, but rather modulate biological pathways/behaviour that may contribute susceptibility to one of many neuropsychiatric illnesses (Linden, 2012). Although the relationship between these functional polymorphisms and mental illness is relatively modest, the association between this variance and

heritable cognition are moderate and associations derived from neuroimaging methods are relatively strong. These findings together, suggest that the closer the proximity between the gene and the studied phenotype, the stronger the association will be. In the next chapter, the role of one of the most promising candidate gene variants is discussed. The catechol-O-methyltransferase gene (*COMT*) encodes an enzyme responsible for catabolising the catecholamines (dopamine (DA), noradrenaline (NA) and adrenaline (A)) in prefrontal regions of the brain (Akil et al., 2003). Membrane-bound *COMT* (predominately expressed in the brain) contains a missense mutation on exon 4 (valine > methionine; rs4680) at codon 158 in the amino acid structure (Weinshilboum, Otterness & Szumlanski, 1999). It is suggested that the amino-acid substitution (val>met) leads to a dramatic fourfold reduction in enzymatic activity for dopamine degradation and thus increases DA levels in prefrontal regions of the brain (Akil et al., 2003; Bilder et al., 2004; Chen et al., 2004; Dreher et al., 2009; Meyer-Lindenberg et al., 2005a).

The *COMT* val158met variant has been implicated as a risk factor in several neuropsychiatric disorders (Docherty & Sponheim, 2008; Langley et al., 2010; Paloyelis et al., 2010) and is associated with neurocognitive endophenotypes such as executive cognition (Tunbridge, Harrison & Weinberger, 2006) , emotion processing (Smolka et al., 2005), reward-guided learning (Farrell et al., 2012) and various parameters of personality (Sheldrick et al., 2008; Smyrnis et al., 2007). The *COMT* val158met variant has also been associated with robust patterns of neural activation in tasks over multiple imaging modalities (Bertolino et al., 2006; Ettinger et al., 2008; Golimbet et al.,

2006; Krug et al., 2009; Mier, Kirsch & Meyer-Lindenberg, 2010). These studies employ neurocognitive tasks used when investigating psychiatric populations to identify potential biological deficits that help to explain various symptoms and sub-clinical phenotype dimensions. However, as *COMT* val158met putatively modulates both prefrontal and striatal DA levels (Akil et al., 2003; Bilder et al., 2004; Chen et al., 2004; Dreher et al., 2009; Meyer-Lindenberg et al., 2005a), it may be suggested that the downstream effects of *COMT* val158met may be dynamic and widespread (Hariri, 2011). There have been several meta-analyses on both the cognitive effects of *COMT* val158met, many of which suggest that the variant only explains a small amount of the variance in cognitive phenotypes (Barnett et al., 2007; Barnett, Scoriels & Munafo, 2008). This may partially be due to interactions with age, sex, gene × gene interactions, epistatic mechanisms (Hariri, 2011) or due the inclusion of increased sample heterogeneity as sample sizes increase and/or effect size reductions. It has also been noted that effect sizes of gene variants are larger in imaging studies suggesting that observations between genes and neurobiological pathways (such as functional/structural variability of the brain) are more proximal and explain larger components of variability than cognitive parameters (Congdon, Poldrack & Freimer, 2010; Rasetti & Weinberger, 2011). It could also be suggested that many of these cognitive parameters lack specificity as they recruit many neurobiological pathways and do not assay specific associations but rather sum genetic influence from large gene networks (Kovas & Plomin, 2006; Scerif & Karmiloff-Smith, 2005) .

The first neurogenetic studies probing the putative effects of *COMT* val158met investigated its role in prefrontal DA function using tasks that

recruit broad fronto-parietal and cortico-limbic networks (Barnett et al., 2007; Barnett, Scoriels & Munafo, 2008). More recently, it has been investigated with reference to the neurobiological pathway associated with reward processing. Much of this research has been motivated by *COMT* val158met's association with substance use, disorders of impulsivity and motivation (Docherty & Sponheim, 2008; Langley et al., 2010; Meyer-Lindenberg et al., 2006b; Paloyelis et al., 2010; Tunbridge, Harrison & Weinberger, 2006). Unlike many of the uncertainties surrounding *COMT* val158met and 'cognition', a body of contemporary research is now investigating *COMT* in the context of rapid behavioural adaption (Frank et al., 2007), reward-related activation (Camara et al., 2010; Marco-Pallares et al., 2009) and lab-based impulsivity (Gianotti et al., 2012; Paloyelis et al., 2010; Smith & Boettiger, 2012). There have been many consistencies within the literature, many of which support the role of *COMT* in the 'reward-deficiency hypothesis' where individuals expressing the high-activity enzyme (val158) do not experience sufficient reward from environmental pleasures (Wichers et al., 2008). This posits that the *COMT* genotype may contribute to suboptimal reward experience and any disorders characterised by this phenotype (Der-Avakian & Markou, 2012). With this in mind, it proved intriguing to probe the effects of the *COMT* val158met genotype using assays of reward-responsiveness, a reward process significantly modulated by the dopaminergic pathways in which *COMT* is implicated. There were two main goals of this study (each of which will be tested in each experimental chapter): First, 'Optimizing Endophenotypes'; Neuroimaging phenotypes appear to characterise genetic influence with increased sensitivity (Rose & Donohoe, 2012); however,

various issues make larger scale neuroimaging studies difficult (e.g. time consuming, expensive etc.). Identifying behavioural phenotypes that are closer to specific neurobiological pathways may also increase the penetrance/effect size of a gene variant. We believe that *COMT* val158met was an ideal candidate in this case considering its previous implications and relatively well-characterised neurobiological function. We also suggest that neuroimaging is not the only method by which significant gene association can be identified, as long as the variant/s in question have well defined functional consequence (unlike many significant GWAS variants) and the neurobiological pathways of the cognitive domain are well defined and robust. Second, 'Increasing the proximity between genetic variance and neurobiological pathways'. Many associations between gene variants and behaviour have been identified, however many of these used agnostic approaches, which observe multiple gene variants, requiring high levels of statistical stringency. Agnostic genotype-phenotype association studies are particularly susceptible to false positives as the experiment-wise statistical corrections may not be considered (Sullivan, 2007). Several of these studies also measures of personality rather than assay for the performance of a specific neurobiological process. One of the aims of this thesis is to employ behavioural parameters with well-characterised and highly specific neurobiological processes.

In the first study, we aimed to expand the functionality of the *COMT* val158met variant by probing its effects on several parameters of reward responsiveness, a process selectively modulated by DA. I suggest that hypothesis-driven gene-trait exploration in domain-specific modalities

(experiment-wise corrected) have the potential to inform us of the neurobiology underlying components of heritable cognition.

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COMT val158met predicts reward responsiveness in humans

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Keywords: decision-making, reward, risk-taking, dopamine, genetics, individual differences.

Candidate Contributions: T.M.L tested all subjects, organized SNP genotyping, performed the analysis, interpreted the data and wrote the manuscript. D.E.L and E.A.R provided comments on manuscript, assistance on analysis and interpretation of the data.

15.1. Abstract

A functional variant of the catechol-O-methyltransferase (*COMT*) gene (val158met [rs4680]) is frequently implicated in decision-making and higher cognitive functions. It may achieve its effects by modulating dopamine-related decision-making and reward guided behaviour. Here we demonstrate that individuals with the met/met polymorphism have greater responsiveness to reward than do carriers of the val allele and that this correlates with risk seeking behaviour. We assessed reward responsiveness and risk seeking with tasks that measure how participants (N=70, western European, university and postgraduate students) respond to reward and take risks in the presence of available reward. Individuals with the met/met genotype (n=19) showed significantly higher reward responsiveness, $F(2,64)=4.02$, $p = .02$, and reward-seeking behaviour, $F(2,68)=4.52$, $p = .01$, than did either val/met (n=25) or val/val (n=26) carriers. These results highlight a scenario where genotype-dependent reward responsiveness shapes reward seeking, therefore suggesting a novel framework by which *COMT* may modulate behaviour.

15.2. Introduction

Although the heritability of behaviour is considerable, the search for specific mechanisms has yielded few replicated associations between genotypes and specific traits. One of the most promising candidates is a functional polymorphism (rs4680), which produces a valine (val)-methionine (met) substitution at codon 158 (val158met variant) of the catechol-O-methyltransferase (*COMT*) gene. Evidence shows that the val158met polymorphism, present in humans, modulates *COMT* enzymatic activity which in turn promotes the catabolism of presynaptic dopamine (Weinshilboum, Otterness & Szumlanski, 1999). In animal models, manipulation of *COMT* enzymatic activity alters frontal dopaminergic function (Gogos et al., 1998; Yavich et al., 2007). Researchers have therefore suggested that the *COMT* val158met genotype may modulate dopamine (DA) availability in prefrontal and striatal pathways in humans (Akil et al., 2003; Chen et al., 2004; Meyer-Lindenberg et al., 2005a). However, the relationship between *COMT* and prefrontal DA function in humans remains indirect.

The *COMT* genotype is associated with variability in a variety of dopaminergic phenotypes, including executive function and cognition (Mier, Kirsch & Meyer-Lindenberg, 2010). Indeed, researchers argue that sensitivity to reward may be a crucial factor in performance on executive function tasks (Beck et al., 2010; Jimura, Locke & Braver, 2010). For example, the simple performance-based feedback inherent in tasks such as the Wisconsin Card Sorting Task may be rewarding, despite the absence of explicit reward. Moreover, evidence shows that simply knowing one has answered correctly, in the absence of *any* feedback, activates ventral striatum, an area associated with mid-brain reward circuitry (Satterthwaite et al., 2012). Therefore, *COMT*

genotype-dependent differences in cognitive performance may relate to the intrinsic reward associated with correct performance on cognitive tasks, regardless of explicit incentives.

Based on proposed links between dopamine, reward and cognition, recent research has sought to characterize the *COMT* genotype by probing the val158met variant with reinforcement-learning tasks, rather than conventional measures of cognitive/affective function. This work suggests that the *COMT* val158met variant may modulate task adaptation ability (Frank et al., 2007; Krugel et al., 2009) as well as exploratory behaviour during learning (Frank et al., 2009). However, the *COMT* variant's exact role in governing individual differences in reward responsiveness remains unknown. Preliminary evidence based on experience sampling methods suggests increased reward sensitivity in met homozygotes (Wichers et al., 2008). However, much of this evidence linking the *COMT* genotype to reward sensitivity has been inferred from neuroimaging measures (e.g. (Marco-Pallares et al., 2009)).

The present study aimed to bridge the gap between measures of reward responsiveness, the degree to which people's behaviour depends on the presence or possibility of gaining rewards, and *COMT* genotype by providing behavioural evidence of genotype dependent differences in reward responsiveness and reward seeking. We hypothesized that relative to carriers of the val allele, met/met participants would show increased responsiveness to rewards by developing a greater bias toward a more frequently reinforced target in a signal detection task with asymmetric reinforcement (Pizzagalli, Jahn & O'Shea, 2005) and by attempting to obtain more rewards in a risky

reward-guided decision-making task (Lejuez et al., 2002). Based on the finding that the *COMT* met allele appears to enhance the degree to which individuals experience rewards as rewarding (Pizzagalli et al., 2008), we also predict that the met allele should enhance the degree to which reward responsiveness motivates reward seeking. Thus, we anticipate the presence of a differential relationship between reward responsiveness and reward seeking across the genotype groups.

15.3. Methods And Materials

Participants

An initial pool of 244 volunteers was recruited to a panel that was genotyped for the *COMT* val158met variant (rs4680). Participants in this panel were recruited by advertisement from among the University community (e.g., students, employees) based on the following criteria: no experience of psychiatric/neurological symptoms or diagnosis in either themselves or any first-degree relatives; no illegal (or recreational) substance use/dependence (excluding nicotine); and no alcohol abuse/dependence. The sample did not deviate from Hardy-Weinberg Equilibrium (χ^2=.005, p>.9) (Table 6). To avoid problems of population stratification, participants in the present study were recruited from the larger panel based on being of western European descent and where either undergraduate or postgraduate-student volunteers. From the original panel of 244 participants, seventy participants were recruited back to complete the behavioural tasks using an opportunistic schedule based on availability, whilst inviting back more met/met and val/val participants. This process permitted the creation of larger between group sample sizes for genotype cells which are small in random samples. The process has been used before in behavioural/imaging genetics (Marco-Pallares et al., 2009). All participants provided written informed consent prior to DNA extraction and to participation in the present study. The University's Ethics Committee approved all study procedures. Researchers and participants were blind to participants' *COMT* genotype status during both the behavioural data collection. Participants completed the two tasks in randomly assigned orders. The *COMT* genotype groups did not differ in age or sex for participants recruited for the study (Table 6).

15.3. Methods And Materials

COMT rs4680	Met/Met	Val/Met	Val/Val	p
Genotype [a]	27% (n=66)	41% (n=101)	32% (n=77)	>.5
Genotype[b]	27.1% (n=19)	35.7% (n=25)	37.1% (n=26)	n/a
Age [c]	22.9 (3.8)	21.6 (2.4)	23.7 (6.4)	>.5
Sex [d]	M (n=9) F (n=10)	M (n=10) F (n=15)	M (n=8) F (n=18)	>.5

Table 6 | Table shows means (except where noted; standard deviations appear in parentheses). [a] Group differences tested for Hardy-Weinberg Equilibrium (larger genetics panel). [b] *COMT* genotype cell sizes in behaviour sample . [c] Group differences tested with 1-way ANOVA. [d] Group differences tested with chi-square.

Genotyping

Participants provided gDNA samples via buccal swabs (Isohelix, Cell Project Ltd, Kent UK). All 70 participants were successfully genotyped for the *COMT* val158met (rs4680) single nucleotide polymorphism (SNP). Source Biosciences (Life-Sciences Division, Nottingham, UK) provided genomic services. SNP genotyping was performed using a MATRIX PlateMatePlus. Polymerase chain reaction (PCR) was performed using KBiosystems Super Duncan thermal cycler. An ABI PRISM 7900HT Sequence Detection System was used to visualize allelic discrimination at the rs4680 loci with a fluorogenic 5' nuclease TaqMan ® SNP assay (Applied Biosystems, California).

Procedure

Reward Responsiveness Task: To measure reward responsiveness, we used a line discrimination task with asymmetric reinforcement, closely modelled after that described in (Heerey, Bell-Warren & Gold, 2008; Pizzagalli, Jahn & O'Shea, 2005). Asymmetric reinforcement, in which responses to one stimulus receive more frequent rewards than responses to

another, leads to the development of response bias by increasing participants' likelihood of reporting the more frequently reinforced stimulus. Individuals who develop greater levels of response bias are more responsive to rewards (Pizzagalli, Jahn & O'Shea, 2005; Pizzagalli et al., 2008) .

Trials began with a fixation cross (500ms), followed by the presentation of a cartoon face with no mouth. After 500ms, either a short (22mm) or long (24mm) mouth appeared on the face. It was visible for 100ms before disappearing. The face remained on screen until the participant responded with a button press indicating the presence of either the short or the long mouth. Following the response, participants saw a screen that either displayed feedback ("Correct! +5 pence") or remained blank (no-feedback trials) for 1750ms (Figure 4). Participants completed three blocks of 100 trials. Both versions of the mouth appeared equally often in pseudo-random order such that there were no more than four successive trials of the same mouth.

Participants received reward feedback on forty correct responses per block. In order to induce a reward-related response bias in the task, we distributed the rewards asymmetrically across the mouths. The more frequently reinforced mouth received thirty rewards per block and the remaining ten rewards occurred after responses to the other mouth. We used a pseudo-random reward schedule such that no more than three correct trials in a row received reinforcements. Participants never received feedback on incorrect trials. Reinforcements scheduled for incorrect trials were delayed until a later unreinforced correct trial of the same type occurred. The length (short or long) of the more frequently reinforced mouth was counterbalanced across participants. We excluded four participants from analysis for confusing

the response keys (3 val/val individuals and 1 val/met individual). A post-task debriefing interview confirmed that no participants were aware of the reinforcement asymmetry. We used a standard signal detection analysis to calculate d', a measure of discrimination accuracy [d' = z(*H*) – z(*F*)] and "criterion," the degree to which participants showed a bias toward the more frequently reinforced mouth (c =-½[z(*H*)+ z(*F*)]; see (Heerey, Bell-Warren & Gold, 2008) .

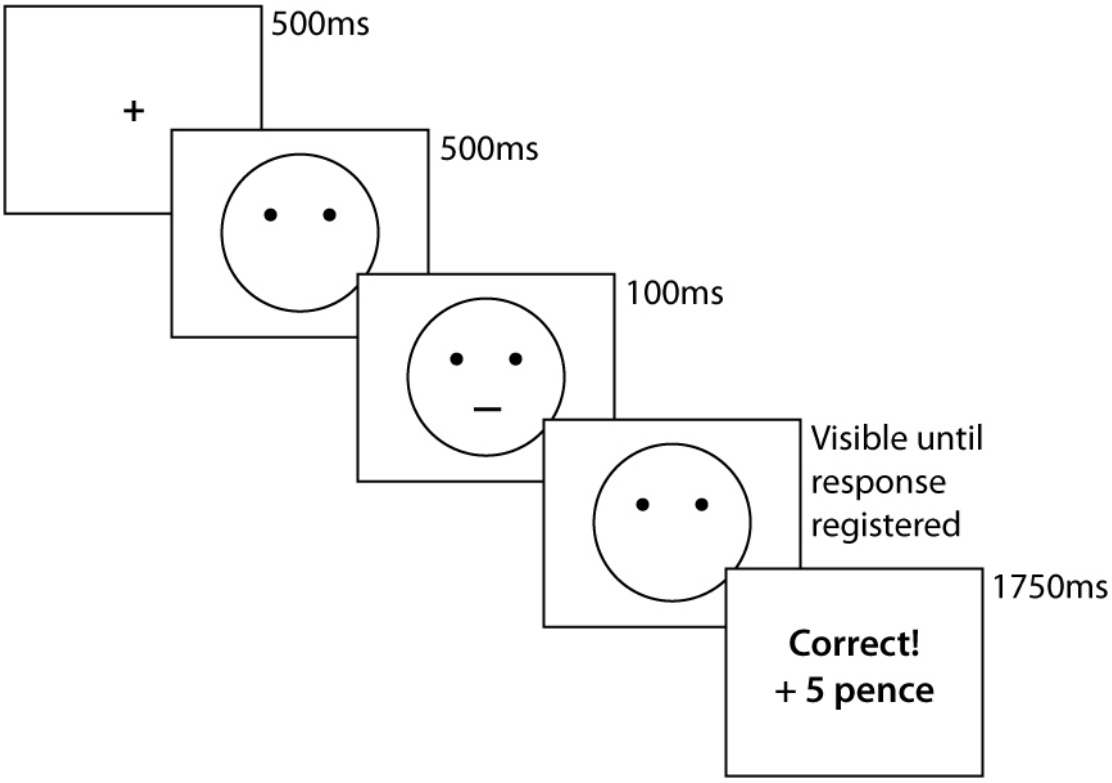

Figure 4 | Trial timeline for a feedback trial in the reward sensitivity task.

Balloon Analogue Risk Task (BART): Participants completed the BART (Lejuez et al., 2002) as a measure of risk-taking/reward-seeking behaviour. On each trial of the task, participants saw a coloured balloon that they could inflate by clicking a button labelled "pump" with a mouse. For each

mouse click, participants earned 5 pence, which accumulated during the trial in a temporary “bank.” They could click as often as they liked until either the balloon burst or they chose to end the trial by clicking a button labelled “stop”. On trials in which the balloons burst, participants forfeited all the money in the temporary bank. If participants stopped a trial before bursting the balloon, the money they earned in the trial transferred to a permanent bank for safekeeping. Participants received these earning as a monetary bonus at the end of the task.

Balloons in the task had three strengths or thresholds for bursting (weak: 1 to 8 pumps; medium: 1 to 32 pumps; strong: 1 to 128 pumps), each shown in a different colour (blue, magenta and yellow). Participants received no explicit information about the different thresholds for bursting the balloons and balloon colours were randomly assigned to balloon strengths across participants.

The task consisted of four blocks: one block of 30 trials in which 10 balloons of each type appeared in random order; and three learning blocks (20 trials each) in which all the balloons were the same colour (colour blocks occurred in random order).

There were no differences between men and women on any of the dependent variables, either within or across allele groups (p-values> .23) (Table 7). Results are therefore collapsed across participant gender. Correlations between age and performance were also non-significant, within and across groups (p-values > .315).

15.4. Results

Sex	stimulus discriminability (‘d)			*p*
	block1	block2	block3	
Male	1.87 ±1.52	1.84 ±1.8	2.15 ±1.4	.497
Female	1.83 ±1.53	2.07 ±1.22	2.03 ±1.19	
	reward responsiveness (c)			
	block1	block2	block3	
Male	-0.27 ± 0.47	-0.26 ± 0.51	-0.23 ± 0.52	.315
Female	-0.06 ± 0.55	-0.16 ± 0.4	-0.14 ± 0.5	
	balloon analogue risk taking			
	Adjusted	No. Pops	Total Points	
Male	15.27 ±4.03	34.27 ±9.28	4100.96 ±657.41	.721
Female	14.57 ±4.09	31.64 ±8.93	4100.57 ±652.67	

Table 7 | Descriptive data for behavior in tasks separated by gender. P-values for stimulus discriminability (‘d) and reward responsiveness (c) calculated using repeated measures ANOVA, with trial and gender as within and between subject factors, respectively. Gender differences in the BART where calculated using one-way ANOVA.

Reward Responsiveness: We used mixed-model ANOVAs to compare d’ and criterion across task blocks (1-3) using the three allele-combinations (met/met [n=19], val/met [n=23] and val/val [n=24]) as the between-subjects variable. Participants performed the line-discrimination equally well regardless of genotype group, $F(2,65)=.70$, $p=.40$, $\eta_p^2=.01$ (Figure 5a). Critically, results showed genotype-dependent reward-responsiveness differences, such that the met homozygotes developed greater response bias than the other allele groups, $F(2,64)=4.02$, $p=.02$, $\eta_p^2=.11$ (Figure 5b). There was also a Genotype $\times$ Block interaction suggesting that bias towards reinforced stimuli increased over blocks, $F(2,63)=2.43$, $p=.05$, $\eta_p^2=.07$, particularly at block 3, in which met

15.4. Results

homozygotes showed significantly greater response bias than the other allele groups, $F(2,64)=6.37$, p =.003, η_p^2=.17. Indeed, the proportion of people in each genotype group who developed a bias toward the more frequently reinforced stimulus (coded as 'present' if there was greater bias in block 3 than in block 1 and 'absent' if not) showed a linear increase across the allelic combinations (val/val: 29%; val/met: 47%; met/met: 63%). Together, these results show that whereas genotype does not affect perceptual sensitivity in the task as indexed by line discrimination performance, it does influence responsiveness to environmental rewards. We therefore suggest that met/met groups increased reward responsiveness should lead them to make riskier decisions in the pursuit of reward.

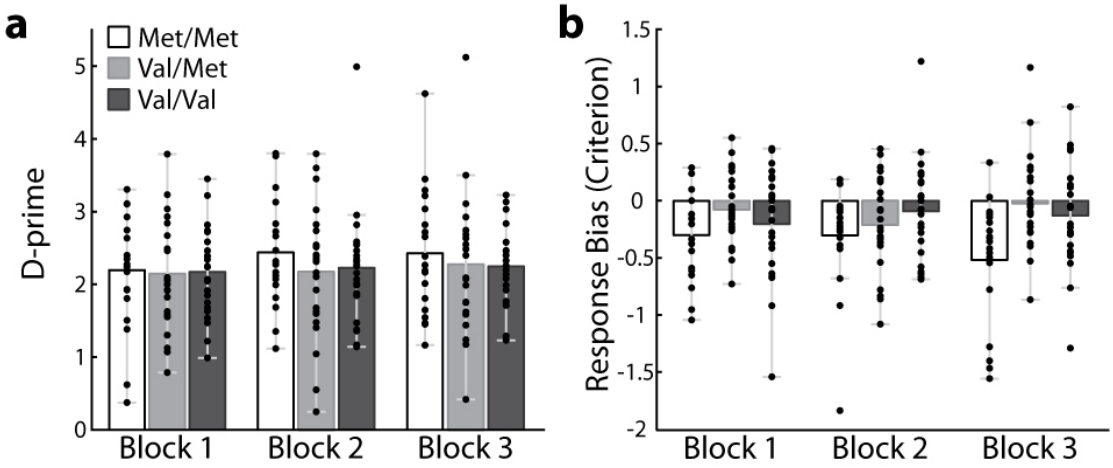

Figure 5 | Reward Sensitivity Results. Data from 66 healthy participants (18-52 years, mean 21.6, SD±4.3; met/met n=19, val/met=23, val/val=24). **a)** There were no genotype differences in d' across task blocks. **b)** Met /met participants showed significantly greater response bias than val/met or val/val groups. Error bars span 3 × IQR (interquartile range).

BART: Number of burst balloons, number of pumps adjusted for burst balloons, and task earnings served as the dependent measures. The met homozygotes demonstrated a riskier strategy by bursting more balloons,

15.4. Results

$F(2,68)=6.59$, $p=.002$, $\eta_p^2=.16$ (Figure 6a), but they also pumped un-burst balloons more, $F(2,68)=7.46$, $p=.001$, $\eta_p^2=.18$ (Figure 6b), and therefore earned more on each trial, $F(2,68)=3.21$, $p=.05$, $\eta_p^2=.09$ (Figure 6c). Because participants attempt to increase their payoffs with each pump, this response pattern is indicative of greater reward seeking despite the risks involved with each successive pump of a balloon. Although the met/met participants' behaviour appeared riskier, it was advantageous, particularly as balloon strength increased. In support of this idea, there was a Genotype x Balloon strength interaction, $F(2,67)=4.36$, $p=.002$, $\eta_p^2=.12$, driven by met/met participants' higher earnings on the strongest balloons, $F(2,68)=4.52$, $p=.01$, $\eta_p^2=.12$.

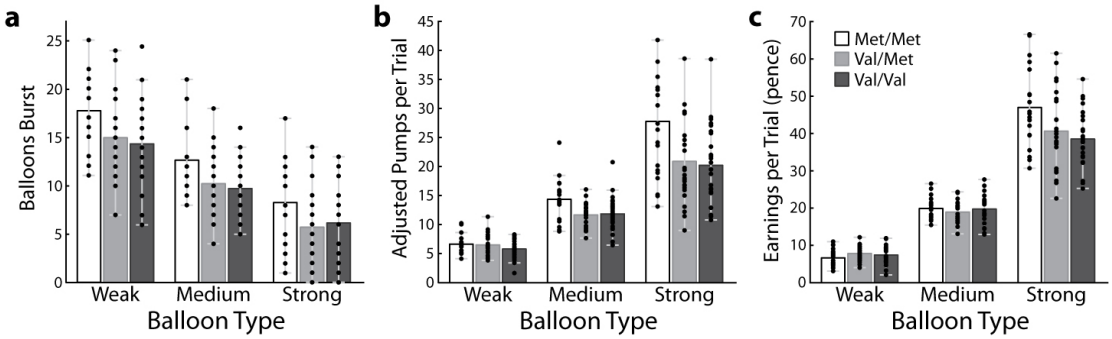

Figure 6 | BART Results. **a)** The met/met group burst more balloons but **b)** pumped un-burst balloons more successfully, leading to **c)** greater earnings. Results include 70 participants; error bars span 3 × IQR (interquartile range).

Cross-task correlations: We have argued that the met allele enhances the degree to which reward responsiveness motivates reward-seeking behaviour. Thus, the reward-responsiveness/reward-seeking relationship should be stronger in the met/met group than in the val/val group.

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To test for the presence of this predicted interaction, we performed a hierarchical regression analysis with reward seeking as the dependent variable. Step 1 of the model included reward responsiveness and *COMT* genotype as the predictors and step 2 included the reward-responsiveness x *COMT* genotype interaction. Results showed that over and above the main effects, the genotype x reward-responsiveness interaction was statistically significant (ΔR^2=.08, $b_{unstandardized}$=6.45, t(62)=2.59, p=.01), suggesting differences in the relationship between reward-responsiveness and reward seeking across genotype groups[1].

To examine these differences more closely, we computed the correlation between reward responsiveness[2] and reward seeking within genotype groups, transformed these to z-scores using Fisher's r to z transformation, and examined differences in the strength of the relationship between the met/met and val/val groups. Reward-sensitivity significantly predicted reward-seeking in the met/met group (Burst-Balloons: r=.54, *p*=.02; Adjusted-Pumps: r=.47, *p*=.04; see Figure 7), but not in either of the other groups (Val/Met: Burst-Balloons, r=.17, *p*=.43; Adjusted-Pumps, r=.30, *p*=.16; Val/Val: Burst-Balloons, r=-.16, *p*=.48; Adjusted-Pumps, r=-.02, *p*=.92). As anticipated, we found significant differences between the met/met and val/val groups in the strength of the relationship between reward responsiveness and reward seeking (Burst-Balloons: z=2.31, $p_{one\text{-}tailed}$=.01; Adjusted-Pumps: z=1.60, $p_{one\text{-}tailed}$=.05), suggesting that reward responsiveness motivates reward seeking more strongly among met/met than among val/val participants.

15.4. Results

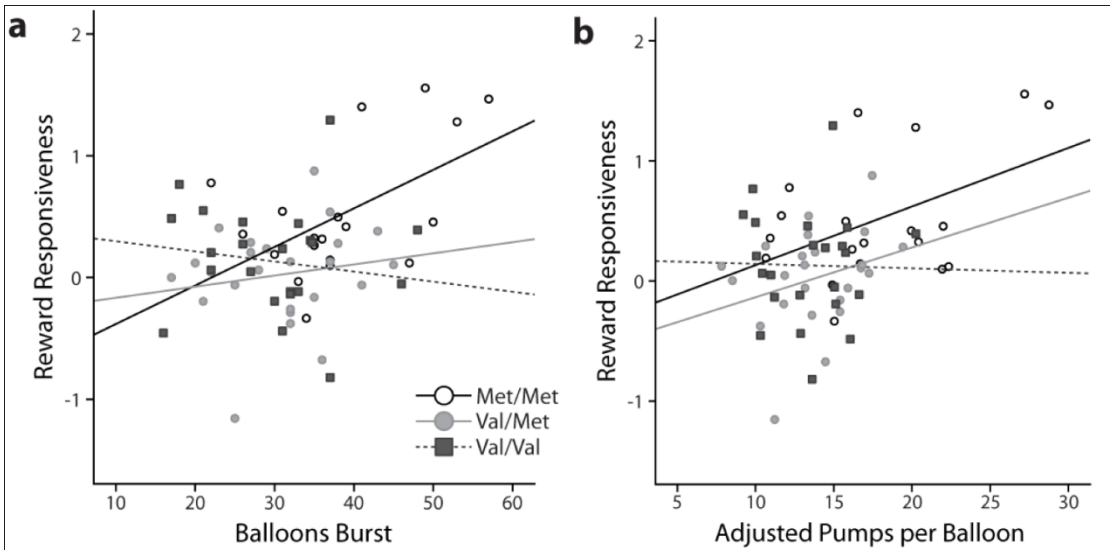

Figure 7 | Correlations between reward responsiveness and reward seeking across genotype groups. **a)** Total burst balloons; **b)** average adjusted pumps per balloon

15.5. Discussion

Here, we show that a common genetic variant (val158met, rs4680), hypothesized to alter cortico-striatal dopamine dynamics (Bilder et al., 2004; Meyer-Lindenberg et al., 2005a), predicts reward responsiveness during asymmetric reinforcement and sequential risk-taking. This complements previous pharmacological and radioligand imaging evidence suggesting that modulation of dopamine influences response to reward (Pizzagalli et al., 2008; Santesso et al., 2009; Vrieze et al., 2011) and hints at a link between the *COMT* genotype and dopamine function in humans. In the BART, met/met participants were more willing to take calculated risks when rewards were attainable. The degree to which they did so related to the development of response bias under an asymmetric reinforcement schedule. This was not the case for val/met or val/val groups. The genotype x reward-responsiveness interaction in our data suggests that available rewards may motivate reward seeking more strongly for met/met than for other participants, perhaps because met/met individuals experience rewards as more pleasant (Wichers et al., 2008).

These findings suggest that enhanced reward responsiveness may be a unifying mechanism underlying previously documented val158met differences in reinforcement learning (Frank et al., 2007), motivated decision-making (Frank et al., 2009) and neural responses to reinforcement (Bogdan & Pizzagalli, 2009; Strauss & Gold, 2012). Together, these results suggest that the met/met participants are more responsive to available rewards than are val carriers, as their decisions, although riskier (as recently shown; (Amstadter et al., 2012)), also proved more financially rewarding. Thus, we argue the met/met group displayed ‘functional impulsivity’ (Dickman, 1990) in the extent

to which they adjusted task performance to optimize their rewards. The association between reward responsiveness and advantageous reward seeking in the met/met group suggests that the magnitude of reward representation may modulate the degree to which people learn to maximize environmental rewards (Sapra, Beavin & Zak, 2012). Indeed, research suggests that met/met individuals adapt to task contingencies more flexibly (Frank et al., 2007), a finding that resonates with the present study's results.

Together, these results suggest that reward-responsiveness is one mechanism by which the *COMT* genotype exerts its effect on broad range of tasks with inherent feedback, motivation and reward components. We therefore hypothesize that increased ability to adjust behaviour based on trial outcomes is the missing link between *COMT* and its general cognitive performance effects. A number of the behavioural assays that demonstrate *COMT* genotype differences are executive function tasks in which performance feedback serves as a motivational incentive, even in the absence of explicit reward (Aarts, van Holstein & Cools, 2011; Barnett, Scoriels & Munafo, 2008; Jimura, Locke & Braver, 2010). Individuals with the met/met variant may outperform those with other variants simply because they are more motivated to maximize intrinsic and extrinsic rewards.

Insofar as the *COMT* genotype modulates the tonic-phasic dopamine balance as researchers suggest (Bilder et al., 2004) it may increase incentive-driven 'proactive control' over rewarded stimuli (Frank & Fossella, 2011; Jimura, Locke & Braver, 2010). Our data support this theory by demonstrating that the *COMT* genotype does not influence basic perceptual sensitivity but does influence reward responsiveness. If dopamine does indeed modulate

cognition/motivation dynamics as research suggests (Aarts, van Holstein & Cools, 2011; Frank & Fossella, 2011; Rogers, 2011), our results suggest that *COMT* may modulate the dynamics between cognition and motivation. The stability of the reward-related behaviour for the met/met individuals across both tasks, along with the consistency and directional effects of the *COMT* variant suggest that the val158met polymorphism may modulate a neurobiological platform by which individuals interpret and respond to rewarding stimuli.

Finally, we note that recent work has highlighted concerns about false positive associations in behavioural genetics studies (Sullivan, 2007). We have minimised this risk by testing only pre-defined genetic hypotheses (*COMT* effects on reward responsiveness and reward-seeking). Additionally, we demonstrate consistent performance across both tasks and carefully embed our findings in an extensive context of previous neurobiological and behavioural work. Although our sample size is small (in the met/met group particularly), given the strength and stability of our findings and the degree to which they follow from previous literature, we suggest that our results are reliable. Nonetheless, these results do, of course, require independent replication.

There are two additional limitations to the study. First, although our participants were screened for illegal substance use, we did not assess their nicotine use, which relates to risk-taking behaviour on the BART (Lejuez et al., 2003). However, based on their ages and education levels, we do not have reason to suspect that our groups differed in smoking behaviour, making it unlikely that smoking explains the genotype differences. Second, although

we did not explicitly control IQ across the groups, participants were all intermediate or advanced university students, suggesting that they possess average or better intelligence. IQ, however, has not been shown to correlate with performance on the BART (Lejuez et al., 2002), or other measures of reward responsiveness (e.g., (Luman, Oosterlaan & Sergeant, 2005)).

In sum, this study validates several hypothesized associations between the *COMT* val158met genotype and dopamine-related reward responding. Specifically, results demonstrate robust and specific *COMT* genotype-dependent reward focus in laboratory tasks and potentially in the broader environment. Indeed, understanding the association between the *COMT* locus and reward responsiveness/reward seeking may also help explain *COMT* 's involvement in neuropsychiatric disorders characterized by decision-making deficits (Docherty & Sponheim, 2008; Langley et al., 2010; Paloyelis et al., 2010) as well as the genetic contributions towards heritable symptoms states associated with these disorders (Anokhin et al., 2009; Bogdan & Pizzagalli, 2009).

16. Experimental Chapter 2: Preface

Perhaps owing to high heritability, diverse genetic architecture and/or symptom heterogeneity, there have been several significant advances in the identification of endophenotypes for schizophrenia (SZ). There are several defining markers that both reflect the clinical parameters of the disorder (symptom severity, illness course, treatment response) and capture core processes that delineate the specific neurobiology of the disorder (Ivleva et al., 2012). Both behavioural (Barch et al., 2009a) and imaging based NCEs (Barch et al., 2012; Minzenberg et al., 2009) may predict susceptibility in prodromal groups (An et al., 2010; Yee et al., 2010; Piskulic et al., 2012), high-risk groups (Choi et al., 2011; Giuliano et al., 2012), first-degree relatives (van Haren et al., 2012) and healthy controls with genetic risk (Alfimova et al., 2011; Carless et al., 2011; Hargreaves et al., 2012; Rasetti et al., 2011;). There are several approaches by which one may probe for the functional effects of a SZ risk gene, including behavioural, structural/functional imaging and metabolic/neurochemical anomalies. One critical assumption is that the parameters one measures must reflect genetic susceptibility rather than a state feature or a downstream functional consequence of the disorder. For example, recent evidence suggests that although prefrontal volume reduction (a candidate endophenotype for SZ) is moderately heritable (Cannon & Keller, 2006; White, Andreasen & Nopoulos, 2002; Winkler et al., 2010), it does not share genetic overlap with the disorder (Owens et al., 2012). The well-recognised reduction of prefrontal volume in SZ patients are independent of the familial influences that increase genetic susceptibility and may be attributed to state dependent neurobiological changes such as substance abuse, medication or illness course (Owens et al., 2012). In comparison,

putative measures of prefrontal function may be both heritable and specific to SZ (Barch et al., 2012; Carter, Barch & CNTRICS Executive Committee, 2012; Luck et al., 2012; Ragland et al., 2012). It may be now suggested that volumetric variability may not be an appropriate endophenotype to probe for the functional effects of genetic risk variants. Although there is potential for genetic variance to modulate cortical morphology, it is unlikely that this genetic variance contributes to the genetic susceptibility to SZ. The endophenotype approach should ideally be employed in a manner that elucidates biological mechanisms that confer risk to the disorder, rather than explain simply sample variance. A large cortical morphology study showed no significant association with a major psychosis risk variant (*ZNF804A*) and macroscopic brain structure in healthy controls (Cousijn et al., 2012). This finding supports the notion that genetic susceptibility to SZ does not manifest as volumetric reductions.

On the other hand, neurocognitive endophenotypes are heritable and seem to be significantly associated with genetic susceptibility, albeit with modest effect. As a result, the effects of single gene variants on behavioural NCEs are relatively modest. Working memory (WM) is a well-established endophenotype and the pathophysiological mechanisms by which deficits in WM occur has been studied extensively (Barch et al., 2009a; Barch et al., 2012). In the context of neuropsychiatric genetics, WM related activity is conventionally measured by: (1) Task-related BOLD activation (measured as the hemodynamic response to encoding, maintenance and manipulation (or combinations of sub processes) of information in an online store (Blokland et al., 2011; Plichta et al., 2012). (2) Functional connectivity; measures

correlations between spatially remote neurophysiological events, probed by seed voxel/s or the interaction between regions and experimental treatment (Rasetti & Weinberger, 2011) .

The majority of studies report dysfunction of the DLPFC (dorsolateral prefrontal cortex) and aberrant functional coupling between the DLPFC and the medial temporal lobe (Meyer-Lindenberg et al., 2005b; Meyer-Lindenberg, 2010a; Meyer-Lindenberg, 2010b; Meyer-Lindenberg, 2012;). However, the nature of the dysfunction has often been contested and the precise pathophysiological mechanism WM related processing remains unknown. Studies consistently report hypoactivation and increased activity states or alternatively, complex dysfunctional states that may reflect disproportional engagement and/or compensatory neural networks (Cannon et al., 2005; Karlsgodt et al., 2009). Nevertheless, aberrant DLPFC activation remains one of the most consistent pathophysiological manifestations of genetic susceptibility in SZ research. Several studies have demonstrated that candidate SZ risk genes may modulate WM-related activity, especially genes that contribute to the neurobiological pathways underlying WM, such as prefrontal dopaminergic process (Bilder et al., 2004). In the post-GWAS-era, the roles of novel SZ risk loci have been investigated using WM-related activation as an endophenotype. These studies however, have observed no association between risk allele dosage and WM processing (Esslinger et al., 2011; Paulus et al., 2011; Rasetti et al., 2011). This may be due to modest odds ratio of the variants (O'Donovan et al., 2008) or that the risk genes do not influence neurobiological process associated with WM. However, studies have shown that risk genes from SZ GWAS (such as *ZNF804A*) do modulate

WM performance (Walters et al., 2010) and WM-related activity showing functional coupling abnormalities in risk carriers (Esslinger et al., 2009; Paulus et al., 2011; Rasetti et al., 2011). This finding has been partially replicated between studies and across tasks, suggesting that *ZNF804A* confers susceptibility by modulating synchrony between neural networks during WM. The genetic risk score (GRS) method has also been employed to quantify how cumulative genetic risk may influence WM-related activity. The findings suggest that increasing genetic loading correlates with increasingly dysfunctional DLPFC activation (Walton et al., 2012). However, this method only tests the notion of WM dysfunction as a manifestation of genetic susceptibility rather than identifying the underlying pathophysiological process.

Cognitive impairment is widely regarded as an integral component of pathophysiology in SZ but also transcends other dimensions and modulates other important factors such as social behaviour. The most widely recognised example of which is face/emotion recognition (Eack et al., 2010; Calkins et al., 2010; Greenwood et al., 2007). Facial affect deficits are acknowledged as stable trait marker schizophrenia (Carter et al., 2009; Mathersul et al., 2009). The trait meets several of the criteria for an endophenotype and may be useful in the elucidation of novel biological mechanisms in SZ pathophysiology. We aim to revisit the *ZNF804A*–WM processing relationship, using an additional emotion/facial affect-processing component. Previous work within the lab has quantified the neural networks this 'emotional WM task' recruits and how aberrant processing may manifest in patients with SZ (Jackson et al., 2008; Wolf et al., 2011b). We suggest that the *ZNF804A*

variant will modulate activation in regions where emotion processing and WM converge, such as DLPFC (Becerril & Barch, 2011; Ursu et al., 2011). We sought to investigate the role of *ZNF804A* on emotional WM related BOLD to expand the parameters of *ZNF804A* associated susceptibility. The study aims to determine whether facial affect processing can be used to capture modest amounts of genetic susceptibility and if *ZNF804A* related WM dysfunction is exclusively related to variance in functional connectivity across WM parameters. The study also aims to contribute to the initiative of Chapter 13. Optimizing Endophenotypes. We suggest that the use of emotional faces as a stimulus may recruit a specific neurobiological platform and capture a larger proportion of the variance the risk loci may modulate.

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ZNF804A genotype modulates neural activity during working memory for faces.

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Short Title: ***ZNF804A* genotype and working memory for faces**

Keywords: *ZNF804A*; genetic imaging; working-memory; emotion; schizophrenia, dorsolateral prefrontal cortex

Candidate Contributions: T.M.L performed data analysis and interpretation and wrote the manuscript. D.E.L collected data, provided comments on manuscript, assistance on analysis and interpretation of the data. C.W and M.C.J collected the data. S.J.J assisted with the analysis. A.B, R.D and J.T provided comments on the manuscript and performed genotyping.

17.1. Abstract

Abstract

Background: Genetic susceptibility to schizophrenia (SZ) has been suggested to influence the cortical systems supporting working memory (WM) and emotional face processing. Genetic imaging studies link the SZ risk variant rs1344706 on the *ZNF804A* gene to psychosis via alterations in functional brain connectivity during WM, but no work has looked at the effects of *ZNF804A* on WM with emotional face processing components.

Methods: We therefore investigated healthy controls that were genotyped for rs1344706 with an emotional WM task during functional magnetic resonance imaging. We suggested that variation at the rs1344706 locus would be associated with similar alterations as patients previously tested using the same WM task for emotional faces.

Results: The rs1344706 risk allele (TT) was indeed associated with altered activation in the right dorsolateral prefrontal (rDLPFC) cortex. We established that the rDLPFC was activated in a task-dependent manner, suggesting that the differences in activation between rs1344706 genotype groups reflected alterations in task processing. Furthermore, we demonstrate that the rDLPFC region has significant overlap with the rDLPFC previously been shown to be altered during task processing for patients with SZ.

Conclusions: The findings support an association between rs1344706 and alterations in DLPFC activity during WM for faces. We further suggest that WM for faces may be a useful intermediate phenotype in the investigation of genetic susceptibility to psychosis.

17.2. Introduction

Introduction

Genome wide association studies (GWAS) have identified a locus on the *ZNF804A* (rs1344706) as a well-supported risk variant for schizophrenia (SZ) and a broader spectrum of clinical phenotypes (Dwyer et al., 2010; O'Donovan et al., 2008; Riley et al., 2010; Steinberg et al., 2011; Williams et al., 2011a). In order to quantify the potential functional effects of GWAS variants such as *ZNF804A*, functional magnetic resonance imaging (fMRI) is used to study how genetic architecture contributes to neural systems. This method may help to establish how risk variants may modify the neurobiological pathways that are disrupted in psychiatric populations (Meyer-Lindenberg & Weinberger, 2006; Meyer-Lindenberg, 2010a).

Working memory (WM) and face processing are recognised as heritable deficits in SZ (Forbes et al., 2009b; Greenwood et al., 2007). WM and face processing are also implicated as the biological basis for neuropsychiatric symptomology (Germine et al., 2011; Gonzalez-Ortega et al., 2012; Harvey et al., 2009; Tully, Lincoln & Hooker, 2012). SZ patients show alterations in task processing for WM and emotional faces as revealed by functional neuroimaging (Hall et al., 2007; Karlsgodt et al., 2011). Relatives for SZ patients (familial high-risk groups) also display similar alterations (Broome et al., 2010; Choi et al., 2011; MacDonald et al., 2009). The rs1344706 genotype (T= risk allele) is associated with alterations in functional connectivity between prefrontal and inter-hemispheric prefrontal/hippocampal networks in healthy controls during WM (Paulus et al., 2011; Rasetti et al., 2011), face processing and resting state (Esslinger et al., 2011). The functional effects of the rs1344706 variant may extend to a broad range of

cognitive phenotypes such as social cognition (Hargreaves et al., 2012; Walters et al., 2010) and attentional networks (Balog, Kiss & Keri, 2011; Lencz et al., 2010). ZNF804A may influence cell adhesion (Hill et al., 2012) and regulate expression of other genes (Girgenti, Loturco & Maher, 2012) whereas the rs1344706 variant may have a functional role in the transcription of the *ZNF804A* gene (Hill & Bray, 2011). However, it is not understood how the rs1344706 variant influences complex neurocognitive phenotypes, with emerging evidence suggesting the variant has little/no effect on macroscopic cortical structure (Cousijn et al., 2012; Donohoe et al., 2011a; Sprooten et al., 2012).

The rs1344706 variant may modulate prefrontal cortical functional connectivity implicated in the WM process (Esslinger et al., 2009; Esslinger et al., 2011). However, the robust alterations in prefrontal neural activation during WM observed in schizophrenic patients (Cannon et al., 2005; Manoach, 2003; Kim et al., 2010) and first-degree relatives (Choi et al., 2011; Brahmbhatt et al., 2006; Broome et al., 2010; MacDonald et al., 2009) were not associated with the rs1344706 allele in SZ patients, first-degree relatives or healthy controls (Rasetti et al., 2011). That said, both heritability (twin studies) and SZ related genetic risk score (cumulative total of SZ risk alleles) are both significant predictors of neural activity in the dorsolateral prefrontal cortex (DLPFC) during WM (Blokland et al., 2011; Walton et al., 2012).
In order to further explore the effects of the rs1344706 genotype on the WM network, we added a face-processing component to a WM task. We suggest that the addition of emotional valence to WM items will recruit a specific neural network and a novel context to probe for functional effects of the

rs1344706 variant. Studies using WM stimuli with emotional valence reveal that SZ patients have relatively intact limbic function (amygdala activity) in response to emotionally valenced items, but show altered activity in the DLPFC (Becerril & Barch, 2011) that may reflect a deficit in emotion recognition (Linden et al., 2010). During WM for faces, SZ patients failed to utilize conventional neural resources (hypoactivation in right PFC) and instead, recruited a contralateral homologue (hyperactivation in the left PFC and sensory cortical regions) to manage the WM demands (Wolf et al., 2011b).

In the present study, we test the hypothesis that the rs1344706 risk variant on the *ZNF804A* gene will modulate brain activation during face WM in healthy controls. We use the same WM task using faces (previously described (Jackson et al., 2008; Jackson & Raymond, 2008; Wolf et al., 2011b), to probe for the neural effects of rs1344706 on WM for emotional faces in healthy individuals. We suggest that the specific cortical architecture involved in face WM (Jackson et al., 2008; Linden, 2007) may provide increased sensitivity and specificity. More specifically, we predict that the rs1344706 variant will modulate WM processing for faces in a manner that reflects the alterations first observed in schizophrenic patients (Walton et al., 2012; Wolf et al., 2011b).

17.3. Methods And Materials

Materials and methods

Participants

Forty-three healthy participants of European Caucasian descent with no family history of neurological or psychiatric illness where recruited for the study. Participants provided written consent prior to the study, which was approved by the School's ethics committee. Participants from each rs1344706 genotype group did not differ in education, age, sex and handedness or WM capacity (Table 8) who had normal or corrected vision. Data was from a subsample of participants from a larger genetic imaging study (Wolf et al., 2011a), for which *ZNF804A* rs1344706 genotype data was available.

	rs1344706 genotype			
	GG	GT	TT	*p*
gender (male/female)	6/5	9/12	9/2	.12[a]
handedness (right/left)	9/2	18/3	10/1	.39[a]
age (years)	29.5±10.3	34.2±8.8	31.45±10.1	.82[b]
education (years)	14.8±1.2	14.5±3	14.4±2.2	.47[b]
working memory (Cowan's k)	1.58±.1	1.54±.07	1.42±.1	.49[c]

Table 8 | Distribution of demographic characteristics. *ZNF804A* genotype groups described by gender, handedness, age and education. Statistical significance (*p*) given for; chi^2-test [(a)], ANOVA [(b)], and repeated-measures ANOVA [(c)].

ZNF804A genotyping

Subjects were genotyped for the *ZNF804A* rs1344706 G/T SNP. Genomic DNA was extracted from venous EDTA samples (Invisorb® Blood Giga (Invitek GmbH, Germany)). Amplification of the target sequence on the

17.3. Methods And Materials

ZNF804A gene was carried out using PCR (*ZNF804A* CCACTAGCAACAACTCCCTCA -3', *ZNF804A* reverse: 5'-TCTAGAGTCATGCAGGCACA -3'). The following PCR protocol was used: 10 minutes at 95°C, followed by 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 30 s, followed by 72°C for 2 min. The amplicon was visualized on a 2% agarose gel stained with SYBRsafe (Invitrogen, UK) under UV light, following separation at 100V in tris- borate electrophoresis buffer. The PCR product was digested with the BfuCI restriction endonuclease (New England Biolabs, England, UK) and reaction buffers at 37°C for 16 hours. The resulting digested samples (TT genotype = 216 and 186 bp fragments, GG genotype = 186, 154 and 62 bp fragments) were separated on a 2% agarose gel as previously described and scored for genotypes (GG=11,GT=21,TT=11). Hardy-Weinberg-Equilibrium was checked with χ^2 =2.63, p>.1.

Stimuli

Six adult, male greyscale Ekman face images each displaying happy, neutral or angry expressions were used. Each image covered approximately 1.43°× 1.36°.Scrambled greyscale face images selected at random were displayed to cover the face locations when participants encoded less than four faces. All stimuli used were evaluated for appropriate emotional valence/expression (Jackson et al., 2008).

WM for Emotional Faces Paradigm

In an event related design, we investigated visual WM for emotional faces and task-related brain activity through manipulation of facial expression (happy,

neutral and angry) and number of faces to be remembered (load 1,2,3,4). Faces were presented at randomly alternating locations in a 2 × 2 array in the center of the screen, and the center of each image within the matrix was positioned at a visual angle of approximately 1.271^{o} from fixation to ensure that the face display was in direct line of sight (Figure 8). Each of the twelve conditions consisted of sixteen trials divided into eight match and eight non-match trials. Participants indicated whether the single probe face presented after the array was ‘absent’ or ‘present’. Facial expression and number of faces varied randomly between trials and face expression was kept constant for each individual trial. All trials started with a fixation (2000ms) towards a central cross that served as a baseline predictor. This was followed by a two-second presentation of the face array, a delay of one-second and the probe face, where participants had to indicate either a match or non-match response. There were 192 trials distributed over 4 runs of 48 trials to minimize fatigue effects. In each trial, 343 volume images were taken, resulting in WM sessions lasting 686 seconds, with trials lasting less than 14 seconds. The task was generated and responses were recorded using E-Prime software (Version 1.1; Psychology Software Tools, Inc). WM capacity for emotional faces was measured by individual Cowan’s K values for each emotion and load condition (Cowan’s K values = array size * (Hits – False Alarms) (Cowan et al., 2005)).

17.3. Methods And Materials

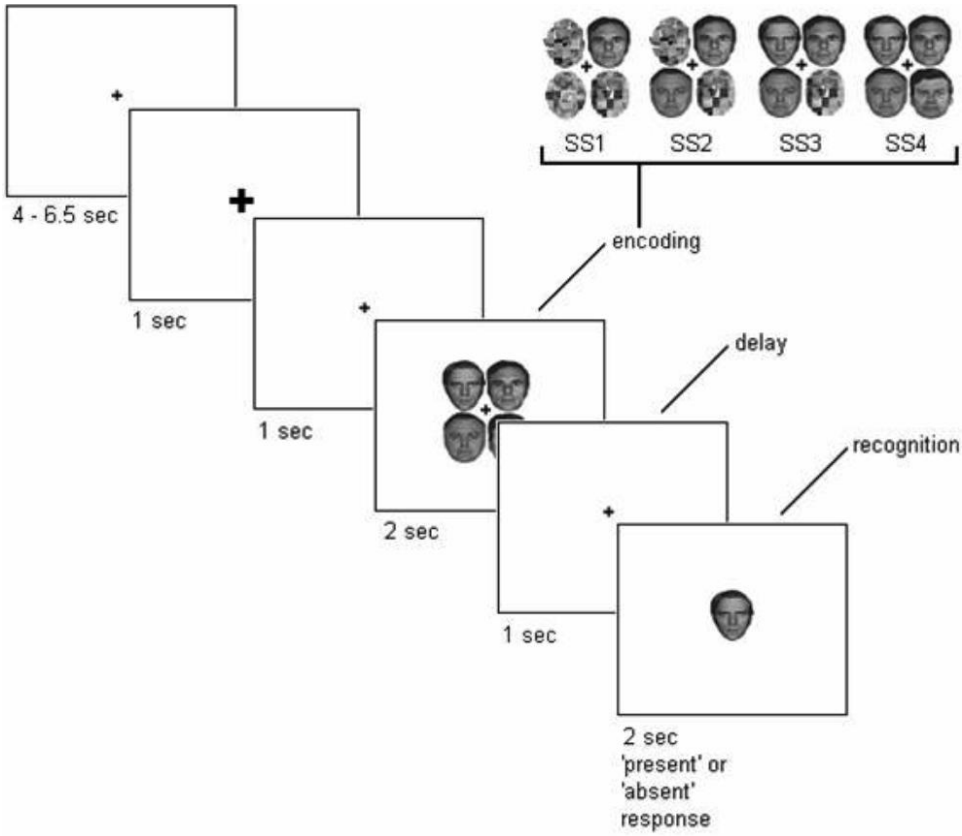

Figure 8 | The emotional faces WM paradigm. Dynamic of the trial and session structure. After a jittered fixation interval, participants were given 2s to encoding emotional faces (between 1-4 faces, empty array components were replaced with scrambled faces). Participants then experienced a 1s delay followed by a 2s interval in which to respond.

Imaging Procedure

We acquired fMRI data (T2* weighted echo planar imaging sequence; TR = 2000_{ms}; TE = 40_{ms}; matrix size = 96 × 96; FOV =256 × 256 mm^2; voxel size = 3 × 3 × 3 mm^3; 90° flip angle; 20 axial slices; 5 mm slice thickness) on a 1.5 Tesla Philips whole-body MR scanner. Imaging data analysis was performed using the BrainVoyager 1.9.10 software (Braininnovation, Maastricht, The Netherlands). Functional images were co-registered with the structural 3D image, spatially normalized to the Talairach system (Lancaster et al., 2000) and resampled at a voxel size of 1 × 1 × 1 mm^3. Functional

images were scan-time corrected using sinc interpolation, 3D motion corrected using trilinear interpolation, spatially smoothed (8 mm Gaussian kernel), and filtered into the time domain using high pass filter (3 cycles per time course; 0.006_{Hz}). From each WM session, the first two volumes from each session were discarded to reduce potential T1 saturation effects. The 43 participants each completed 4 WM sessions. The resulting 172 single subject design matrix files were incorporated into a general linear model (GLM) analysis with 20 predictors including; fixation (1), conditions for all correct trials (12), all error trials (1) and predictors derived from the head motion correction for each subject (6). All but the motion predictors were convolved with a two-gamma haemodynamic reference function. The predictors from all 4 sessions were concatenated into a single predictor per subject. At the first level, we estimated beta values for the remaining 14 predictors (12 conditions: 3 emotions (happy, neutral & angry) x 4 WM loads, and separate predictors for modeling baseline activity (1) and all error trials (1) for each participant with the least squares estimate of the GLM. The estimated beta values were entered into a random effects GLM to test for potential effects of rs1344706 genotype.

Analysis of Neuroimaging Main Effects (Emotion, Load and rs1344706)

ZNF804A rs1344706 effects were tested with a 3x4x3 random-effects ANCOVA with the factors emotion (happy, neutral, angry) and load (1,2,3,4) as within subject factors and rs1344706 (GG, GT, TT) as between subject factor. Main effects and interactions were computed separately for each factor. Cluster thresholds for all analysis (emotion valence, WM load and

rs1344706 genotype) were calculated with BrainVoyager QX Cluster-level Statistical Threshold estimated based on a Monte Carlo simulation with 1000 iterations, whole brain corrected $p<.05$ ($p<.0001$, 4 voxels). This threshold technique utilized a level of stringency similar to family wise error (FWE) that is needed to control for false-positives in imaging genetics (Meyer-Lindenberg et al., 2008). In a whole-brain analysis, beta values were extracted within clusters that showed significant main effects of emotional faces, WM load, rs1344706 genotype and potential interactions. Individual beta values were extracted as averages for each of the 12 task conditions for all voxels significant voxels.

17.4. Results

Main effects of emotion, load and rs134476 genotype (behaviour)

A repeated measures ANOVA showed that main effect emotional face valence on WM capacity $F_{(2,84)}$ =5.187, *p*=.008 where capacity for emotional faces has higher than neutral faces $t_{(42)}$ =4.527, *p*<.001. There was also a significant main effect of load on WM capacity $F_{(3,120)}$ =40.38, *p*<.001. There were no main effect of rs1344706 genotype on WM capacity for emotional faces (Table 8) and no significant interactions (genotype × emotion and genotype × load; *p*>.5 in both cases).

Main effects of emotion, load and rs134476 genotype (neuroimaging)

Main effects of emotion are documented (Table 9). Post-hoc tests show these regions are driven by increased activity for emotional faces (*p* <.001 in all cases). Main effect of WM load implicates regions where activation is higher for multiple faces compared to singles faces (Table 10). Post-hoc analysis indicated that neural activity in these regions show a linear increase of neural activity corresponding with increase WM load (*p* <.001 in all cases). All regions showing a main effect of load and/or emotion are in line with those previously reported on a subset of the present data (Jackson et al., 2008).

brain region	BA	Voxels	X	Y	Z	$F_{(2,80)}$	*p* <
right inferior frontal gyrus	46	174	47	28	12	14.31	0.00001
left inferior frontal gyrus	47	138	-28	7	-16	13.80	0.00001

Table 9 | Brodmann Area (BA), voxel cluster sizes (mm^3), peak Talairach coordinates for the main effect of emotional face valence.

17.4. Results

brain region	BA	Voxels	X	Y	Z	$F_{(3,120)}$	$p <$
superior temporal gyrus	39	395	53	-57	27	11.49	0.00001
right medial frontal gyrus	8	394	2	37	42	11.34	0.00001
right lingual gyrus	18	147	2	-80	6	10.63	0.00001
right lingual gyrus	18	142	8	-71	-3	9.79	0.00001
right inferior parietal gyrus	40	96	60	-32	33	10.39	0.00001

Table 10 | Brodmann Area (BA), voxel cluster sizes (mm^3), peak Talairach coordinates for the main effect of WM load.

There were no significant interactions between *ZNF804A* genotype and WM load or emotion. However, there was a significant main effect of *ZNF804A* genotype on neural activation in the rostral region of the right inferior frontal gyrus (rDLPFC) (Figure 9a). Post-hoc analysis revealed significant rs1334706 allele differences in right inferior frontal gyrus activation during the WM task for emotional faces (GG vs. TT; (t(3.2), p = .004)) and (GT vs. TT; (t(6.67, p<.001)) but no differences between (GG vs. GT; (t(-1.195), p = .42)) (Figure 9b), suggesting the effects of rs1334706 on WM for faces are recessive (G allele vs. TT) in nature, rather than additive/dominant.

17.4. Results

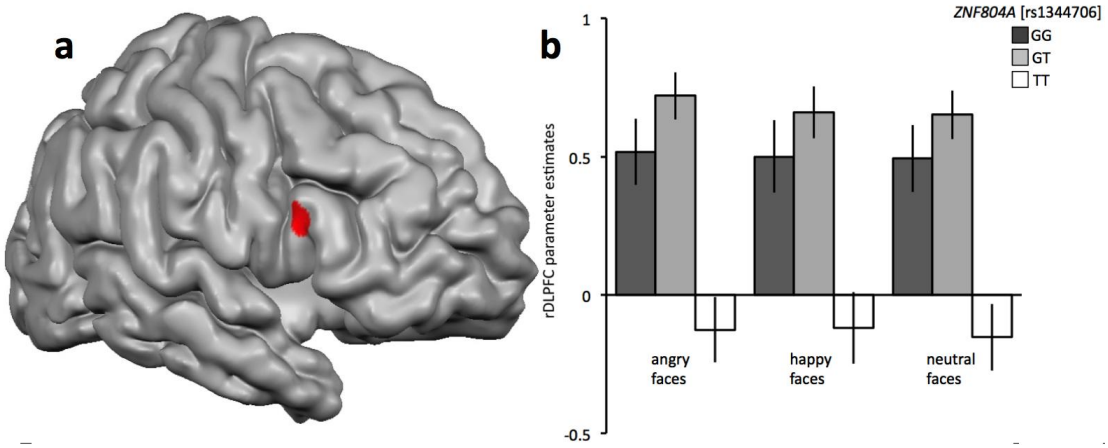

Figure 9 | (a) ZNF804A rs1344706 genotype effects on the rostral portion of right inferior frontal gyrus (rDLPFC) during WM for emotional faces in 43 healthy participants. (b) Parameter estimates for mean neural activity averaged across all 12 conditions in the tasks and separated into rs1344706 genotype groups in 43 healthy controls (TT=risk allele).

brain region	BA	Voxels	X	Y	Z	$F_{(2,40)}$	*p*
right inferior frontal gyrus	44	45	56	7	21	14.4	0.000019

Table 11 | Brodmann Area (BA), voxel cluster sizes (mm^3), peak Talairach coordinates for the main effect of rs1344706 genotype.

A post-hoc analysis discovered that maximum capacity for WM (kmax) (Cowan et al., 2005) significantly correlated with the parameter estimates of the rDLPFC voxel cluster (r=.32, *p*=.037), suggesting the cortical region was recruited in order to deal with task-relevant information (Figure 10).

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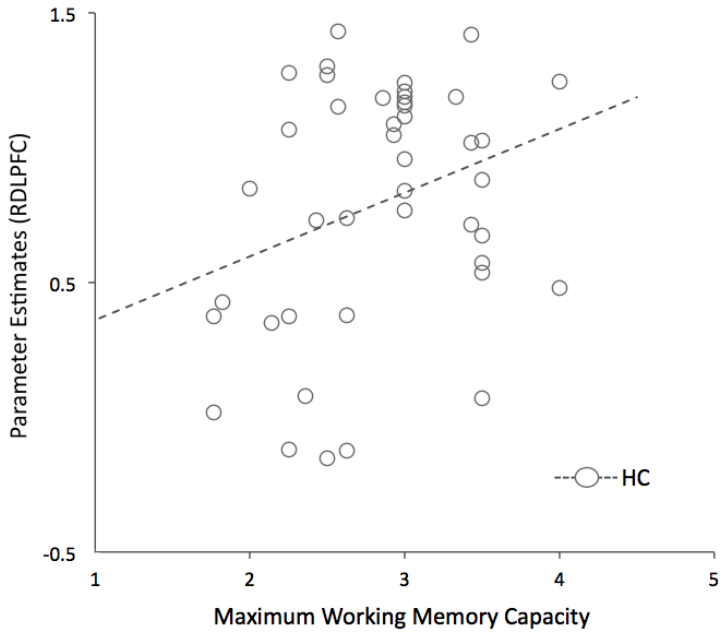

Figure 10 | Relationship between rDLPFC parameter estimates (beta means across whole task) and maximum WM capacity (kmax) for faces for 43 healthy controls (HC).

At this point, it is noteworthy that this region was also significantly under-activated in patients diagnosed with SZ during the same WM task for emotional faces (Wolf et al., 2011b). To help validate alterations in the rDLPFC during WM for emotional faces as a potential intermediate phenotype for SZ, we conducted an exploratory investigation using the rDLPFC cluster (Table 11) that was modulated by rs1344706 (Figure 10) in a ROI analysis. Using the time series from a random effects GLM on 16 individuals; n=8 healthy controls, n=8 cognitively spared patients with schizophrenia; all of whom met inclusion criteria and completed identical methodological protocols (Wolf et al., 2011b). The SZ sample did not significantly differ from the HC sample in; age, ethnicity, handedness, education and face WM performance. We extracted the beta means for all 12 conditions in the rDLPFC ROI and found a significant main effect of SZ diagnosis on activation in the cluster (post-hoc). In this analysis, SZ patients showed a reduced activation

compared to healthy controls $F_{(1,15)}$=18.06, *p*<. 0005. Please note that the ROI time series extracted was from a previous study (Wolf et al., 2011b) and is purely illustrative in this investigation. It serves to demonstrate the potential of altered activation in the rDLPFC as an intermediate phenotype for SZ during WM for emotional faces.

17.5. Discussion

The critical finding of the present study was the main effect of the rs1344706 variant on the ZNF804A gene in the rDLPFC. Neuroimaging methods have identified abnormalities in this cortical region during WM in patients with SZ (Potkin et al., 2009b), high-genetic risk individuals (Brahmbhatt et al., 2006; Choi et al., 2011;) and healthy rs1344706 risk allele carriers (Esslinger et al., 2011; Paulus et al., 2011; Rasetti et al., 2011). These studies have not found an effect of *ZNF804A* genotype on neural activation during WM. However, we suggest that the additional process of emotional faces and/or higher WM loads may reveal significant deficits in WM in SZ patients and healthy carriers of SZ associated loci (Wolf et al., 2011a; Wolf et al., 2011b). This is the first study to identify alterations in neural activity in *ZNF804A* risk allele carriers during WM. This novel discovery may be due to the introduction of emotional face processing during WM and/or additional WM demand. The inclusion of complex stimuli such as emotional faces may recruit a wider and more complex network of neural resources during WM (Becerril & Barch, 2011; Chen et al., 2009; Linden, 2007). Specifically, the rDLPFC has been implicated in regulating/attenuation of emotional responses and a neural basis for modulating emotional experience through interpreting and labelling of emotional face expressions (Hariri, Bookheimer & Mazziotta, 2000). We suggest that the inclusion of the emotional faces in the WM task is responsible for modulating the effects that *ZNF804A* has on this cortical region. This relationship between maximum WM capacity and neural activity in the rDLPFC was significant suggesting that alterations between rs1344706 allele groups may be attributable to the face processing component of the WM task. However, we cannot rule out the

possibility that the addition of social content to WM stimuli or the general observation of faces drove the rs1344706 genotype effects. WM for emotional faces may be a potential neurobiological mechanism through which the risk genotype affects a key cognitive function and ultimately may contribute to psychopathology.

It is a subject of on-going debate what neural processes cause the variability between SZ patients and controls in prefrontal activation during WM (Karlsgodt et al., 2011). It has been suggested that increased activation can represent neural inefficiencies and the compensatory recruitment of extra cortical resources to deal with WM tasks in SZ patients (Potkin et al., 2009b). Patients with SZ may fail to recruit the DLPFC during the WM tasks (Glahn et al., 2005), which may reflect poor integration of neural networks or individual differences in performance and/or motivation (Wolf et al., 2009). Many confounding factors such as medication, disease chronicity/duration (Barch et al., 2001; Glahn et al., 2005; Zanello et al., 2009) may also influence neural alterations in WM processing in SZ patients, therefore it is important to consider that genetic variability in healthy individuals may not always reflect the same pathological process as in clinical cases (Barch et al., 2001). Nevertheless, dysfunction in the DLPFC has remained a constant observation in imaging studies aiming to quantify the neural correlates of reduced WM capacity in SZ patients. The rDLPFC is also a frequently implicated cortical structure in the putative effects of the *ZNF804A* variant in healthy controls (Esslinger et al., 2011; Paulus et al., 2011; Rasetti et al., 2011). The emotional WM paradigm we have previously used reliably recruits the DLPFC as a component of WM related architecture (Jackson et al., 2008; Linden,

2007). It is suggested that DLPFC be implicated in emotional WM by modulating the emotional salience of WM content in order to guide behavioral performance (Becerril & Barch, 2011). The previous patient study showed reduced activation in the rDLPFC as key component of aberrant neural activation in SZ patients (Wolf et al., 2011b). We therefore presented the effects of the *ZNF804A* risk allele in comparison with the patient data in order to demonstrate that, at least for the rDLPFC activation to this paradigm, the effect of SZ risk is uniform in the direction of hypoactivation. It is certainly encouraging that the prefrontal hypoactivation in the rs1344706-associated cluster was also hypoactive for SZ patients. The results may also help to elucidate clinical impairments associated with rDLPFC dysfunction such as negative symptoms (Gonzalez-Ortega et al., 2012) such as social anhedonia (Becerril & Barch, 2011; Germine et al., 2011; Gonzalez-Ortega et al., 2012; Harvey et al., 2009; Tully, Lincoln & Hooker, 2012). Direct comparison with patient data is important in order to determine whether effects observed in individuals at genetic risk for a disorder reflect this risk, or rather the resilience of the unaffected individuals.

Our results conform to neurobiological models of functional abnormalities in SZ patients and high-risk groups, which have widely documented changes in the DLPFC. Our data provides preliminary evidence that the *ZNF804A* risk carriers may fail to maintain a prefrontal network during the WM task in a similar manner to SZ patients. It could be argued that this novel finding was due to the encoding, maintenance and/or retrieval of emotional faces, which will have to be unravelled further in future studies.

17.5. Discussion

Although the mechanisms that mediate rs1344706 effects on WM networks are unknown, sensitive techniques such as functional imaging can thus allow us to trace subclinical effects potentially mediated by GWAS-discovered variants. The effects of genetic variation are more readily observed/more proximal in neuroimaging phenotypes compared to behaviour (Linden & Thome, 2011; Linden, 2012). Although the sample size of the present study is within an estimated range needed to observe genetic effects on memory (Rasch, Papassotiropoulos & de Quervain, 2010), a larger sample may have made the approach more sensitive to additional measures such as *ZNF804A* genotype x load or emotion interactions. However, it is of importance to consider that stringent multiple comparison correction measures were used, suggesting robust findings for the identified region.

Our study adds to the increasing body of evidence for altered rDLPFC function in carriers of the *ZNF804A* psychosis risk variant. Linking altered brain activation with behavioural and ultimately clinical measures is still a challenge, but will be an important enterprise in order to identify the mechanisms that lead from the gene to the disease and fulfil the main hope of psychiatric genetics, that it will elucidate new target pathways for clinical interventions.

18. Experimental Chapter 3: Preface

Unlike most neuropsychiatric disorders, Alzheimer's disease (AD) is a well-established clinicopathogenic entity and may be delineated with high specificity (~80%-95%) from other forms of dementia such as fronto-lobar degenerations. Although evidence suggests that AD is a relatively heritable disorder (Gatz et al., 2006), the parameters by which genetic susceptibility modulates risk are not fully understood. It appears that familial cases of early-onset AD (FAD) may be explained by rare penetrant variants on genes implicated in AD pathophysiology (such as PS1/2 & βAPP mutations, although these rare variants only contribute to ~.5% of all AD cases (Goate & Hardy, 2012)). There is also considerable evidence implicating two SNPs in exon four of the *APOE* gene which together contribute to the production of predominant genotype-dependent isoforms (ε2, ε3, ε4). The *APOE* ε4 isoform is to date the single largest risk factor in AD genetic susceptibility (Corder et al., 1993; Roses, 1994), and explains ~20-50% of the genetic basis for AD (Corder et al., 1993; Corder et al., 1994; Raber, Huang & Ashford, 2004). GWAS have discovered and replicated association between AD and several novel variants that could also potentially contribute to the pathogenesis of AD (Carrasquillo et al., 2010; Corneveaux et al., 2010; Harold et al., 2009; Kamboh et al., 2010; Lambert et al., 2009; Seshadri et al., 2010). Interestingly, the variants identified are also situated on genes that modulate neurobiological networks previously implicated in AD pathophysiology (Jones, Harold & Williams, 2010; Sleegers et al., 2010; Wollmer, 2010) . Although the effect sizes of the susceptibility loci are modest, they may also help to identify novel neurobiological processes underlying AD risk. The focus of this experimental chapter is to investigate the potential pathophysiological

mechanisms of the newly identified risk variant (rs11136000) on the *CLU* gene (Harold et al., 2009; Lambert et al., 2009). There is emerging molecular evidence suggesting *CLU* and *APOE* have similar mechanistic roles in the brain (Bertram & Tanzi, 2010; Jones, Harold & Williams, 2010; van Es & van den Berg, 2009; Wollmer, 2010) . The GWAS implicating *CLU* contributes to an existing body of evidence suggesting a role of protein *CLU* encodes (Clusterin) in AD pathophysiology (Bertram & Tanzi, 2010). Genetic imaging has been used as a tool to explore how the genetic susceptibility conferred by APOE may manifest. A body of evidence now suggests that the neurobiological effects of *APOE* and familial Alzheimer's disease gene mutations may be quantified using functional magnetic resonance imaging (fMRI) (Bondi et al., 2005; Bookheimer et al., 2000; Braskie et al., 2012b; Ercoli et al., 2006; Small et al., 2000; Ringman et al., 2011; Wierenga et al., 2010). The *APOE* ε4 appears to be associated increased BOLD activation during cognitive tasks (such as episodic, semantic and working memory), processes that may adopt additional compensatory neural recruitment as a result of preclinical/presymptomatic AD pathophysiology (Bookheimer et al., 2000; Bookheimer & Burggren, 2009; Filippini et al., 2009; Filippini et al., 2011; Trachtenberg, Filippini & Mackay, 2012;Trachtenberg et al., 2012b). These findings show that genetic susceptibility to AD may manifest many years preceding the first signs of cognitive disruption. However, it is not known how the *CLU* variant may increase genetic risk. To address this question, we created similar parameters to the *APOE* /fMRI studies (Bondi et al., 2005; Bookheimer & Burggren, 2009; Filippini et al., 2009;) to explore the potential effects *CLU* has on neural correlates of cognition during WM which I

previously outline as a suitable measure of quantifying AD susceptibility (Chapter 5.1-5.3.). We suggest that any pathophysiological mechanisms observed implicating the *CLU* genotype (using task-related BOLD) will be similar to those identified when exploring the effects of *APOE* on task-related BOLD. The studies suggesting the *APOE* genotype modulates BOLD during tasks across a range of memory tasks. The most consistent findings support the hypothesis that individuals with increased genetic risk to AD show pronounced BOLD activation in response to increasing task demand. We aim to test this hypothesis in our study by manipulating WM load. It is suggested that the increase in BOLD reflects compensatory recruitment and/or additional neural resources in response to task demand, so we suggest the most pronounced deficits would be observed at high WM load. This compensatory activation may reflect metabolic inefficiency, inefficiency of neural sub-populations or deficits in network connectivity (Brown et al., 2011; Machulda et al., 2011; Small et al., 2000; Trachtenberg, Filippini & Mackay, 2012; Trachtenberg et al., 2012b). The mechanistic effects of *APOE* and *CLU* risk genotypes are relatively unknown, therefore, genetic imaging is an attractive technique that may offer novel insights into AD pathophysiology, improve improved risk prediction and lead to the development of novel treatment strategies.

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Neural hyperactivation in carriers of the Alzheimer's risk variant on the clusterin gene

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Keywords: dementia; genetic imaging; working memory; clusterin; hippocampus; prefrontal cortex

Candidate Contributions: T.M.L performed data analysis and interpretation and wrote manuscript. C.W and M.C.J collected the data. S.J.J assisted with the analysis. A.B, R.D and J.T provided comments on the manuscript and performed genotyping. D.E.L collected data, provided comments on manuscript, assistance on analysis and interpretation of the data.

19.1. Abstract

Recent GWAS identified a risk variant for Alzheimer's disease (AD) at a locus (rs11136000) of the clusterin gene (*CLU*). Here we use functional magnetic resonance imaging (fMRI) during working memory to probe the effect of the risk variant on brain activation in healthy individuals. Participants with the *CLU* risk genotype had higher activity than participants with the protective allele in frontal and posterior cingulate cortex and the hippocampus, particularly during high memory demand. These results inform pathophysiological models of the preclinical progression of AD.

19.2. Introduction

Functional imaging studies have suggested that carriers of the apolipoprotein E (*APOE*) ε4 risk allele for Alzheimer's disease (AD) present with higher levels of neural activity during cognitive tasks (Bookheimer & Burggren, 2009). The association of higher activity for *APOE* ε4 in task dependent areas has been independently replicated in older samples (Bondi et al., 2005; Seidenberg et al., 2009; Smith et al., 2011; Wierenga et al., 2010). It is widely regarded that the higher activation reflects recruitment of more neuronal resources in risk allele carriers to engage with the task (Bondi et al., 2005) possibly to compensate for early preclinical changes in the neurobiology of memory-related areas (Prvulovic et al., 2005).

However, *APOE* is not the only apolipoprotein gene implicated in AD. Recent GWAS (Genome Wide Association Studies) have identified and replicated a risk locus (rs11136000) on the *CLU* (*APOJ)* gene (Bertram & Tanzi, 2009; Carrasquillo et al., 2010; Corneveaux et al., 2010; Harold et al., 2009; Lambert et al., 2009). Although clusterin has been implicated in the pathophysiology of AD (Bertram & Tanzi, 2009) little is known about how the gene and its protein product contribute to the manifestation of the disease. *CLU* levels have previously been correlated with symptom severity, entorhinal/hippocampal cortex atrophy and amyloid-beta (Aβ) burden (Thambisetty et al., 2010). Imaging studies have also demonstrated that the risk locus is associated with variations in cortical morphology (Biffi et al., 2010). However, the functional differences between individuals with risk and protective genotypes have not yet been studied in pre-clinical cases.

In the present study we trace the effects of the risk variant on brain activation in a young healthy population using a visual working memory task

with functional neuroimaging previously described (Jackson et al., 2008). We used an 'emotional faces' WM task as testing memory for faces has been shown to provide highly sensitive indices of memory performance and usefully contribute to early detection of memory deficits in prodromal stages of AD (Werheid & Clare, 2007). Based upon the functional imaging studies of the *APOE* ε4 variant (Bookheimer & Burggren, 2009; Seidenberg et al., 2009) we hypothesized that individuals expressing the genotype associated with higher risk (homozygous, CC) (Harold et al., 2009) would have higher neural activation in a task related network. An alternative formulation of the hypothesis would be that the carriers of the protective allele (CT/TT) would achieve the same level of task performance with less brain activation and thus, more efficiently.

19.3. Methods And Materials

We studied 43 healthy subjects (age range 18-51, median age 29.1, 22 males, 21 females, 3 left handed, 40 right handed). All subjects were of Caucasian ethnicity as ethnic matching is critical in genetic imaging and association studies (Hariri & Weinberger, 2003). Participants and relatives had no history of neuropsychiatric, neurological or neurodegenerative disease. Participants also had no chronic somatic illness or history of substance abuse. Subjects were tested using a robust face WM paradigm for functional magnetic resonance imaging (fMRI) as previously described (see Chapter 15.3. Methods and Materials). Data were from a subsample of the participants of a larger genetic imaging study (Wolf et al., 2011a) for whom information about the *CLU* SNP data was available. Subjects were genotyped for *CLU* rs11136000 (CC: 13, CT: 24, TT=6) and pooled according to hypothesized risk allele (Risk Carriers: CC, Non- Risk CT/TT (Harold et al., 2009). Hardy-Weinberg-Equilibrium was checked (x^2=.036, *p*=.85) and independent-samples t-test (2-tailed) determined no significant differences in gender (t(1.59), *p*=.212) and age (t(1.12), *p*=.174) between risk and protective groups. We acquired fMRI data (T2* weighted echo planar imaging sequence; TR = 2000 ms; TE = 40 ms; matrix size = 96 × 96; FOV =256 × 256 mm2; voxel size =3 × 3 × 3 mm3; 90° flip angle; 20 axial slices; 5 mm slice thickness) on a 1.5 Tesla Philips whole-body MR scanner.

We estimated activation levels for correct trials of each of the 12 conditions (3 emotions (happy, neutral & angry) x 4 WM loads) using a random effects general linear model (GLM) of the experiment. One separate predictor modeled all error trials, and 6 motion confounds were derived from the head

motion correction for each subject. All but the motion predictors were convolved with a two-gamma haemodynamic reference function. Genotype (risk/non risk) was used as a between subjects factor.

Here we focus on the genotype effects and genotype x load interactions. Effects were thresholded at an initial voxel-level threshold of $p < 0.05$, which was then corrected at the cluster-corrected false-positive level of $p = 0.05$ (threshold of 1000 voxels). For clusters with significant main or interaction effects, we extracted the individual peak beta values for post-hoc comparisons (ANOVA) for parametric effects of genotype and memory load. These beta values were subjected to a repeated measures 3-way ANOVA with the within subject factors of emotion (3 levels) and load (4 levels) and the between subject factor of genotype (2 levels: CC carriers vs. CT/TT carriers). We also performed pair-wise comparisons (independent-sample t tests) between the CC, CT and TT group to test for dose effects of the risk allele.

19.4. Results

A main effect of genotype, reflecting higher activation for the risk group, was observed in the right dorsolateral prefrontal cortex (rDLPFC) (Figure 11a), the right hippocampus/entorhinal cortex (hippocampal formation, rHF) (Figure 11b) and the dorsal posterior cingulate (dPC) (Figure 11c) (cluster threshold of 1000 voxels). All three clusters also survived a threshold $p < .01$ (cluster threshold of 100 voxels), but not a more conservative threshold of $p < .001$.

The rDLPFC (Figure 11a) and dPC (Figure 11c) showed an interaction between genotype and load in which increased brain activity in the risk group was particularly marked under high memory load (loads 3 and 4). We therefore also performed t-tests for whole brain group differences at just the higher loads (WM loads 3 & 4). For areas demonstrating a significant genotype x load interaction at higher loads (rDLPFC & dPC) clusters demonstrated a more pronounced effect with higher significance (Table 12a & 12c). There were no differences in the magnitude of genotype main effect between all four WM loads and High WM loads in the rHF, supported by the absence of a genotype × load interaction (Table 12b).

These effects were further corroborated by a dose dependent rs11136000 genotype effect, which was documented in the rDLPFC & rHF (Figure 13a & 13b). In these regions, there was additive up-regulation of brain activation associated with the C allele, where homozygous expression of the C allele was associated with highest mean beta values (CC>CT>TT) as reflected in pairwise comparisons (Table 13).

19.4. Results

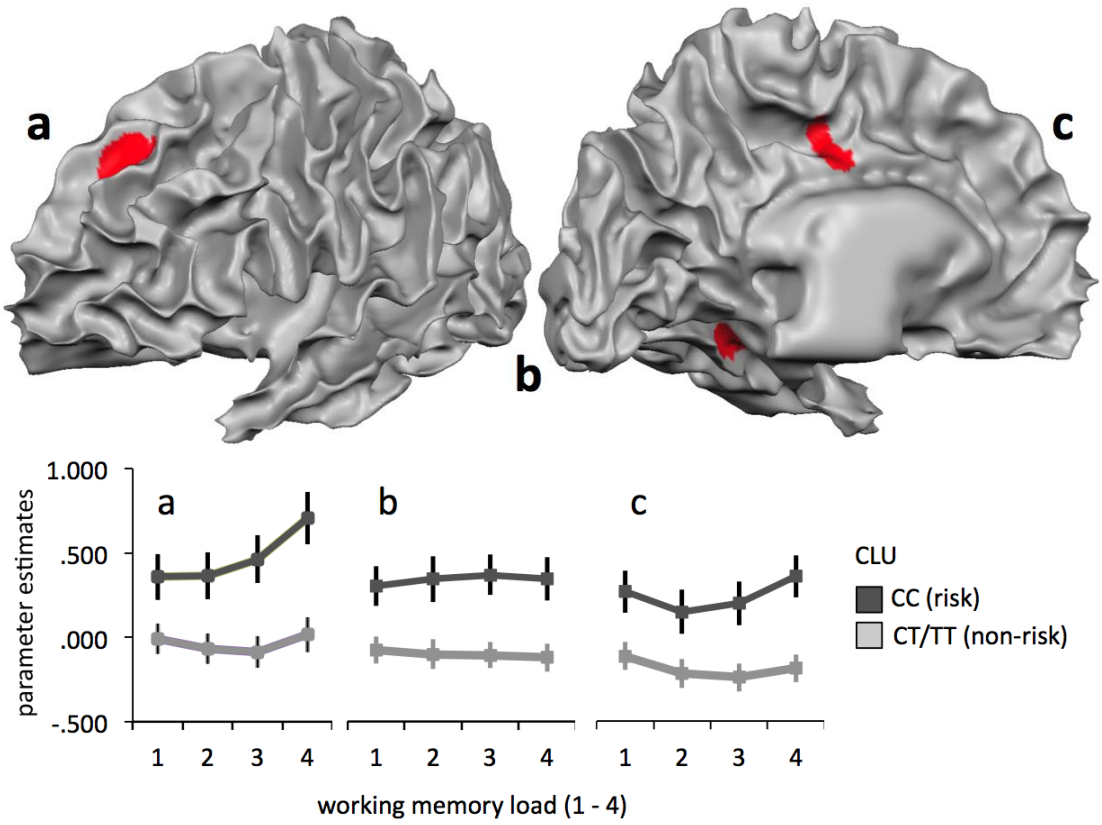

Figure 11 | Impact of *CLU* (rs11136000) genotype on neural activity during emotional working memory paradigm $p_{corrected}$ <.05. Post-hoc analysis below parametric maps (a, b & c) demonstrate parameter estimates across WM loads (1- 4). Risk genotypes represent the 'CC' genotype (n=13), the 'Non-Risk' genotype represents the CT & TT genotypes pooled together (n=30).

ROI	peak voxel	*CLU*		*CLU* × load		*CLU* (load 3-4)	
		$F_{(1,41)}$	*p*	$F_{(2,123)}$	*p*	$t_{(84)}$	*p*
a.	X (40) Y (15) Z (35)	9.84	0.003	4.96	0.003	12.99	0.001
b.	X (-30) Y (-29) Z (-7)	9.47	0.004	-	ns.	8.85	0.01
c.	X (3) Y (-26) Z (40)	9.22	0.004	3.24	0.05	10.36	0.001

Table 12 | Talairach coordinates for peak voxel in clusters from Figure 11 as determined by Talairach Daemon (475). F and *p* Values (cluster mean) for main effects of genotype, load X genotype interactions and high load main effects (loads 3 & 4).

19.4. Results

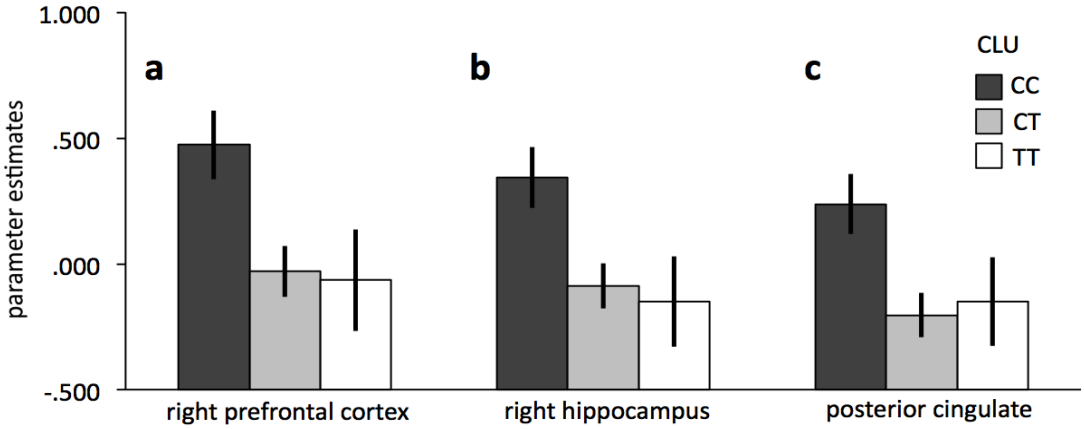

Figure 12 | Mean neural activity during the whole task. Significant clusters and their respective cortical areas separated according to genotype (rs11136000: CC (n=13), CT(n=24), TT(n=6)).

ROI	peak voxel	*CLU* $F_{(2,40)}$	*p*	*CLU* × load $F_{(3,123)}$	*p*	pairwise comparisons	*p*
a.	X (40) Y (15) Z (35)	4.81	0.013	3.01	0.009	CC > CT CC > TT	0.005 0.03
b.	X (-30) Y (-29) Z (-7)	4.68	0.015	-	ns.	CC > CT CC > TT	0.007 0.03
c.	X (3) Y (-26) Z (40)	4.54	0.017	-	ns.	CC > CT CC > TT	0.005 0.05

Table 13 | Significant main effects of genotype in all 3 regions with addictive, dose-dependent effects of genotype in rDLPFC and rHF. Pair-wise comparisons suggest significant difference in neural activity increases in a dose-dependent manner.

19.5. Discussion

Healthy individuals with the AD risk genotype on the *CLU* gene activated several brain areas (DLPFC, hippocampus, cingulate) that were not active in the controls. Their performance on the WM task equaled that non-risk carriers, and one interpretation is thus that the carriers of the protective allele performed the task with more efficient use of neural resources. Correlations between AD risk (*APOE* isoform status) and neural hyperactivation have previously been reported in the right dorsolateral prefrontal cortex (Wishart et al., 2006) and hippocampus (Bookheimer et al., 2000).

This finding of functional changes in young healthy individuals who may have a slightly increased risk of developing AD would conform to neuropathological models where cellular changes of AD can precede the clinical phenotype by several decades (Donev et al., 2009). It is of note that the hyperactive areas included some of those implicated relatively early in the cascade of AD pathology such as HF and PC (Braak & Braak, 1998) . This hyperactivation conforms to pathophysiological models of AD vulnerability which posit an initial left-shift of brain activation in response to cognitive demand, resulting in higher activation during early stages of AD pathology and for difficult tasks, followed by hypoactivation once compensation mechanisms have collapsed and the disease manifests itself clinically (Prvulovic et al., 2005).

In keeping with this model, the hyperactivation of risk carriers in DLPFC and cingulate was more marked at memory loads 3 and 4 than 1 and 2. These loads were supra-capacity because the limit for face WM is commonly thought to be at two faces (Jackson et al., 2009).

19.5. Discussion

What then are the mechanisms through which the risk genotype may lead to compensatory hyper-activation? It could be argued that as *CLU* belongs to the same protein family as *APOE* that it may have similar pathophysiological effects, which may explain the similar presentation of compensatory neuronal resources. *CLU* encodes an extracellular multifunctional glycoprotein that may interact with itself, amyloid proteins and lipids, as well as assisting in synapse turnover (Bertram & Tanzi, 2009) in a similar manner to *APOE*. It has a potential role in the pathogenesis of AD including the hallmark features of Aβ deposition, aggregation and fibrillogenesis (Bertram & Tanzi, 2009). The cellular mechanisms of neural hyperactivation in carriers of AD risk genes are unknown. The exaggerated calcium signalling observed in association with several AD risk genes and implicated in AD neuropathology (Cheung et al., 2008; Cowburn et al., 2007; Small et al., 2000) may be a factor, but further work on the cellular biology of the *CLU* risk variant is needed to pursue such a hypothesis. Another possibility is that AD risk is associated with dysregulation of neurovascular coupling, as has been suggested for clinical AD (Girouard & Iadecola, 2006).

The genetic mechanism underlying the association between the specific variant (rs11136000) and AD also remains unknown. It is possible that rs11136000 directly influences gene expression or splicing, that it is in linkage disequilibrium (LD) with another variant that does, or that risk is conferred by some other mechanism. However it seems clear from our data that whatever mechanism is involved, impacts on brain function occur many years before the onset of dementia and can be detected by subtle effects on activation in fMRI experiments.

19.5. Discussion

A limitation of the present study was the sample size, although it was within the standard range for current genetic imaging studies (Rasch, Papassotiropoulos & de Quervain, 2010). Furthermore, although effects were significant at a cluster-level thresholded level of p<. 05, they did not withstand more rigorous corrections for multiple comparisons, which calls for replication in larger samples.

The current genetic imaging approach can guide further invasive work into the specific pathological mechanisms underlying the effects of risk alleles and serve as additional vulnerability marker. The development of such vulnerability markers of AD-related pathology is important for the early intervention and prevention of dementia.

20. General Discussion

It is becoming increasingly apparent that genetic variance is associated with parameters of neurocognition, including cognitive, neurophysiological and neuroimaging measures. Recent studies have replicated the associations between novel risk variants and several phenotype dimensions. These variants transcend associations beyond clinical traits and extend to complex behavioral and neuroimaging phenotypes. This suggests that components of heritability found in the human genome may have a dramatic impact on an individual's neurocognition. However, indexing the specific parameters of genetic variance is a demanding challenge. It remains uncertain how these risk variants confer risk at a neurobiological level. Functional genomics is beginning to determine how risk variants may alter the transcription, expression and functionality of important regulatory components in the brain. Imaging/behavior genetics is an exciting and informative method by which we can begin to understand how genetic variants modulate components/networks that govern neural activity and behavior. These neurocognitive components/networks are often used to index pathogenic process and/or response to treatment (biomarkers). They may also occupy the topography between disease symptom and heritable risk (endophenotypes). Lastly, both novel behavioral and imaging methods may characterize domains of neurocognition that index genetic contributions to psychiatric disorders (intermediate phenotypes). These methods may index various neurobiological deficits each of which reflects a component of neuropsychiatric pathophysiology. Biomarkers usually identify disease with high levels of specificity but reflect disease state (disease outcomes) rather than trait (components of predisposition) markers. Endophenotypes reliably index

heritable components of neurocognition that are significantly implicated in psychiatric disorders, however, many of which recruit complex neural networks, many of which are as complex as disease/symptom phenotypes (Insel & Cuthbert, 2009). This means that the effects of single variants are small and can only be captured in larger samples (Flint & Munafo, 2007). Intermediate phenotypes are extremely sensitive to covert changes/deficits in neurobiology and may be suitable to detect common and subtle variations in the genome. However, at present, the genetic factors that influence neuroimaging intermediate phenotypes remain largely unknown. Furthermore, it is unclear whether these measures are robust in larger samples. For example, in SZ, BOLD activation during WM seems to be affected by several confounding factors that may influence the nature of the pathophysiological deficit (Cannon et al., 2005; Glahn et al., 2005; Karlsgodt et al., 2009; Kim et al., 2010). Nevertheless, these methods are essential in quantifying the neurobiological mechanisms that are disrupted as a result of genetic susceptibility. Neurocognitive endophenotypes and/or intermediate phenotypes aim to probe selective components of neurocognition to delineate/dissociate the effects of genes and neurobiological pathways. However, many endophenotype/intermediate phenotype strategies index parameters that are governed by complex neural networks (Rose & Donohoe, 2012). A plethora of genes and loci herein may govern these neural networks. The multifaceted neurobiological pathways that support WM performance (for example; Table 1) or genetic components that support cortical morphology (for example; Table 4/5) provide examples that neurocognitive parameters are characterized by genomic complexity. In order to make more accurate

estimations about effect sizes, proportion of estimated variance and contribution to neuropsychiatric risk, we must first aim to develop measures that quantify domain specific components of neurocognition. This investigation uses novel behavior/imaging measures (NCE/NCIPs) that aim to increase the proximity between genetic susceptibility and domain specific neural networks. The measures probe neural pathways, which have been mapped and validated using combinations of molecular/behavior/imaging methods. The assays aim to recruit key/specific components of neurobiology that are disrupted in neuropsychiatric illness and probe for effects of predicted genetic variance based on the previous understanding of the genes neurobiological effects (*a priori*). The success and limitations of this approach will now be discussed with relevance to the three experimental projects. The extent to which genetic factors that affect these pathways are not yet quantified (like conventional NCEs) so potentially may be more appropriately defined as neurocognitive intermediate phenotypes (NCIPs).

20.1. Psychiatric Genetics And Neuroeconomics

Mechanisms of attention, memory and other 'high order' cognitive processes are implicated as key biomarkers/endophenotypes/intermediate phenotypes (Ivleva et al., 2012). In recent years, neuroeconomics has become of increasing relevance to neuropsychiatry, with findings suggesting that disturbances in the brains global valuation system may be a key mediator of neuropsychiatric vulnerability (Hasler, 2012). Sharp (Sharp, Monterosso & Montague, 2012) argues that reward processing is a fundamental facilitator of learning and motivation and is disrupted in a broad spectrum of psychiatric disorders. Reward processing and decision-making paradigms investigate the formation of preference, mechanisms underlying action selection/execution and the evaluation of outcomes (Ernst & Paulus, 2005). Neuropsychiatric populations find it difficult to respond to rewards in a dynamic and context-appropriate manner (Sharp, Monterosso & Montague, 2012). In recent years, we have witnessed the sub classification of reward-processing components via behavioral and imaging parameters (See Table 2) suggesting specific domains in which reward processing may be disrupted. This thesis uses reward-processing sub-components to clarify the basis by which genetic variance may increase psychiatric susceptibility (Lancaster, Linden & Heerey, 2012). Single-cell, pharmacological and genetic studies suggest that manipulation of DA may lead to specific disruptions of reward processing and decision-making (Aarts, van Holstein & Cools, 2011; Frank et al., 2007; Guitart-Masip et al., 2012; Kurniawan, Guitart-Masip & Dolan, 2011; Kayser et al., 2012; Schultz, 2012; Treadway et al., 2012). Considering this evidence, recent studies are beginning to investigate whether reward processing is

affected by functional polymorphism that alters DA availability between humans.

Our investigation studied the putative effects of the functional polymorphism val158met on the catechol-O-methyltransferase gene (*COMT*). *COMT* was a promising candidate gene for neuropsychiatric illness considering its putative functional *e*ffects (Akil et al., 2003; Bilder et al., 2004; Chen et al., 2004; Meyer-Lindenberg et al., 2005a; Weinshilboum, Otterness & Szumlanski, 1999), however, the variation at this loci does not seem to directly increase neuropsychiatric susceptibility (Allen et al., 2008). However, it appears that *COMT* may modulate domains of psychopathology such as reward-processing components in a manner that may lead to an increase in neuropsychiatric susceptibility. It is also apparent that other dopaminergic gene variations may also modulate selective reward-processing components in a similar manner. We studied how *COMT* val158met affects reward responsiveness/representation whose neural mechanism may be modulated by cortical regions where *COMT* specifically governs DA availability. We suggested that *COMT*, through its modulation of prefrontal DA-ergic activity, would modulate reward-seeking behavior. Based on previous literature (Wichers et al., 2008) we also suggested *COMT* would moderate how reward responsiveness predicted one's propensity to seek reward. We found that *COMT* val158met modulated both reward responsiveness and reward-seeking behavior and predicted the interaction between these two sub-components of reward-guided behaviour. We embed this finding in a body of emerging literature suggesting that *COMT* modulates parameters of reward processing. Similar lines of work suggest that *COMT* val158met modulates

inter-temporal choice selection (Paloyelis et al., 2010; Smith & Boettiger, 2012) and risky-choice making (Amstadter et al., 2012; Farrell et al., 2012; Gianotti et al., 2012). Interestingly, it appears that pharmacological manipulation via *COMT* inhibition (achieved using tolcapone) seems to increase reward efficacy for individuals with the high activity *COMT* (val/val genotype). Conversely Tolcapone action on met/met individuals seem to reduce reward-processing efficacy and reward reactivity, conforming to an 'inverted U' model of dopamine effects on reward-processing/decision making (Farrell et al., 2012). It is suggested that tolcapone may influence reward-processing parameters via modulation cortico-striatal connectivity (Kayser et al., 2012). During the course of this our investigation, the aforementioned results (Chapter 15.4) looking at the effects of *COMT* on the Balloon Analogue Risk Task (BART) have been replicated in a younger population (Amstadter et al., 2012). Furthermore, it also appears that higher levels of striatal DA (putative effects of the $DAT1_{VNTR}$) predict reduced reward-seeking/risky decision making behavior on the BART (Mata et al., 2012). This converging evidence suggesting that dopaminergic genetic contributions may influence risky decision-making adds to a body of findings implicating dopamine as a key mediator of risky decision-making (Schultz, 2012; Simon et al., 2011).

There is also emerging evidence supporting a genetic contribution to reward-responsiveness. Parameters of reward responsiveness (such as hedonic capacity) may be heritable (Bogdan & Pizzagalli, 2009), transcend diagnostic boundaries and play a prominent role in several neuropsychiatric disorders (Diekhof, Falkai & Gruber, 2008; Dowd & Barch, 2012; Pelizza &

Ferrari, 2009). The present investigation employed a parameter of reward processing using a signal detection paradigm to produce asymmetric responses that bias towards frequently reinforced stimulus (Pizzagalli, Jahn & O'Shea, 2005). There are several lines of evidence implicating the dopaminergic system as a key modulator of this specific reward component including pharmacological studies (Pizzagalli et al., 2008; Santesso et al., 2009) and radioligand positron emission tomography (PET) imaging (Vrieze et al., 2011). We demonstrated that the *COMT* val158met variant, (which serves as a proxy for individuals differences in DA between individuals) also modulates reward responsiveness (Figure 5b), suggesting that genetic variance may help to explain individual differences in reward response, representation and hedonic capacity. Although the specific heritability of bias towards rewarded stimulus is unknown, it appears that other genetic variants may also modulate this component of reward processing. It appears that genetic variants that alter neurochemical pathways of the opioid system (*OPRM1*) (Lee et al., 2011), serotonergic system (*5HTTLPR)* (Nikolova, Bogdan & Pizzagalli, 2012) and hypothalamic-pituitary-adrenal axis (HPA) (*MR*) (Bogdan et al., 2010), (*CRHR1)* (Bogdan et al., 2011) may also have an impact of the reward response. Interestingly, the gene variants that modulate serotonergic and HPA-stress pathways seem to have a dramatic impact on the reward response specifically during stressful conditions (Bogdan et al., 2011). This gene × environment interaction suggests that conventional 'risk loci' would be more appropriately conceptualized as 'loci of plasticity', which mediate the impact that environmental stimuli have on phenotypic dimensions such as reward processing (Bogdan, Hyde & Hariri, 2012; Bogdan, Nikolova &

Pizzagalli, 2012). In our study, we show evidence for a gene × environment interaction, where the *COMT* genotype modulates reward seeking behavior, particularly in individuals who display high levels of reward responsiveness (Figure 7). During the course of our experiment (Lancaster, Linden & Heerey, 2012), it has been shown that risky decision-making during the BART does in fact reflect individual differences in reward sensitivity (Cavanagh et al., 2012). We suggest that the *COMT* genotype modulates the machinery by which the interpretation of reward drives an individual's propensity to seek/benefit from rewarding environments. This is supported by previous evidence suggesting that *COMT* moderates the relationship between positive life events and the appraisal of those events (Wichers et al., 2008). It is suggested that *COMT* modulates the 'experience of reward' and explains a large proportion of individual variability. Together these findings suggest that genetic contributions to DA availability (*COMT, DAT1* etc.) may modulate a 'reward valuation system', where reward-worth is analyzed and action/selection is modulated in the context of this computation. This hypothesis is supported by neuroimaging studies demonstrating that *COMT* modulates neural activity during reward anticipation (Dreher et al., 2009; Schmack et al., 2008; Yacubian et al., 2007) and delivery (Camara et al., 2010; Foti & Hajcak, 2012; Marco-Pallares et al., 2009).

Individual differences in the 'valuation system' have considerable implications for the major classes of psychiatric disorders. Anhedonia is a core deficit in disorders such as MDD, SZ, BP, and addiction (Der-Avakian & Markou, 2012). Anhedonia is conventionally defined as the inability to experience pleasure from events that an individual would usually experience

as pleasant. There is evidence suggesting that anhedonia/reward valuation disruptions are mediated by the DA system (Chau, Roth & Green, 2004). Although *COMT* has been associated with several neuropsychiatric disorders, the impact on clinical phenotypes is unclear. An alternative explanation is that *COMT* is associated with phenotypic traits (such as anhedonia), which may explain association in smaller samples/samples where anhedonia is widely expressed. However, the heterogeneity of neuropsychiatric disorders may dilute any associations between a domain specific phenotypes and genotype. As many genes are broadly considered 'loci of plasticity' rather than risk markers, it may be possible that the effects of genes such as *COMT* are more apparent under specific environmental stressors.

Considerations should also address epistatic relationships between genes and modulation of gene networks within the domain of reward processing. Emerging evidence suggests that a host of genes that mediate dopaminergic tone in the brain modulate reward-processing components (See Table 2). The impact of a gene may also only be observed in the presence other genetic markers. Several studies have observed epistatic relationship between gene networks for cognitive parameters such as WM (Buckholtz et al., 2007; Tan et al., 2007b) yet little work has address gene × gene interactions in reward processing (Camara et al., 2010; Yacubian et al., 2007). However, recent studies are being to detail the cumulative effects of dopaminergic genes on reward contingencies. These studies use 'biologically informed multi-locus profiles' (BIMLP) to calculate the collective impact of multiple genetic loci on a neural system. These profiles are designed to capture the impact that various functional variants have on a common neural

system. BIMLPs collectively measure a broader scope of genetic variance in order to capture the impact of a neurochemical system rather than a single variant (Bogdan, Hyde & Hariri, 2012). This method of genetic inference has been successful in predicting substantial variance (~11%) of reward reactivity in striatal pathways (Nikolova et al., 2011). In order to further understand the genetic dopaminergic contributions to reward responsiveness and reward seeking, future studies should employ the BIMLPs method using DA genes to quantify the parameters by which heritable components of dopaminergic neurobiology govern these reward subcomponents. The pharmacological manipulation of DA (via *COMT* inhibition) may also modulate these reward domains as demonstrated under other reward contingencies (Farrell et al., 2012). Lastly, it could be speculated that the *COMT* genotype may also modulate the impact that *COMT* inhibition has on reward responsiveness and reward seeking behavior.

Compared to endophenotype/intermediate phenotypes such as WM and emotion recognition, reward processing is a well-studied component of behavior with multiple lines of converging evidence implicating a series of well defined neuroanatomical and neurochemical pathways. It is becomingly increasingly apparent that deficits in reward processing are evident in the major classes of psychiatric disorders (Gold et al., 2012; Hasler, 2012; Sharp, Monterosso & Montague, 2012; Strauss & Gold, 2012) and quantifying the genetic variance associated with this network may greatly help in the understanding of neuropsychiatric deficits and may assist in the development of treatment.

20.2. Quantifying Psychosis Susceptibility

The expanding genetic architecture of psychosis (loci and genes identified by GWAS) contributes to complex network of gene variants that seem to only confer modest proportions of susceptibility. With the advent of novel genotyping strategies (deep-sequencing, whole exome, CNVs etc.) and with increasingly larger samples sizes, we will soon be given an informative depiction of the heritable psychosis landscape. Although several significant 'hits' in psychosis GWAS have small effect sizes, the novel mechanistic insights these variants can provide should not go overlooked. Many of the GWAS 'hits' were situated on genes for which functionality was not well understood. Nevertheless, significant advances have been made regarding some of the most promising candidate loci. The exploration of the *ZNF804A* locus (rs1344706; or markers in LD) shows promise as a marker of neuroplasticity in several functional aspects of neurobiology. The molecular effects of the *ZNF804A* risk loci on brain structure remain uncertain. Early studies suggest that the locus may modulate regions of grey and white matter (Lencz et al., 2010; Voineskos et al., 2011b; Wei et al., 2012), however, converging evidence from large studies have failed to demonstrate association between *ZNF804A* and macroscopic structure (Cousijn et al., 2012; Sprooten et al., 2012). These findings support the hypothesis that the heritability of brain structure is not weighted by variance in psychosis susceptibility genes (Owens et al., 2012). It could also be suggested that the sample sizes were too small (even though they are large by conventional imaging genetic protocol) to detect the moderate effects of the variant. However, one could also argue that using the global measure of brain structure may not be an accurate representation for *ZNF804A* mediated

susceptibility. The functional parameters of *ZNF804A* risk have also been probed at a cognitive level in large samples. These studies implicate *ZNF804A* locus with neurocognitive domains such as social cognition. In these studies, the *ZNF804A* variant has been associated with variability in negative attribution style, where risk carriers show increases tendency to attribute negative events to individuals rather that situational factors (Hargreaves et al., 2012), a finding supported by similar genetic imaging research (Walter et al., 2011). However, converging evidence suggests the effects of *ZNF804A* do not simply increase risk to psychosis. Neurocognitive functions seem to be modulated by the *ZNF804A* gene in SZ patients, but not controls and individuals expressing susceptibility outperform individuals without (Becker et al., 2012; Walters et al., 2010). It may also be possible that the *ZNF804A* locus effects are modulated by IQ (Chen et al., 2012) and gender (Zhang et al., 2011a). At a molecular level, early evidence suggests that rs1344706 may modulate transcriptional activity through allelic differences in DNA-protein interactions (Hill & Bray, 2011; Hill et al., 2012). *ZNF804A* is implicated in processes such as neural migration, neurite outgrowth and synapse formation (Hill et al., 2012) and at present, *ZNF804A* appears to affect a host of phenotypes via unknown mechanisms. The most successful pursuits to discover the mechanisms of *ZNF804A* mediated susceptibility appear to be obtained via functional neuroimaging, which show that *ZNF804A* risk status is associated with relatively robust connectomic deficits during WM (Esslinger et al., 2011; Paulus et al., 2011; Rasetti et al., 2011). However, the neurobiological mechanisms underlying functional connectivity are not fully understood, making interpretation of these findings

difficult. Nevertheless, the sensitivity of fMRI is adequate to detect small effect sizes in relatively small samples. We employed a candidate endophenotype approach combining elements of WM and emotion processing (to our knowledge, a component of SZ pathophysiology not previously used to quantify effects of *ZNF804A*). We demonstrate that *ZNF804A* susceptibility is associated with a strikingly similar neural dysfunction as patients with SZ during a WM task (Wolf et al., 2011b). We suggest that this abnormality (RDLPFC hypoactivation) is mediated by the face-processing component of the WM paradigm as previous work suggests that neural activity in DLPFC during WM is independent of *ZNF804A* effects (Rasetti et al., 2011). Although our sample is relatively small, three major factors support this hypothesis. Firstly, the region for which *ZNF804A* rs1344706 associated alterations (rDLPFC) was also significantly reduced in SZ patients. Second, the cortical region identified has repeatedly been implicated as a component intrinsic to face/affect processing (Becerril & Barch, 2011) which SZ patients fail to engage (Morris et al., 2012). Third, the region (rDLPFC) was activated in a task-dependent manner (Figure 10). We suggest that using face/affect processing tasks to explore the neural circuitry associated with *ZNF804A* may give novel insights into its functionality. Neuroimaging work looking at disorders such as mood disorders has previously highlighted the specific roles of cortico-limbic structures and neurochemistry during face/emotion processing (Bevilacqua & Goldman, 2011). One recent study used an fGWAS approach to quantify the genetic contribution to face/affect processing, suggesting a role for variance within the *TMEM212* gene (Brown et al., 2012). Despite the extensive range of clinical phenotypes that *ZNF804A* is

associated with, no known work has explored the role of rs1344706 in the context of affect disorder neuroimaging endophenotypes/intermediate phenotypes. Future work should consider the functional effects of *ZNF804A* on these parameters, as potential associations could yield key evidence supporting a role for *ZNF804A* in a domain specific component of neurobiology.

Although the functional effects of GWAS hits for psychosis appear to be relatively small (O'Donovan et al., 2008; Ripke et al., 2011), this has not impeded the discovery of novel associations between loci and neurocognitive phenotypes. A marker on the transcription factor 4 gene (*TCF4*; rs9960767) (Stefansson et al., 2009) is a suitable example of how domain specific phenotypes can be identified from GWAS hits with small effects, using translational cross-species approaches. The functional effects of this variant are again, unknown (Williams et al., 2011b) however, evidence suggested that it may have a role in neurodevelopment (Sepp et al., 2011) and interact with other szGWAS risk loci (Kwon, Wang & Tsai, 2011)
. The identification of potential *TCF4*-associated SZ phenotype was first identified in mutant mice lacking the gene displayed profound deficits in fear conditioning and sensorimotor gating (Brzozka et al., 2010) and neurocognitive/clinical features in humans with *TCF4* variation (Blake et al., 2010; Forrest et al., 2012). This phenotype was then investigated in humans where risk carriers showed disruptions in gating function as measured by prepulse inhibition (PPI) (acoustic startle response) (Quednow et al., 2011) and P50 suppression (auditory evoked potential) (Quednow et al., 2012). Gating function is a well-established endophenotype of SZ (Hong et al., 2008)

and *TCF4* variants seem to be important modulator of this function (Roussos, 2012). Moreover, an interaction between *TCF4* genotype and smoking status effects on P50 suppression where the most profound deficits where identified heavy smokers expressing *TCF4* risk alleles, suggesting a potential gene × environment interaction. Although these findings may be driven by epistatic interactions or other environmental factors, these results suggest an important role of *TCF4* in early process dynamic. More recently, other variants (including rs9960767) on the *TCF4* gene have also been associated with neurocognition, disease onset, cortical morphology and *TCF4* expression (Wirgenes et al., 2012). These findings highlight a scenario where the functional effects of szGWAS hits may help disentangle the genetic and phenotypic heterogeneity apparent in SZ. By identifying the specific components of SZ etiology, it will be possible to distinguish the biological pathways downstream of diagnosis/symptomology and the environmental factors that may mediate these predispositions (Roussos, 2012). These findings support a polygenic model of psychosis where complex gene networks regulate specific neurobiological pathways, which contribute to one or more phenotype/trait. Although these preliminary studies have been successful at identifying the roles of specific genes in SZ, it must be considered that psychiatric disorders are broad, multifaceted, heterogeneous phenotypes with overlapping symptomology. To fully capture the phenotypic effects of risk loci discovered in GWAS, research must focus on capturing the specific components of genetic susceptibility. It must be appreciated that a substantial proportion of psychosis susceptibility is present in data already obtained (Lee et al., 2012a). Our objective is to create genetic models that

explain this phenotypic variance (Manolio et al., 2009; Eichler et al., 2010). One potential method would be to work within a framework of polygenic contribution (Weng et al., 2011). Many early studies employed a single variant approach to investigate the neurobiological effects of promising genes. However, in order to capture a larger proportion of the genetic variance linked mechanistically to the etiology of neuropsychiatric disorders; studies must consider the impact of gene networks on neurocognitive components.

This may involve the creation genetic risk scores based on a specific neurobiological pathway. This could be applied to aid in the classification of disorders or aid in risk prediction. GRS could also be used to capture broader components of genetic risk in endophenotype/intermediate phenotype studies (Walton et al., 2012; Whalley et al., 2012). Using a polygenic approach to examine behavioral and/or neuroimaging data may identify promising genetically mediated phenotypes/traits underlying neuropsychiatric disorders. In order to holistically represent genetic variability/susceptibility within a neural system, the functional effects/effect sizes of each variant must be considered in each neurobiological profile. Novel statistical methods are beginning to use multifocal profiles or convergent genomic methods to aid in phenotypic dissection and genetic risk prediction (Brown et al., 2012; Hibar et al., 2011a). These methods may aid in the prediction and classification of neuropsychiatric disorders and disambiguate the neurobiology underlying complex domains of cognition.

As the scope of genomic analysis/sample size increases, novel loci will add to an expanding genetic landscape and reflect a more precise estimation of the genetic susceptibility associated with psychosis phenotypes. How we

choose to evaluate the role of this variance will determine the impact that GWAS have on the entire field of psychiatry. Complex phenotype dissections using behavioral and/or imaging parameters appear to be sensitive and informative methods for quantifying the mechanistic role of genetic variance in neuropsychiatric susceptibility (Linden, 2012).

20.3. Genetics Of Cognitive Aging & Alzheimer's Disease

Unlike disorders of affect/mood/impulse, Alzheimer's disease is a relatively homogenous disease with distinct pathophysiological mechanisms and hallmark neuropathology (Schellenberg & Montine, 2012)
. Perhaps for this reason, establishing the biological mechanisms of predisposition has been a remarkably productive pursuit. The homogeneity of the disease may potentially limit the number of neurobiological pathways that contributes the pathophysiological process. The identification of autosomal dominant mutations (APP, PSEN1/2; (Gerrish et al., 2012)) and late-onset AD (LOAD) susceptibility variants on *APOE*/*SORL1*/*GAB2* (Wollmer, 2010; Zetzsche et al., 2010) had a major impact on the understanding of AD pathogenesis and explained a significant proportion of AD susceptibility (Schellenberg & Montine, 2012). Apart from the potential environmental factors that may also influence AD susceptibility, AdGWAS may identify the remaining components of variance that mediate AD susceptibility. It was hoped that AdGWAS could be used to identify novel molecular pathways relevant to AD. The identification of SNPs with small effect sizes has aided in the discovery of previously unidentified mechanistic pathways for AD susceptibility (Musunuru et al., 2010). The AdGWAS demonstrate several functional implications that may improve AD etiology and therapeutic strategies. The identification and replication of *APOE*, *CLU*, *SORL1* and *ABCA7* suggest a role of lipid metabolism in the pathophysiology of AD susceptibility (Jones, Harold & Williams, 2010; Guerreiro et al., 2010; Wollmer, 2010; Zhang et al., 2011b) . Several loci that confer susceptibility implicate innate and adaptive immunity responses as a key mechanism. Risk variants on *CLU* and *APOE* may modulate these pathways as well as

variance on *CR1* and the MS4A region (Schellenberg & Montine, 2012; Crehan et al., 2012). Lastly, several of the GWAS loci are situated on genes that encode proteins implicated in processes at the cell-membrane, particular endocytosis. SNPs on *BIN1*, *PICALM* and CD2AP suggest that deficits in intracellular vesicle trafficking could also contribute to AD susceptibility. The remarkable progress witnessed using GWAS approaches must now be complemented with additional techniques that quantify the functionality of the genetic variance identified. Recent initiatives have sought to investigate the relationship between AD traits/states and GWAS risk loci. Several studies have demonstrated links between AdGWAS loci (*CR1*, *PICALM*, *TOMM40*, *APOE*) and biomarkers such as CSF Aβ1-42 (Bruno & Sidtis, 2011; Pomara et al., 2011; Pomara, Schott & ADNI Investigators, 2012; Schjeide et al., 2011) and senile plaques (Kok et al., 2011). More specifically, links have been made mechanistically linking the GWAS *CLU* (rs11136000) variance to splice variation (Szymanski et al., 2011), *CLU* expression (Allen et al., 2012; Ling et al., 2012), variation in plasma clusterin levels (p*CLU*) (Schurmann et al., 2011) and linking p*CLU* levels to rate of cortical atrophy (Thambisetty et al., 2010; Thambisetty et al., 2011). Several studies also document the combined role of AdGWAS genes in cognitive decline and cognition (Barral et al., 2012; Keenan et al., 2012; Mengel-From et al., 2011; Verhaaren et al., 2012).

The functional effects of AD susceptibility loci identified using neuroimaging phenotypes are of particular clinical interest. So far, the most striking findings suggest that these variants have a neurobiological effect on brain structure/function, far preceding the first signs of cognitive impairment. Our study is the first genetic imaging study to quantify the functional effects of

the AdGWAS loci on the *CLU* gene (Lancaster et al., 2011). We demonstrated that individuals expressing the *CLU* risk allele displayed compensatory neural processing in response to WM task-demand in a similar manner in individuals with the *APOE* ε4 risk allele (Trachtenberg, Filippini & Mackay, 2012; Trachtenberg et al., 2012a). Since our findings were reported, additional studies have documented association between the *CLU* risk locus and functional connectivity of neural networks during WM (Erk et al., 2011) and white matter microstructure (Braskie et al., 2011). The median age of participants in these studies was ~29, 32 & ~24 years respectively. Since this trio of studies, an additional study (Thambisetty et al., 2012) suggests that the *CLU* variant shows faster rates of cognitive decline in individuals that transition into MCI and/or AD in presymptomatic stages. Furthermore, the *CLU* locus was associated with increased resting cerebral blood flow (rCBF) in cortical regions associated with memory process. It was suggested that the increase in rCBF was a compensatory increment in neural activity, marking a transition from normal aging to MCI and/or AD. Interestingly the three studies (Erk et al., 2011; Lancaster et al., 2011; Thambisetty et al., 2012) all implicate frontal, hippocampal and/or cingulate regions as functional neural systems compromised by *CLU* risk status. The functional abnormalities in these cortical regions are among the first to suffer the neural insult of AD related neuropathology, and may be compromised at a molecular level long before the presentation of AD related symptoms (Braak & Braak, 1998; Donev et al., 2009). There is also converging evidence that *CR1* genotype may have an impact on AD vulnerable regions such as the entorhinal cortex in younger individuals (mean age ~23 years). Furthermore, the *CR1* is associated with

rate of global cognitive decline, an effect that is mediated by amyloid plaque deposition (Bralten et al., 2011). Considering that *CLU* and *CR1* are involved in different neurobiological pathways (lipid metabolism and immunity, respectively), it is plausible that these loci mediate risk to AD via different molecular mechanisms and at different times during the aging process, leading to different phenotypic associations. Although there are promising candidate biomarkers of AD, many of which have high levels of sensitivity and specificity (review; (Linden, 2012)), it is difficult to ascertain which are mediated by genetic susceptibility, rather than physiological insult or pathophysiological adaptations that occur as a result of disease onset. The mechanisms that govern AD heritability are herein unknown and it is unclear how/when genetic susceptibility is mediated. Neuroimaging endophenotypes offer a promising novel method for quantifying the genetic contributes that mediate AD susceptibility (Biffi et al., 2010). Longitudinal studies may also offer insight into the trajectory of genetically mediated cognitive decline. Using these approaches, it will be possible to disambiguate the role of genes/biologically informed multifocal profiles (*CLU* and/or *APOE*; lipid processing for example) using specific intermediate/endophenotypes such as the brain's structure and/or function. Characterizing genetic susceptibility via these parameters may help clinicians predict risk status, calculate disease trajectory and measure treatment responses. Neuroimaging techniques can make these measurements before the symptom onset, which may give an individual more time to intervene with disease progression. Advances such as genomic structural imaging (Thompson, Martin & Wright, 2010), Aβ deposition imaging with PET ($^{[18F]}$FDDNP or $^{[11C]}$Pittsburgh Compound B $^{[(11)\ C]}$PiB) may

be appropriate an intermediate phenotype/endophenotype to quantify genetic susceptibility and/or heritability (Sojkova & Resnick, 2011; Sojkova et al., 2011a; Sojkova et al., 2011b). Cognitive aging is also a suitable phenotype to measure considering its high heritability (estimates between~26%-54%; (pp167 (Ritsner, 2009)). Heritable parameters such as speed of processing, memory parameters and cognitive control (Finkel & Pedersen, 2000; Finkel et al., 2000) all decline with age. It is possible that AD risk loci modulate the rate of decline for which certain loci are associated with pronounced or reduced cognitive deficits in later life. At present, three models (Figure 13) predict different genetic effects on the rate of cognitive decline with age. It is suggested that pathogenic variants may mediate cognitive deficits early in life that manifests as disruption in an earlier time window (Figure 13a) or conversely risk loci have a pronounced effect of cognition in later life (Figure 13b & 13c). The latter effects may manifest as a simple function of gradient (Figure 13b) or via a rapid transition from normal to pathogenic (Figure 13c).

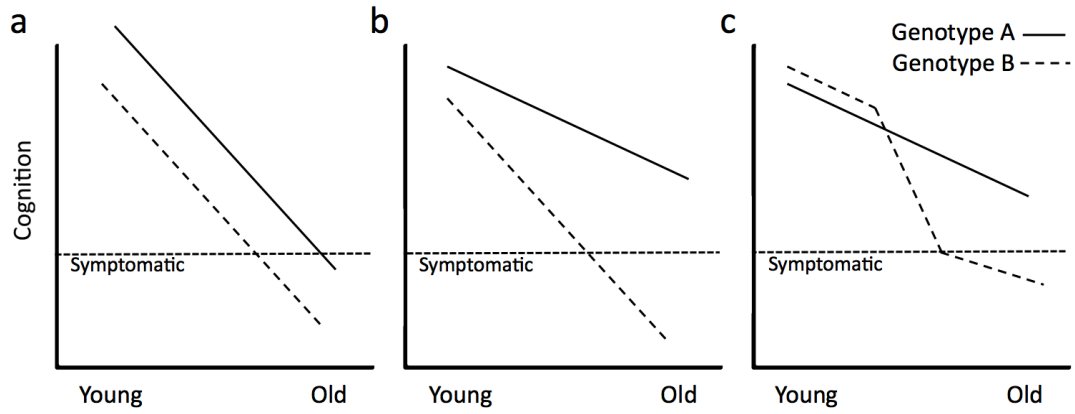

Figure 13 | Adapted from (pp162; (Ritsner, 2009)). Three proposed models explaining how genetic susceptibility might mediate the cognitive aging process.

20.3. Genetics Of Cognitive Aging & Alzheimer's Disease

Previous work suggests that several AD susceptibility genes abide to these models, however the role of many candidate variants is yet to be explored. The *BDNF* val66met polymorphisms; previously associated with phenotypic differences at an intra/extracellular, neurochemical, neurophysiological and cognitive level (Cathomas et al., 2010; Murphy et al., 2012a; Pezawas et al., 2004) has been demonstrated to modulate trajectories of cognition during aging (Harris et al., 2006) suggesting that that *BDNF* may modulate cognitive ageing via models B or C. There is strong evidence suggesting that *APOE* isoform variants modulate trajectories of cognitive aging (Deary et al., 2002). The *APOE* genotype seems to modulate cognition in a manner that conforms to model C, suggesting that *APOE* ε4 is a mediator of antagonistic pleiotropy (Jochemsen et al., 2012). Furthermore, neuroimaging evidence suggests that this *APOE* isoform related variability in cognition could be explained by compensatory neural activity during early life that is disproportionately reduced in later life (Filippini et al., 2011). It is not yet known how/if single or multiple AdGWAS variants influence cognitive aging. However, modeling genotype-dependent trajectories of neurocognitive aging (using parameters of behavior and/or neuroimaging) may inform us of the disease-course to which pathogenic alleles may contribute. One could hypothesize that the trajectory model that a risk allele follows may predict the mechanistic pathways it follows and improve understanding of the functional consequence of the variant. Preliminary evidence suggests that the *CR1* variant is associated with multiple AD-phenotypes including cognitive decline, even controlling for *APOE* genotype (Chibnik et al., 2011) most suitably fitting model B. This study also found no effect of the *CLU* loci on cognitive decline

(with or without correction for *APOE*). The lack of association between *CLU* and cognitive decline was replicated; however the *CLU* risk allele predicted accelerated rates of cognitive decline for individuals in presymptomatic stages of AD progression (Thambisetty et al., 2012). Although imaging phenotypes suggest the AD susceptibility (mediated by loci on *CLU*, *APOE*) may be observed in early life, the trajectory of cognitive decline mediated by these 'lipid processing' risk genes is unclear. It could be argued that these conform to model C. In this model, compensatory phenotypes are witnessed in early life, followed by a sharp, age-related decline at a particular threshold. *CLU* and *APOE* variants both seem predictive of cognitive impairment, but only in later life. In order to fully quantify the extent to which AD susceptibility loci modulate cognitive decline during the again process, we must again consider aging as fractionated processes, consisting of many phenotypes, some of which may be sensitive to healthy aging, some of which may modulate pathogenic processes in aging. One must also consider environmental confounds (e.g. diet (Barberger-Gateau et al., 2012)) when exploring age × genotype interactions. It may also to useful to explore how combinations of behavioral, imaging and molecular phenotypes are affected by AD susceptibility on longitudinal basis to determine when/if pathophysiological processes are present or simply undetectable by behavioral parameters. This technique will undoubtedly improve understanding of the neurobiological underpinnings in AD susceptibility.

20.4. Differential Susceptibility & Antagnostic Pleiotrophy

Within the three themes of research in this thesis (the genetics underlying neuroeconomics, psychosis susceptibility and Alzheimer's disease respectively), many genotype-phenotype associations have been significant, where the risk allele is associated with a superior phenotype. GWAS identify an allele at a location in the genome that is associated with a specific phenotype. The differences in allele frequencies between populations are used to create an odds ratio (OR), which represents the strength of association between a genetic variant and a phenotype. ORs are used to estimate the effect size of a variant. Based on these calculations, the risk allele for a genetic variant are hypothesized. Prior belief postulates that 'risk alleles' will be associated with a pathogenic phenotype, mechanistically linked to disease. Although this assumption has held true in many cases, there are several instances when the 'protective or no-carrier' locus is significantly linked with a pronounced pathogenic phenotype or conversely; the pathogenic allele is associated with a superior phenotype. This has been the case for many of the candidate genes previously discussed such as *COMT* (Mier, Kirsch & Meyer-Lindenberg, 2010), *5HTTLPR* (Hankin et al., 2011a; Hankin et al., 2011b; van Ijzendoorn, Belsky & Bakermans-Kranenburg, 2012), *ZNF804A* (Becker et al., 2012; Walters et al., 2010), *CLU* (Barral et al., 2012), *APOE* (Tuminello & Han, 2011). These studies provide empirical support for the notion that genes associated with neuropsychiatric illness should be explored in the context of variability rather than risk and may modulate phenotypes 'for better or worse'. These findings stress the importance for creating novel behavioral and imaging paradigms, in order to identify specific domains of neurobiology and associated phenotypes. These findings conform

to diathesis-stress models emphasizing the importance of assaying environmental parameters when considering behavior/imaging genetic associations. Although the mechanisms by which susceptibility loci confer risk are relatively unknown, emerging evidence suggest that many of these markers have significant roles in the etiology of disease process. These findings are certainly convincing enough to further investigate the role of these variants within parameters of environmental exposure, during development/aging using phenotypic assays sensitive enough to detect small/specific proportions of variance. Once the genetic architecture orchestrating variance for these phenotypes has been mapped, we may predict disease onset, course, severity and treatment response, understand the neurobiology underlying domains of neurocognition and plan novel treatment strategies modeled upon the deficits we observe.

20.5. General Conclusions

Strong evidence suggests that components of the genome contribute to neuropsychiatric susceptibility. However it remains unclear how these variations confer risk. Imaging/behavioral genetics play a key role in the process of identifying the candidate endomechanisms by which genetic variants modulate vulnerability. Using these methods, it is possible to dissect the biological substrates underlying components of neurocognition, which may help improve psychiatric classification and nosology. The investigations in this thesis support the theory that single genetic variants (SNPs) are associated with variability in specific components of trait pathophysiology.

In order to make informative predictions about neuropsychiatric susceptibility, it is also necessary to understand the magnitude of effect size for common/rare gene variants associated with a clinical phenotype. Will it be possible to uncover all of the genetic effects that increased susceptibility to neuropsychiatric illnesses? The modest effect sizes for common variants combined with a lack of neurobiological understanding makes interpretation of common variants identified via candidate/GWA studies findings difficult. This lack of translation between genetics and clinical and phenomenological psychiatry is disconcerting to those investing in psychiatric research (Sullivan & 96 Psychiatric Genetics Investigators, 2012). However, novel methods that capture highly informative genetic markers (polygenic models, multi loci informed biological profiles, epistasis models), the most appropriate phenotypes (subclinical traits such as connectomic neuroimaging measures/domain specific neurocognitive phenotypes), combined with information regarding environmental factors, will uncover principles of

psychopathological susceptibility that can revolutionize the way we diagnose, predict, prevent, and treat neuropsychiatric illness.

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